Leonard F. Koziol
Deborah Ely Budding

Subcortical Structures and Cognition

Implications for Neuropsychological Assessment

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ISBN 978-0-387-84866-2 e-ISBN 978-0-387-84868-6
DOI 10.1007/978-0-387-84868-6

Library of Congress Control Number: 2008940617

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Dedication and Acknowledgments

I may not have gone where I intended to go, but I think I have ended up where I intended to be.

Douglas Adams

This book was made possible as a result of the extraordinary influence and support of many people. This manuscript is dedicated to these individuals. First, I thank Mark Moulthrop, Ph.D. I was extremely fortunate to have him as my clinical neuropsychology supervisor nearly 30 years ago. Mark taught me how to think about cognition and its measurement, and even more importantly, he taught me how to think about patients. I am forever grateful for his influences upon my thinking.

I also thank my patients. By this, I mean each and every clinical case I personally saw in consultation, as well as those cases presented to me by students for supervision. This is an extremely voluminous number of cases, an astonishing tally, but a little bit of every one of these patients is represented in this book, because this book is about understanding their problems. Without the experience I gained by evaluating the diagnostic issues presented by these patients, there would be little reason for this book. Thank you for allowing me to learn from you. I also thank my graduate and post-graduate students. Your questions compelled me to think, which allowed me to learn.

Several individuals provided practical assistance in completing the manuscript. Drs. Phillip Kent, Keith Kobes, Doug Callan, Adam Piccolino, Kevin Duffy, Dana Chidekel, Deborah Miora, Raymond List, Karin Suesser, and Diane Engelman all provided comments and literary assistance in reading through various versions of different chapters. Catherine Gottlieb, MLIS, provided invaluable editorial research and editorial research consulting. Becky Fong proved to be an exceptional illustrator. All of your contributions were critical to the completion of this manuscript. Thank you.

Special thanks goes to Deborah Budding. She did more than anyone could ever ask for in making this book a reality. It would be an understatement to say her ideas, her literature searches, her sharing and updating of citations, her constant availability, and her literary and editorial expertise were invaluable.

She was the inspirational and energizing catalyst that made this book possible. I was extremely fortunate to have the privilege of working with her.

I also thank Mark and Janel Blakely for the photographs of Kaitlyn. Those pictures in Chapter 4, Fig. 4 illustrates "reinforcement learning" in a way that could never be described in words. I greatly appreciate your contribution, which allows others to learn as I did. I also thank the Wambach family for their precious support. Finally, I thank my brother Don, who has never really known that he has always been an inspiration to me.

Thank you.

Leonard F. Koziol

First, I would like to give profound thanks to Len Koziol for sharing his knowledge, wisdom, and time with me. His generosity and trust have been awe-inspiring. He is a rare person of honor and integrity. I am also fortunate to have had a number of remarkable people as mentors, colleagues and sources of support over the years and during the writing of this book. My parents, grandparents, and sisters provided early inspiration in addition to ongoing opportunities for learning from experience. Barbara Counter, Ph.D. encouraged me to follow my instincts. Arnold Purisch, Ph.D. opened my eyes to the possibilities held within the world of neuropsychology and continues to serve as a valued mentor. Lorraine Gorlick, LCSW, Ph.D. has shared her tremendous patience, fortitude, and humor with me while demonstrating how it is possible to be still and still moving. Dana Chidekel, Ph.D. inspires and challenges me to keep moving, even when I don't feel like it, and shared her editorial and writing prowess on a number of chapters. Deborah Miora, Ph.D., Jayme Jones, Ph.D., and Denise McDermott, M.D. have lent ongoing moral support—with accompanying appreciation for both work and play—in addition to direct assistance with this project. Cathy Gottlieb, MLIS lent both research and moral support and is listed in the dictionary under the definition of "friend." Finally, my husband, Bill, who continues to inspire me, cook for me and make me laugh, and my stepdaughter, Alex and sons, Nicholas and Matthew—who have waited forever for me to be finished—have made all of this worthwhile. Thank you all. I am deeply grateful.

Deborah Ely Budding

Preface

A little revolution now and then is a good thing.
Thomas Jefferson

If everyone is thinking alike then somebody isn't thinking.
George S. Patton

Most clinical neuropsychologists are taught a cortico-centric model of cognition. From this viewpoint, the neocortex is considered to play the most important role in generating human thinking and behavior. This book departs from that view by additionally considering subcortical contributions to cognition. Our focus concerns subcortical structures that have traditionally been considered only as co-processors of movement. These structures contribute to cognition and emotion. We propose that the cortex, basal ganglia, and cerebellum operate in parallel to generate adaptive behaviors and we examine the role of neuropsychological testing and evaluation within this framework. We believe that this adds needed dimensionality for assessing complex behavioral systems.

This book was written for practicing neuropsychologists and for those in training. This book would be useful for both graduate and post-graduate students as well. Although we primarily had neuropsychologists in mind in writing this manuscript, we believe that the ideas described in this book are also useful for people in other related professions. Anyone working in a medically or health related profession who wants to learn more about how cognition and behavior are organized within the brain should be familiar with the content of this manuscript.

In writing this book, we made the assumption that the reader is already familiar, or in the process of becoming familiar, with all fundamental concepts of cortically based brain–behavior relationships. Anyone who is not familiar with this information should consult a traditional neuropsychology textbook.

Because the intended audience of this book is clinically based, its focus is very practical. We strive for the reader to acquire a practical understanding of cortical–subcortical functional relationships. This book was not geared toward people primarily involved in research. The book was not meant to include an exhaustive review of the literature. Instead, the book offers an integrated view

of cortical–subcortical functioning that we believe has practical clinical applicability. However, whether or not you fit the profile of our intended reader, we encourage you to read on and we hope that you find the information in this book useful if not inspiring.

Park Ridge, Illinois — Leonard F. Koziol
Manhattan Beach, California — Deborah Ely Budding

Contents

1 Introduction: Movement, Cognition, and the Vertically Organized Brain 1
A Case of Dementia? 3
Why Do We Have a Cortico-centric Bias? 5
Vertically Organized Brain Systems 6
A Theoretical and Historic Context 9
How to Do Things in a Changing Environment 11
When to Do Things—Intention Programs 13
Theories of Types of Behavioral Processing and the Frontostriatal System 14
Analogous Memory Systems 16
The Phylogenetic Perspective 17
Excitation Versus Inhibition 19
Adjustment of Motor "How"—The Changing Characteristics of Excitation and Inhibition 20
Summary 22
References 23

2 The Basal Ganglia: Beyond the Motor System—From Movement to Thought 27
Anatomical Structures and Subdivisions of the Basal Ganglia 28
Basal Ganglia Circuitry 33
Specific Projections into the Striatum 34
Direct and Indirect Pathways 36
The Subthalamic Pathway 37
The Striosomal Pathway 38
Basal Ganglia–Subcortical Loops 38
What Does the Cortico-striatal System Do? 41
Three Selection Pathways—An Interim Summary 42
Application of Motor Behavior to Cognition 42
Examples of the Frontostriatal System in Operation 44
Sensitivity to Context: The Basal Ganglia in Learning 45

Higher-Order Cognition and Working Memory 46
How Does Working Memory Work? 50
Context and Higher-Order Control in Combination 54
The Basal Ganglia and Automatic Processing 55
Alternating Episodes of Automatic Versus Higher-Order Control 57
An Integrated Cortical–Subcortical Model of Behavioral Selection 58
The Striatum Learns and Mobilizes Procedures 58
The Prefrontal Cortex Decides upon Behavior 59
Pathology/Developmental Disorders 61
Summary 62
References 62

3 Frontal–Subcortical Real Estate: Location, Location, Location 69
Divisions of the Frontal Cortex and the Anterior Circuits 70
The Dorsolateral Prefrontal Circuit (DLPFC) 71
Orbitofrontal Circuit (OFC) 75
The Medial Frontal Circuit (MFC)/Anterior Cingulate Circuit 77
The Motor Circuits 79
Motor, Cognitive, Motivational, and Affective Analogues 80
Frontal System Syndromes 82
Summary 90
References 90

4 Learning and the Basal Ganglia: Benefiting from Action and Reinforcement 95
The Basal Ganglia and Learning 96
The Inferotemporal and Parietal Loops 100
Categorization and Classification 101
Positive and Negative Reinforcement Learning 108
Summary 118
References 119

5 The Cerebellum: Quality Control, Creativity, Intuition, and Unconscious Working Memory 125
Surface Anatomy of the Cerebellum 126
Cortex and Cerebellum—Superficial Comparison of Infrastructure 128
Infrastructure of the Cerebellum 129
The Cerebellum and Non-Motor Functions 131
The Cerebellum in Procedural Learning 133

The Cerebro-Cerebellar Circuit 134
The Cerebellum and the Principle of Lateral Crossed Control 137
The Olivo-Cerebellar System 137
Theories of Cerebellar Function 138
A Hybrid Model of Cerebellar Function 140
Three Brain Systems in Parallel 142
Dysmetria—What Does It Signify? 143
Working Memory, Expertise, Creativity, and Giftedness 145
Clinical Presentations 148
The Cerebellar Cognitive Affective Syndrome 149
The Posterior Fossa Syndrome 151
Agenesis of the Cerebellum 153
Very Pre-Term Infants 153
DSM-IV Behaviorally Defined Conditions 154
The Cerebellum as a Modulator 155
Dysmetria—Undershooting and Overshooting—An Important Paradigm 157
Summary 157
References 158

6 Automaticity and Higher-Order Control in Communication: A Brief Introduction to Language and Social Cognition 167
Gesture, Communication, and Speech 169
The Declarative-Procedural Model of Language 171
Social Cognition—Automatic and Higher-Order Control Systems 174
Reflexive and Reflective Systems 177
Social Intuition, Social Skill, and Non-Verbal Communication 178
Implications of Dual-System Models for Social Cognition and Language 180
Summary 182
References 183

7 The Vertically Organized Brain in Clinical Psychiatric Disorders 187
Obsessive-Compulsive Disorder 191
Attention Deficit Hyperactivity Disorder 194
Schizophrenia 199
The Basal Ganglia in Schizophrenia 200
The Cerebellum in Schizophrenia 202
Mapping Anatomy and Symptomology 203

Other Clinical Disorders . . . 205
Autism Spectrum Disorder . . . 205
Mood Disorders . . . 207
Alzheimer's Disease . . . 207
Summary . . . 208
References . . . 209

8 Familiarity and Novelty—Evaluating the Frontostriatal System . . . 219
The Frontostriatal System . . . 221
The Frontostriatal System in Operation . . . 223
Interpretation Paradigms . . . 224
Dynamically Changing Locus of Control . . . 225
Neuropsychological Testing and the Frontostriatal System . . . 226
Test Methodologies for Identifying the Integrity of the Frontostriatal System . . . 228
Verbal Fluency Tasks . . . 232
The Stroop Color Word Test . . . 233
Traditional "Frontal Lobe" Problem-Solving Tests . . . 235
Task Comparisons . . . 243
Continuous Performance and Go–No-Go Tasks . . . 245
Commonly Used Neuropsychological and Cognitive Tests: What Do They Measure? . . . 249
Summary . . . 251
References . . . 252

9 Thought in Action: Procedural Learning, Processing Speed, and Automaticity . . . 257
Processing Speed . . . 259
The Measurement of Processing Speed . . . 260
Processing Speed—A By-Product of Cognitive/Executive Control . . . 262
Practice Effect . . . 263
Types of Practice Effect . . . 265
Procedural Learning in Neuropsychological Evaluation . . . 268
The Wechsler Mazes . . . 269
Trailmaking Tests . . . 270
Perceptual–Motor Skill Learning . . . 271
Subcircuit Differentiation . . . 272
Motor Adaptation . . . 273
Summary . . . 274
References . . . 274

10 The Basal Ganglia and Neuropsychological Testing 277
Interpretation Paradigm 280
Level of Performance 281
Test Score Comparisons/Pattern Analysis 281
Pathognomonic Signs 282
Body-Side Comparisons 282
Clinical Case Examples 283
Case 1 283
Case 2 293
Case 3 298
Case 4 304
Case 5 310
Summary 316
References 317

11 The Cerebellum in Neuropsychological Testing 321
Clinical Case Examples 322
Case 1 322
Case 2 330
Case 3 337
Case 4 347
Summary 360
References 360

12 The Integrated Brain: Implications for Neuropsychological Evaluation 363
It's Not "All Cortex"- It's the Flexibility of Interaction 365
Clinical Applications 368
References 377

Index 381

Chapter 1
Introduction: Movement, Cognition, and the Vertically Organized Brain

Nature does nothing uselessly

Aristotle

How does the mind work? This question has puzzled philosophers, physicians, and artists for centuries. This question has led to remarkable discoveries, and in turn, further questions. Currently, technological advances appear to be outpacing our abilities to keep up with applying them. Yet the same questions continue to arise. Why do we keep losing our keys? Why do we have the same argument over and over again? Why do we hit a hole-in-one on the golf course one day and are lucky to bogey the same hole a week later? These kinds of questions are no less significant than questions regarding why societies fail to learn from history or individuals allow envy or greed to turn them away from important opportunities. Science has long attempted to answer these and other questions. Sometimes what we know can get in the way of discoveries yet to be made, exemplified by earlier assumptions about the "unimportant" prefrontal lobes or the "silent" right hemisphere. Nevertheless, discoveries continue and the neurosciences in turn continue to adapt to these discoveries along with their associated intended and unintended consequences.

The problem of "mind" and "body" has endured endless discussions which we will not further belabor. Much difficulty has arisen in trying to conceptualize cognition in the context of emotion and behavior. Arbitrary separation of these things fails to address the inherent constant interplay between how we think, feel, and act. Leaders of countries, businesses, and families must regularly make decisions about what to do, and in relation to this must try to consider when and how to override emotion or instinct in favor of higher-order thought. Psychotherapy patients endeavor to learn from previous experiences and alter their ingrained "automatic" responses to situations that *feel* similar to earlier interactions but are not the same in reality. While emotional function is essential to all of this, cognition plays a central role.

Cognition, from a neuroscience perspective, has generally been considered almost exclusively in relation to neocortical function. Most of us have been trained to consider our ability to think as part of a cortical system that separates

L.F. Koziol, D.E. Budding, *Subcortical Structures and Cognition*,
DOI 10.1007/978-0-387-84868-6_1, © Springer Science+Business Media, LLC 2009

us from our primate ancestors. This idea becomes perpetuated in advanced studies, as most clinicians in the cognitive neurosciences are taught a cortico-centric model of neuropsychology. In this model, the cortex is considered not only the seat of cognition, but also the center of higher-order control over behavior. We are taught that the evolutionary expansion of neo-cortex is generally what makes us unique thinkers, and it, therefore, makes intuitive sense to look to cortical functioning as the source of cognitive activity.

To support the unique role of cortex, researchers often point to evidence from brain pathology. For example, lesions of the cortex result in a variety of deficits in higher-order cognition (Lezak, 2004). This is usually manifested by instrumental disturbances in thinking that affect the language, visuospatial, executive-related, and memory domains. Similarly, there is a voluminous neuroimaging literature that demonstrates the recruitment of various cortical networks during cognitive activity. When subcortical structures are considered, these brain areas have generally been relegated to the role of engineering movement in tandem with key cortical structures. Thus, within this model, the basal ganglia and the cerebellum are considered primarily as co-processors of movement. Accordingly, disease affecting these regions results in kinetic disturbance.

Basal ganglia pathology is associated with either hyperkinetic or hypokinetic movement disorders typified respectively by Huntington's and Parkinson's diseases (Blumenfeld, 2002). These pathologies are characterized by the loss of voluntary control over movement. Therefore, a general symptom of these conditions concerns a loss of intentional control over movement. Cerebellar pathology is characterized by disorders of coordination, chief of which are the ataxic syndromes. The primary symptom of cerebellar pathology is dysmetria, in which the quality of movement is affected, as movements become erratic in amplitude and direction so that patients appear to lack coordination (Houk & Mugnaini, 2003). This compartmentalization of cognition and motor functions represents a succinct "package," offering clinicians a certain level of simplicity that nonetheless promotes a false sense of security in the understanding of brain–behavior relationships.

But what if that "package" is too simplistic? What if it is so neat that it essentially derails a more comprehensive and accurate understanding of integrated brain function? Within the constraints of this model, the similarly important role of the neocortex in non-cognitive functions is often overlooked or minimized. For example, many regions of the posterior cortices participate in somatosensory functions, and a substantial region of the frontal convexity participates in motor functioning. Therefore, certain regions of the neocortex are heavily involved in activities that in no way would be considered "purely" cognitive.

If the cortex plays a role in non-cognitive functioning, we must consider this influence in the opposite direction. Accordingly, considerable evidence has accumulated implicating the basal ganglia and the cerebellum in cognitive and emotional functioning (Bedard, Agid, Chouinard, Fahn, & Korczyn, 2003; Schmahmann, 1997). In Huntington's disease, which is characterized

by deterioration of the caudate nucleus, personality changes along with executive function decline are often the initial presenting signs of the disorder (Cummings, 1993). Patients with Parkinson's disease, which is characterized by deterioration of the substantia nigra, very commonly demonstrate cognitive deficits such as impairment in working memory and set shifting, cognitive slowing, and affective blunting as intitial symptoms (Lichter, 1991). Patients with posterior and inferior involvement of the cerebellum present with cognitive pathology and emotional dysregulation instead of motor disturbance (Schmahmann, 2004). Therefore, the cortex participates in functions that are non-cognitive and subcortical regions participate in functions that are non-motor.

Understanding this interplay between structures has far-reaching implications. It challenges the primacy of a horizontal, cortico-centric model of brain organization. This traditional model focuses upon "left versus right" and "anterior versus posterior" organization as the main principles structuring cognition. The purpose of this book is to explore subcortical contributions to cognition and emotion. The book will present anatomical and functional evidence. We will then discuss the implications of these findings for neuropsychological assessment. A vertical dimension that includes cortical–subcortical relationships is essential for creating a more accurate view of brain function. This expanded perspective will assist clinical neuropsychologists in navigating through the complicated neural landscape, adding important dimensionality to our ability to "picture" human adaptive function through our assessments.

A Case of Dementia?

To illustrate how critical it is to understand vertical brain organization, it would be useful to consider the following example. This middle-aged patient arrived for differential diagnostic evaluation with few or any subjective complaints, believing he was to receive a disability evaluation (which was not the case). He could not explain why he was not working. He understood that he was brought by his family, but was unable to more specifically explain why they brought him. His family's primary complaints revolved around his moodiness and irritability, which were coupled with disinterest and relative apathy. His interpersonal presentation during the examination lacked initiative and spontaneity. Accompanying affect was flat. Nevertheless, he was fully cooperative. Consider the following test scores (Table 1.1).

Any clinician reviewing these test scores would justifiably conclude that this patient suffers from dementia. However, is this a case of cortical dementia? There are certainly elements of this profile of scores that suggest a cortical dementia, as the characteristics of anterograde amnesia and language difficulty seem so pronounced. One look at the limited amount of learning and storage

Table 1.1 48 year old male/12 years education

WASI FSIQ 84	**CVLT**	
VIQ 72	I.	1
PIQ 103	II.	2
WCST	III.	2
6 categories/104 cards	IV.	2
4 perseverative responses	V.	2
TOL	B	3
Total move 43/ss90	**SDFR**	0
Correct 4/ss100	**SDCR**	0/2int
Init. Tx 116"/ss124	**LDFR**	0
Exec. TX 540"/ss60	**LDCR**	1/3int
Tot Tx 656"/ss60	**Rec**	10/6FP(2 list B)
RV/2 off ss60		
TMT	**WMS III/LM**	
A 66"(30.7/8.8)	I	24/sc5
B 217"(64.4/18.3)	D	0
Sent Rep 36PR		
Token 6PR		
FAS 12/10PR		
An 8/10PR		

that occurs supports this assertion. A closer look at the data implies that problem solving is reasonably well preserved, although the patient works very slowly. One might hypothesize that posterior brain regions are deteriorated but anterior regions are significantly less affected. However, the pattern of relatively intact executive functioning coupled with dramatic slowing in execution of tasks combined with marked difficulties in memory and learning lead to a *possible* anatomical link to the anterior thalamus (Graff-Radford, Tranel, & Brandt, 1992). In truth, one cannot with certainty differentiate diagnoses or localize the source of pathology based on these data. In actuality, this patient had a hypothalamic tumor, far removed from primary cortical pathology. This tumor was impinging upon basal forebrain circuitry and ultimately required neurosurgical intervention. The lesson here is a simple one: By focusing only upon horizontal brain organization, a differential diagnostic conclusion cannot be reached beyond the obvious one of dementia. The obvious temptation would be to jump to *cortical* conclusions, which would be diagnostically misleading but understandable within a two-dimensional model.

Most cognitive test interpretation in clinical neuropsychology has emphasized the horizontal organization of the brain, specifically, lateralized brain–behavior relationships. In most right-handed people, it is believed that the left hemisphere subserves language functions and that the right hemisphere mediates visuospatial functions. Neuropsychological testing approaches clinical evaluation by attempting to ascertain differences in functioning across this lateralized gradient. Additional attention is placed upon the anterior–posterior

dimension (throughout this book, we define posterior cortices as the occipital, parietal, and temporal lobes, since these lobes lie posterior to the central sulcus; we define anterior brain regions as the frontal lobes and the basal forebrain region). This concerns an evaluation of the anterior-mediated executive domain and an assessment of the posterior-mediated perceptual domains. Therefore, traditional test interpretation is characterized by inferring left versus right hemispheric differences in functioning and frontal versus temporal–parietal–occipital lobe differences in functioning. Clinical neuropsychology has become adept at evaluation within this horizontally organized model of brain–-behavior relationships. However, this is an oversimplified model that neglects the vertical organization of the brain. The model does not take into account that subcortical pathology can generate presentations that mimic cortical involvement, and in this way, this model can even distort the clinical picture.

This book describes the vertical organization of brain–behavior relationships and considers methodologies for evaluating these processes. Our main goal is to present an updated and more integrated view of brain–behavior relationships by examining the contributions of both cortical and subcortical brain regions. In this way, we can move from a two-dimensional to a three-dimensional depiction of brain function and in doing so better understand and describe human adaptation as a dynamic process.

Why Do We Have a Cortico-centric Bias?

When the neurosciences were in their infancy, techniques for studying functional neuroanatomy were limited. Many inferences about brain–behavior relationships were made only from behavioral observations of patients with documented cortical brain damage and from laboratory and imaging techniques that were primitive by today's standards. Our knowledge of brain structure was incomplete. The development of neuropsychological testing was rooted in the assumptions of this cortico-centric model. Brain function is dependent upon structure. Patients with brain pathology were tested on cognitive tasks, and the test results were correlated with the site of the cortical lesion. Patients with subcortical pathology demonstrated disturbances in movement. When these movement problems were accompanied by cognitive deficits, it was assumed that the cognitive impairment was a manifestation of cortical deafferentation. The cognitive deficit that was observed was presumed to be the result of disconnecting cortical regions from the rest of the brain.

However, over the past 20–25 years, the development of experimental and diagnostic techniques has allowed for notable revisions in our understanding of functional neuroanatomy. Imaging techniques such as CT scans, PET studies, and fMRI investigations, and physiological techniques such as cell recording and neuronal tracing studies have significantly expanded our understanding of

neuronal structures, their connective patterns, and about how structure relates to function. Additionally, advances in computer science have allowed for greater ability to model the functioning of complex neural systems (Afraimovich, Zhigulin, & Rabinovich, 2004; Basar & Guntekin, 2007; Freeman, 2008; Izhikevich, 2007).

Segregated neuronal connections between associative and paralimbic regions of the neocortex and the basal ganglia and discrete circuitries between these same areas of the neocortex and the cerebellum have been identified. Multiple, parallel, segregated circuits between the cortex and basal ganglia and between the cortex and cerebellum provide the anatomic substrate for supporting not only motor, but also cognitive and emotional function (Middleton & Strick, 2000). Since the brain operates on a "need-to-know" basis (Kolb & Whishaw, 2008), and because function is related to structure, the most obvious and compelling conclusion is that cortical–subcortical connections support a range of highly specialized behavioral functions, including those related to cognition and emotion.

Vertically Organized Brain Systems

There are two vertically organized re-entrant brain systems that interface the cortex and the descending systems. These are the cortico-basal ganglia system and the cerebro-cerebellar system. They are termed re-entrant systems because their circuitries form a "loop"—the circuit re-enters a region near its point of origin. The circuits originate in the cerebral cortex. After passing through the various subcortical structures within each respective system, the circuit re-enters the cortex and terminates very near the same region in which the circuit originated. Therefore, a general feature of these circuits comprises a *cortical–subcortical–cortical* loop of interaction. Within the nervous system, loops of interaction of this type are considered to have a modulatory function. In these two systems, the cortical inputs are always excitatory. Outputs from these subcortical regions are largely inhibitory. This means that these subcortical circuits are regulating or modulating—and thus changing—the nature of input received from various cortical domains. Therefore, *these subcortical regions play an important role in deciding what information is or is not returned to the cerebral cortex* (Andreasen & Pierson, 2008). This "looped" architecture represents an organizational system central to brain–behavior relationships, and therefore, in a broader context, these circuitries are central to neuropsychology.

The prototypical cortico-basal ganglia circuit features an anatomy that is preserved throughout the system of all the circuits that have been identified (Alexander, DeLong, & Strick, 1986). The prototypical circuits can be grouped into seven general categories, as will be discussed in Chapters 2–4 (Middleton & Strick, 2001). However, it has also been argued that there are as many circuits as

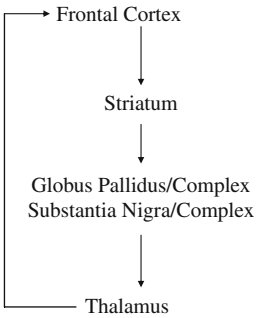

Fig. 1.1 Simplified version of frontal–subcortical circuit

there are specialized functions (Divac & Oberg, 1992). Each circuit is composed of the same number of structures. These structures include the cortex, the striatum, the globus pallidus, the substantia nigra, and the thalamus. Literature has referred to this circuitry as the "cortico-striatal-pallidal-thalamic loop" (see Fig. 1.1).

Each segregated, parallel circuit originates in a specific, circumscribed cortical region. For example, the dorsolateral prefrontal circuit projects specifically to the dorsolateral region of the head of the caudate nucleus, the orbitofrontal circuit projects to the ventral region of the caudate nucleus, the anterior cingulate cortical region projects to the nucleus accumbens, and the auditory and visual association areas of the cortex project to specific regions within the body and the tail of the caudate nucleus (Middleton & Strick, 2001).

Therefore, the basal ganglia receive input from nearly all cortical regions. This has important implications which will be discussed in subsequent sections of this book. Similarly segregated anatomic arrangements are upheld and respected in the globus pallidus and thalamus, while a progressive spatial restriction and compaction occur as these circuits project deep into the basal forebrain region. This spatial compaction has significant implications for the understanding of developmental and "psychological" disorders in particular, as will be discussed in Chapters 3 and 7. Not surprisingly, traditional models of neuropsychological test interpretation have encountered difficulty "explaining" these disorders along lateralized and anterior–posterior gradients.

This general review of the circuitry presents two key points. First, since these circuits originate in associative and paralimbic regions of cerebral cortex, this provides compelling neuroanatomic evidence that the basal ganglia contribute to functions outside the motor domain. Second, because the basal ganglia are anatomically connected to nearly all regions of neocortex, the basal ganglia are in a powerful position to exert influence over a very wide range of functions, including the modulation of perception, cognition, affect, and action (Middleton, 2003).

The second vertically organized brain system is defined by cerebro-cerebellar circuitry (Schmahmann & Pandya, 1997). This re-entrant system demonstrates anatomic and conceptual similarities with the cortico-basal ganglia system. The cerebro-cerebellar circuit originates in the neocortex. Specific regions of the frontal, temporal, parietal, and paralimbic areas of the cerebral hemispheres are all represented as points of origin. Each circuit is again composed of the same cerebellar structures. Cortical regions send segregated projections to their preferred sites of the highly specialized pontine nuclei in the brain stem. Through the mossy fiber input system, specialized projections arrive at specific zones or lobules of the cerebellar cortex (see Chapter 5). The fiber system of the cerebellar cortex projects to specialized regions of the deep cerebellar nuclei, and from there, back to thalamus and on to cortex to a region where the specialized circuit originated (see Fig. 1.2).

The cerebellum, which is actually composed of more neurons than can be found in the remainder of the central nervous system, represents an extremely compact yet powerful computational mechanism (Houk & Mugnaini, 2003). Once again, relying on the anatomic principle that circuitries in the nervous system are established and organized around a "need-to-know" functional basis, these segregated circuits must be contributing to, or perhaps more to the point, modulating, the functions subserved by the regions of origin of the circuits (Middleton & Strick, 2000). This principle can readily be understood by examining the organization of sensory and motor cortices, which is beyond the scope of this book. Comprehensive reviews are provided by Kolb and Wishaw (2008) and M. Banich (2004). As is true for the basal ganglia, the cerebellum is also in a position to exert powerful computational or modulatory influence over all domains of behavior.

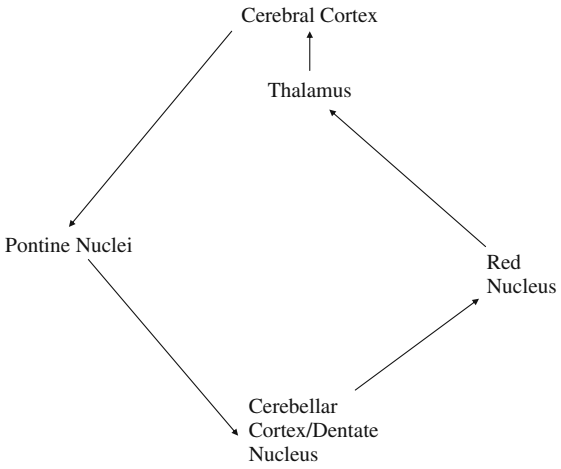

Fig. 1.2 Simplified version of cerebro-cerebellar circuit

To be sure, the neocortex, the basal ganglia, and the cerebellum are all complex brain regions. As might be suggested even by only a cursory description of the circuitries summarized above, understanding these systems is a challenging, daunting task. However, complex systems can often be made more intelligible and understandable when we know something about their history. Theory, evolution, and phylogeny, thus provide the background and clues for understanding the purposes and organization of these brain regions and systems.

A Theoretical and Historic Context

We begin with a deceptively simple question: What is the purpose of the organism? The simplest answer is in the following: The purpose of the organism is to survive. How does the organism survive? In short, the organism survives through interaction with the environment. Therefore, the brain must be organized in a way that allows for successful interaction with and adaptation to the environment. In order to interact and adapt successfully, six criteria must necessarily be met. Three of these criteria have to do with sensory processing, and three of these criteria have to do with motor functioning. The nervous system of the complex organism must have the following minimal characteristics:

1. Capacity for object recognition functions
2. Capacity for object location functions
3. Capacity to detect movement
4. The ability to know what to do
5. The ability to know how to do it (or to know how to act)
6. The ability to know when to act

First, the brain needs to "know" what objects exist in the environment. In other words, the brain needs to have information about the objects that are out there in the world. In the terminology of sensory systems, this information is called *object identification* or *object recognition*. However, being able to accurately identify objects is not enough. Without knowledge of where these objects are, any attempt at interaction for survival is impossible. To interact adaptively, the brain needs information about where these objects are located. Therefore, the brain evolved a system of spatial coordinates to identify objects in space. This function is termed *object location*. Object recognition and location are so important that nature allows for storage of this sensory information to persist over time through the medial temporal lobe memory system. Knowing about objects and where they are located is important, but being able to *remember* information about these objects provides even greater adaptive advantage. In fact, it can even be argued that this type of learning and memory is unsupervised, representing the "default condition" of the cortex (Doya, 1999).

Unfortunately, objects in the environment might not be stationary, and moving objects might threaten an organism's survival. From a survival standpoint, it might be necessary to track a moving target. In this regard, sensory systems also need to include the ability to detect movement, which is the third element of sensory organization. Sensory systems are in fact biologically organized in this fashion in order to perceive identity and location, and to detect movement (Ungerleider & Haxby, 1994; Ungerleider & Mishkin, 1982).

For instance, in most vertebrates and certainly in non-human and human primates, sensory systems and subsystems are coordinated to fulfill and accommodate these sensory tasks of perceiving identity, location, and motion. Ventral regions of the sensory or posterior cortices typically subserve object identification or recognition functions. Dorsally organized information-processing streams subserve object location functions. Tucked inside the superior temporal lobe sulcus is a visual information-processing pathway that is specialized for the detection of movement (Banich, 2004).

Very considerable amounts of cortical tissue are dedicated to these object recognition, location, and detection of motion functions. Therefore, it is clear that the organism evolved to have access to appropriate sensory information in order to make necessary decisions about potential behavior. This sensory information often includes cognitive components. The basal ganglia and cerebellum have access to this information through the respective re-entrant circuitries. The functional neuroanatomy of these circuitries will be discussed in Chapters 2–5. These re-entrant circuitries ensure that the entire brain has access to the same sensory and motor information.

Similarly, since humans confront choices regarding where to place attention, there must be a selection or gating mechanism to facilitate decisions about these choices. Over the course of evolution, sensory and cognitive systems increased or expanded. We became capable of analyzing object identification and location information within different specialized sensory modalities. We retained the capacity to respond to orienting stimuli for the purpose of survival, but we also developed the ability to withhold that response when necessary and to selectively attend to different aspects of a complex environment and to solve the problems posed by novel aspects of the environment. Therefore, there are potentially conflicting or incompatible sensory inputs and motor outputs that must be prioritized and selected on the basis of the well-being of the whole organism (Redgrave, Prescott, & Gurney, 1999). Subsequent sections and chapters will demonstrate that the modulatory properties of cortical–subcortical circuits include mechanisms for the selection of attention and action.

Once the brain determines "what" and "where" things are, it must now determine what to do about it. The nervous system needs three types of motor programs to act in relation to this information. These motor programs consist of knowing what action to perform (*what to do*), knowing how to perform the action (*how to do it*), and knowing when to perform the action (*when to do it*). In other words, the action patterns of the organism that interact with the environment need to include multiple different aspects of praxic and intention programs.

Knowing what to do might sound like an obvious function, but this actually poses an interesting organizational problem for a system structured on a need-to-know basis. The brain is organized to digest information as needed. However, not all types of input are the same. For example, certain aspects of the environment are very predictable. In this case, a fixed, routine, automatic response would be highly advantageous (Toates, 2006). In fact, a programmed response that always works would be of obvious immediate survival value since people would immediately "know" what to do, rapidly and effectively every time. However, as we know, the environment isn't so straightforward. While it certainly has recurring elements and themes, it is not always predictable and from a survival standpoint, it cannot be trusted. Specifically, the brain must understand how to deal with novelty. Novelty makes it impossible to preprogram responses that would meet the characteristics of all situations. Under unfamiliar conditions, an organism that possesses only preprogrammed responses would not survive because it could not adapt to circumstances for which it had no response.

This suggests that the brain would need two separate systems for "knowing" what to do. First, the organism needs a stimulus-based system that is composed of those actions and behaviors the organism relies upon routinely to ensure its survival. Second, the organism needs a system that allows it to program new behaviors when it has no preprogrammed behavior to meet novel environmental requirements (Fuster, 1997). In other words, the organism needs a dual-layered model of behavioral control (Toates, 2005). The organism needs a "habit" or procedural system to interact with stimuli that present routinely, as well as a "thinking" or problem-solving system that can adapt to unfamiliar circumstances. These two systems are subserved by the basal ganglia and the frontal cortices respectively. Nature has actually fused these two systems to ensure maximum adaptability. The neuroanatomic product is known as the frontostriatal system. The frontostriatal system allows the organism to decide what to do. This system programs and selects behaviors. However, before discussing the flexibility of this system, let's turn our attention to examining the "how" programs of the brain.

How to Do Things in a Changing Environment

Having decided what to do, we need to next know how to do it. Since all behaviors are dynamic, action requires appropriate amplification or adjustment during different phases of task execution. For example, even a seemingly simple behavior such as reaching for an object requires appropriate force of movement during the initial, middle, and termination phases of the task, with changing vectors of speed, distance, precision, and inhibition as the dynamic behavior unfolds. Similarly, even a routine behavior performed on a repetitive basis might need to be adjusted against the background of an environment presenting with slightly different characteristics.

Take the example of a basketball player or quarterback throwing a ball. The success of this pass depends in part on how far the other player is from the player throwing the ball, and whether they are moving or stationary, guarded or unguarded. These types of variables would influence either undershooting or overshooting of the target. Thus, the player needs not only to estimate how far to throw the ball but must intuitively adjust for the direction, rate, and surrounding circumstances of the receiver. Throwing the ball is not enough. The throw needs to be adjusted to fit the characteristics of the given circumstances. Knowing how to throw the ball includes the appropriate refinement of behavior according to the variables of rate, rhythm, and force. In this regard, the cerebellum appears to play a key role in regulating this behavior. It serves the function of knowing how to perform an action by adjusting behavioral output, accomplishing this task by regulating neural signals through loops of interaction with various regions of the cortex (Hallett & Grafman, 1997). Thus, patients with ataxia and patients with intention tremor can be characterized as demonstrating disturbances in this very general type of behavioral adjustment insofar as such symptoms can be understood in relation to problems controlling appropriate amplification (Houk & Mugnaini, 2003).

How would this type of issue appear in a cognitive or in an emotional system? Loss of appropriate coordination of thinking represents a cardinal symptom of thought disorder. This symptom has actually been referred to as cognitive dysmetria, and has been directly linked to cerebellar circuitry (Andreasen, Paradiso, & O'Leary, 1998; Andreasen et al., 1999; Crespo-Facorro et al., 1999; Volz, Gaser, & Sauer, 2000). The marked circumstantiality of thought seen in certain patient populations can readily be recognized as a type of cognitive "overshooting" or "undershooting" (Schmahmann, Weilburg, & Sherman, 2007). A less dramatic example of this lack of coordination in thought would look like the inability to "make the point" of conversation. Circumstantiality can be viewed as a cognitive analogue of the ataxia or the intention tremor occurring with cerebellar motor pathology. Within an emotional circuit, this type of problem would look like an inability to regulate affect. For example, experimental studies have demonstrated that stimulating various regions of cerebellar vermis to different degrees results in either "under" or "over" expressions of affect (Schmahmann, 2000). Affective blunting and/or exaggeration would be an analogous manifestation of a disrupted "limbic" cerebellar circuit (Schmahmann et al., 2007). For example, a "temper outburst" can be considered an instance of emotional expression featuring inappropriate amplification or force. The ataxia and frequent emotional lability of humans under the influence of alcohol—as well as the characteristics of individuals at risk for abuse of this substance— speaks to important aspects of cerebellar function (Deshmukh, Rosenbloom, Pfefferbaum, & Sullivan, 2002; Fitzpatrick, Jackson, & Crowe, 2008).

When to Do Things—Intention Programs

Finally, knowing what to do and how to do it are essential but not sufficient for successful adaptation. The organism also needs to know when to act, the third general feature of motor programming. Acting too soon or too late can defeat the purpose of adaptation. Persisting with behavior versus stopping a behavior prematurely is an essential component in interacting with the environment. Take our football quarterback. If he waits too long or throws too soon on a timed pass, it will be incomplete. Knowing when to act can make the difference between a touchdown and an interception.

Similarly, when engaging in and completing a complex activity, the organism often needs to switch from one behavior to another. Therefore, we need intention programs that allow us to appropriately initiate and inhibit behaviors, as well as switching mechanisms that allow for ongoing translation of sensory input into appropriate motor "when" actions. This requires us to be able to gate attentional and response selections. Again, subcortical structures, and particularly the basal ganglia, are critical to these processes.

Patients with movement disorders essentially demonstrate disturbances in intentionality. For example, Huntington's and Parkinson's diseases, which are manifestations of basal ganglia pathology, are considered disorders of voluntary movement (Blumenfeld, 2002). Huntington's disease is characterized by the release of fragments of purposeful movements. Parkinson's disease is characterized by difficulties in initiating movements, perseveration in terms of difficulty in switching from one movement to another, and difficulties in stopping movements. These basal ganglia disorders are associated with deficits in knowing when to start a movement, when not to start a movement, when to persist with a movement, and when to stop a movement. These functions comprise the brain's four intention programs. Disorders such as Huntington's and Parkinson's diseases disrupt the brain's intention programs. Therefore, the basal ganglia play an important role in governing intentions. Chapter 2 will explore the role of the basal ganglia in linking volition with automatic behavior so that the resultant behavioral output becomes biologically adaptive.

Again, it is useful to consider examples of how disturbance in intention would present pathology outside the motor domain. Cognitive distractibility, or the inability to refrain from responding to an idea or an external stimulus, is an example of disordered intention. Take the familiar example of someone who starts with the intention of studying for a test or completing an assignment and then becomes distracted by an extraneous influence such as surfing the web. This demonstrates a deficit in adequately linking volition with less relevant automatic or "stimulus-based" responding. At the behavioral level, this common form of distractibility actually reveals a deficit in behavioral persistence. The individual who interrupts others or the student who blurts out statements and questions is demonstrating deficits in knowing when to start or when not

to start behaviors. These problems with inhibitory control over interpersonal "pragmatics" can be understood as deficits in intention programs. Similarly, at the affective/interpersonal level, the child who exhibits "separation anxiety" is demonstrating an inappropriate affective persistence, a deficit in knowing when to persist with or when to stop a behavior, in other words, a perseveration. We believe that cognitive and affective regulations comprise *extensions of motor control systems* so that it becomes critical to recognize and understand these behavioral analogues. We will make use of these types of analogies throughout the book.

Theories of Types of Behavioral Processing and the Frontostriatal System

Most behavioral processing can be categorized according to two general types (Toates, 2006, 2005). These types of behavioral control comprise stimulus-based processing and higher-order control respectively. Stimulus-based control is composed of reflexes (which will not be discussed in detail in this book), habits, skills, and procedures. In short, these are the behaviors that the organism employs on a routine basis in order to ensure its survival in a predictable environment. The stimulus, which is either external or internal, triggers the appropriate response, and this response is adaptive, meeting the requirements of the circumstances, so that the behavior has survival value.

Stimulus-based control has obvious advantages. It allows the organism to exploit or take advantage of the predictable features of the environment. It allows for a high speed of reaction. It avoids the necessity of programming a behavior every time similar circumstances are confronted because the organism already "knows" what to do (For additional review, see Toates, 2006). Stimulus-based processing also has serious disadvantages. It affords the organism little spontaneity because a stimulus must be present to evoke the response. It ties the organism to the immediate, to the here-and-now. In its purest sense, it does not allow the organism the capacity to generate or synthesize new behavior under novel conditions. Therefore, the organism cannot function or adapt successfully under ambiguous or novel circumstances. In unfamiliar situations, stimulus-based control simply does not work.

The second type of behavioral processing is higher-order control. In short, higher-order processing comes into play when stimulus-based control does not work. Managing novelty and ambiguity requires the organism to refrain from responding in the here-and-now, and instead, requires the organism to solve problems. Successful problem solving requires *determining the context for stimulus-based control*. As an example, consider the instructions to the Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtis, 1993). In order to perform this task, the subject is asked to sort cards in the absence of provided categories. The categories are determined through informing the subject whether his or her choice is "right" or "wrong" after each and every card is

sorted. Therefore, the task for the subject is to take these ambiguous circumstances and develop the context for stimulus-based control, which in this case comprises the color, form, and number characteristics of the cards. The problem is solved by discovering the stimulus-based properties governing the task. We believe that *all problem-solving and higher-order control can be understood as breaking a problem situation down into stimulus-based characteristics* (Richer & Chouinard, 2003; Toates, 2006). In this way, higher-order control provides the organism autonomy by allowing for the programming of goal-directed behavior (this will be discussed in Chapter 8). Higher-order control features the enormous advantage of allowing adaptation to an environment that is ambiguous, novel, or unfamiliar. However, higher-order control also presents a significant drawback. *This system functions slowly, which is a disadvantage for adaptation*.

Therefore, one system of behavioral control is fast but not very smart. This is the stimulus-based control system. It always has the proper, adaptive response for the "right" stimulus, but it has no ability to do anything different (Toates, 2005). It works quickly under the "right" stimulus circumstances, but when confronted with novel stimuli, it is inflexible and cannot figure out what to do. Actually, this system can be slowly trained for the acquisition of skills and habits. After learning what to do, it "remembers." This instrumental behavioral system is robust but not very flexible. Conversely, the higher-order control system is very smart but often too slow in its adaptation. It can take a long time to figure out what to do. For example, this system evaluates new circumstances in the present. It thinks about what it knows when it devises a plan of action. It thinks into the future to anticipate outcomes to decide if the behavior under consideration will work. When implementing a new behavior, it monitors and evaluates progress, taking the results of that assessment to further modify the behavior according to circumstances. Therefore, it has great flexibility. However, this is a slow, time-consuming course of adaptation.

During the course of evolutionary and phylogenetic development, there must have been considerable adaptive pressure to retain a system that was fast and accurate. Understandably, fast and accurate behavior increases survival opportunity since it exploits the features of the environment we can count on while conserving resources. There also must have been evolutionary pressure to develop a system that was smart and flexible. Nature did not respond to the pressures of adaptation by choosing between these two systems (Trimmer, Houston, Marshall et al., 2008). Instead, nature's reply to adaptive pressures was to "have it both ways" by developing the frontostriatal system. This dual-layered control system is adaptive for several reasons.

This frontostriatal system has three important characteristics. First, *both ways of responding co-exist as a biologically economical system*. This means that operating in tandem, stimulus-based control can operate when it is advantageous to do so, and higher-order control can become operational when automatic processing does not work. Second, *both systems interact with each other*.

This means that the operations of both systems can shift back and forth, from one system to another, as environmental circumstances change, with frequent, alternating episodes of automatic behaviors and modifications through higher-order control when this becomes necessary. The systems operate independently, yet in a complimentary fashion. This dual-layered model of behavioral control allows for the greatest flexibility in adaptation (Toates, 2005). Most situations actually require alternating episodes of automatic responding and higher-order control. Therefore, this system conserves adaptive resources. Third, *the frontostriatal system allows the organism to benefit from experience*. This is an exceedingly important bonus. Solutions to novel problems can be practised and automated, so that these "new" solutions take on stimulus-based characteristics for future application (Kinsbourne, 1993; Miller & Wallis, 2003).

The procedural learning and memory system lies at the heart of automatic responding. This system allows for programming behaviors to meet the demands of a variety of changing environments. In this regard, a key to understanding how subcortical regions contribute to cognition concerns their relationship to the frontal lobes, and the ways in which they work together to acquire new behavioral patterns. These interactions will be explored in Chapters 2, 4, 8, and 9. Understanding the relationships between these systems provides an essential tool for understanding how cortical–subcortical interactions embody the essential underpinning of cognition.

Analogous Memory Systems

As previously indicated, the ability to remember information about objects would confer a decisive adaptive advantage. Nature provided for this function through the medial temporal lobe memory system (Squire, Stark, & Clark, 2004). This system allows *perceptual* experience to persist. This is important because in a problem-solving situation, the organism has a range of sensory experience to draw upon while attempting to break down a novel situation into stimulus-based characteristics. In fact, this memory system is so important that its functioning is routinely assessed during the course of a cognitive evaluation.

The frontostriatal system includes a habit or procedural memory system that allows the organism to benefit from the experience of its *activity*. It is an instrumental behavioral system that learns by doing. In essence, problem-solving actions and behaviors are retained because these behaviors can be useful for future adaptation. This is one of the functions that allows the organism to adapt to a new environment. Remembering what to do is important when features of a novel environment have now become familiar. However, the procedural memory system, which is essential for adaptation, is routinely overlooked in a cortico-centric model of neuropsychology that neglects the vertical organization of the brain. Simply put, clinical neuropsychology has not yet developed the "habit" of

considering procedural learning and memory, despite the fact that this system's automatic, stimulus-based responding provides an essential feature of adaptive functioning, as well as an important underpinning to the behaviors that often bring individuals to clinical attention. In fact, procedural learning is so important that nature has provided two subdivisions of procedural learning, namely, the cortico-striatal and the cortico-cerebellar procedural learning systems. The former system governs the acquisition of habits, and the latter system mediates response to environmental changes or perturbations (Doyon & Ungerleider, 2002). Most, if not all, behavior requires a combination of these systems, as will be discussed in Chapters 4, 5, and 9.

The Phylogenetic Perspective

The forebrain components of the basal ganglia are well conserved across vertebrates, and all tetrapod vertebrates share a common pattern of basal ganglia organization (Smeets, Marin, & Gonzalez, 2000). The striatum, which is the largest single structure in the basal ganglia, is present in all vertebrates. The striatum is always a sensory input structure. It always receives dopaminergic connections from the midbrain (Strieter, 2005). This is important since the basal ganglia appear to operate within the paradigm of reward-driven association learning mediated by dopamine (Joel & Weiner, 2000). All vertebrates have a nucleus accumbens, a globus pallidus, and a subthalamic nucleus (Marin, Smeets, & Gonzalez, 1998). These are the phylogenetically oldest regions of the basal ganglia, and their structure and function were retained over millions of years of evolutionary development. Therefore, the fundamental scheme of basal ganglia organization evolved with or before vertebrates and was retained thereafter because it had adaptive value (Striedter, 2005; Marin et al., 1998).

We believe this scheme was retained because these regions fundamentally support the integration of motivation with sensory input and motor output, along with a mechanism for intention programs. Motivation is provided by the nucleus accumbens, and sensory input is gated through the striatum. The ventral pallidum is tonically active and ready to "release" behavior by decreasing inhibition on the thalamus, while the subthalamic nucleus regulates the overall tone or neural output of the pallidum (Utter & Basso, 2008). These functions will be discussed in Chapters 2–4. The nucleus accumbens is a phylogenetically old reward center. It is composed of two regions, specifically, a shell and a core (Heimer, Van Hoesen, Trimble, & Zahm, 2008). The shell of the nucleus accumbens is a center of consummatory reward. The core of the nucleus accumbens projects to the ventral pallidum, a primary movement center. This implies that movement, and the subsequent development of procedures or habitual ways of responding that depend upon movement, evolved from motivational systems (Aboitiz, Morales, & Montiel, 2003; Brauth & Kitt, 1980; Parent, 1997). The subthalamic nucleus has been

demonstrated to adjust the magnitude of inhibitory pallidal output, and, therefore, serves as a type of thermostat in regulating motor output (Mink, 2003). Neurotransmitter organization and connectivity within these brain regions is also essentially the same within all vertebrates along the phylogenetic scale (Medina & Reiner, 1995).

In vertebrates, the caudate nucleus, the putamen, and the nucleus accumbens together are referred to as the striatum. In phylogenetically lower vertebrates, such as rodents, the caudate and putamen are one single structure referred to as the caudoputamen or the caudate-putamen suggesting this was the evolutionary origin of these structures. The fibers of the internal capsule course through this unit in rodents (Streidter, 2005). In all primates, the caudate and putamen are clearly separated by the internal capsule, although they remain connected by "cellular bridges." This implies that the caudate and the putamen were derived from each other and that these regions separated or split apart from each other as phylogeny required increasing specialization. In this regard, the isocortex appears to have derived from the dorsal pallidum (Aboitiz et al., 2003).

In primates, the anterior caudate receives projections from prefrontal and orbitofrontal regions, while the body and tail of the caudate receive projections from temporal and parietal regions. The putamen receives input from motor, premotor, supplementary motor, and frontal eye field regions (Rolls & Johnstone, 1992). The caudate and putamen may have derived from the nucleus accumbens region. It is generally accepted that the caudate and putamen separated from each other during the course of evolution as a result and manifestation of increasing sensory and motoric specialization. The caudate became more specialized for sensory functions, and the putamen became more specialized for motoric functions.

It is interesting to compare these developments against the background of cortical changes. The neocortex dramatically increased in size and complexity throughout evolutionary history. Importantly, the basal ganglia kept pace (Divac & Oberg, 1992). These various regions of the basal ganglia not only became larger, but certain regions of the basal ganglia developed separately and took on increasing specialization. The case cannot be made that the basal ganglia enlarged simply because the cortex "got bigger." Instead, structural evolutionary changes in the basal ganglia are correlated with increasing functional or behavioral specialization. As neocortex became more specialized, the basal ganglia became more specialized. The changes are not global or generic. Instead, the developments are very specific. In contrast, the growth of the diencephalon was very modest, while the olfactory tubercle is actually smaller in human primates (Divac & Oberg, 1992). Therefore, over the course of evolution, some structures enlarged, other structures remained proportionately the same, and other structures regressed.

How might these differences be understood? In primates, with increasing associative sensory capacities and increasing specialization of movement, cortico-cortical connections became more important than the growth of

the thalamus. Highly developed sensory capacities generated specialized and differentiated object identification and location properties at the expense of the more primitive olfactory system. The point is that cortical and subcortical structures enlarged and regressed for specific purposes, while all basal ganglia input, intermediate, and output regions increased in size while becoming more differentiated. This is also true of cerebellum, which not only enlarged but also became highly differentiated (Middleton & Strick, 1994).

The striatum always receives sensory input from the largest and presumably most important sensory region of the brain. In amphibians, inputs originate from the dorsal thalamus, while in reptiles, inputs originate from the ventral area of the olfactory cortex. In mammals, striatal inputs arrive from the neocortex (Striedter, 2005). Therefore, in climbing up the phylogenetic scale, the striatum receives more and more highly processed and highly specialized sensory input. A major evolutionary trend is the progressive involvement of the cortex in the processing of the thalamic sensory information projected to the striatum of tetrapods (Smeets et al., 2000). The circuitries from cortex to basal ganglia to thalamus and back to cortex are always at least partially segregated in vertebrates (Smeets et al., 2000). Mammals always direct output from the basal ganglia back to the thalamus and from there, back to cortex, maintaining segregated, parallel circuits. Therefore, the basal ganglia are always a re-entrant system that receives specialized information from cortex and sends information back to cortex via the thalamic relay. But why is this the case?

Excitation Versus Inhibition

When stimuli are detected in the environment, the appropriate sensory receptors relay this information to the thalamus. The nature of this information is always excitatory. The thalamus in turn relays this information to appropriate cortical processing stations for the development of perceptions, such as object identification and object location functions. The thalamus excites cortex so that the cortex can engage in sensory-perceptual information processing. This allows for associations to develop. The formation of "cell assemblies" supports the cognitive development of concepts and ideas (Hebb, 1949; Wennekers, Garagnani, & Pulvermuller, 2006). This information is projected to frontal cortices for the programming of motor activity. However, it needs to be understood that these processes are primarily the product of cortical excitation (see Banich, 2004 or Kolb & Whishaw, 2008 for descriptions of cortical information processing).

What is the point? An organism cannot select what perceptions to attend to and an organism cannot select from a set of alternate behavioral response possibilities simply on the basis of excitatory mechanisms (Miller, 2008). As organisms develop

multiple sensory capacities, this sensory information is in competition for the organism's finite attentional resources (Redgrave, Prescott, & Gurney, 1999). Not only are perceptions and behaviors in competition for attention and expression, but these perceptions and behaviors also might actually be in conflict with one another. An organism that does not possess unlimited attentional capacity cannot possibly attend to all stimuli. The same is true of action, or motor behavior. At any given time, there are several behavioral possibilities from which to choose. All behavior obviously cannot be chosen simultaneously. Therefore, perceptions and behaviors must be prioritized. Selections must be prioritized according to the adaptive purpose of the organism as a whole. In order to solve this selection problem, there must be inhibitory processes and controls in a system that is based upon excitation.

When an organism attends to one perception, it inhibits attention to other input. For example, when the organism switches focus or selects a motor response, the other possible selections are inhibited. Consequently, when a response is changed, the original behavior is inhibited, while a behavior (excitation) that was previously inhibited is now released from inhibition. In short, attentional and behavioral selections require processes of excitation versus inhibition. From a neuroanatomic perspective, thalamo-cortical and cortico-cortical connections are primarily excitatory. The frontal cortices, which are an essential participant in the "looped" architecture of basal ganglia, clearly play an important role in inhibitory control (Fuster, 1997). However, the first region in which massive inhibitory control mechanisms can be found is within the basal ganglia (Miller, 2008). Cortico-basal ganglia "loops" modulate attention and behavior. Inhibitory output from the basal ganglia to the various target nuclei of the thalamus gate the focus of attention and action depending upon the organism's purpose.

This elevates the basal ganglia as a major player in cognition and executive control. The inhibitory mechanisms of the basal ganglia challenge the view of cortical supremacy in cognition. The basal ganglia very likely comprised the brain's first executive system, and they continue to heavily contribute to cognitive and behavioral control. In fact, it has been proposed that the functions of the cortex are *dependent* upon the basal ganglia (Heimer et al., 2008). It is through a body of anatomical evidence that a number of researchers in the field of neuroscience have reasserted the role of subcortical functions in the realm of cognition. After laying out this body of evidence, this books sets out to delineate the direct implications of this for neuropsychological testing and evaluation.

Adjustment of Motor "How"—The Changing Characteristics of Excitation and Inhibition

Cerebellum is not without its evolutionary development. Every vertebrate has a cerebellum, so that from a phylogenetic perspective, it is very old. The cerebellum actually resides outside of the cortex. Perhaps this is why the

cerebellum has not been given much attention within a cortico-centric model of cognition. However, another question to be asked is why does the cerebellum reside out there on its own? If the cerebellum is important to cognitive and emotional functioning, why does it "live" outside of the cortex? No one really knows the "answer" to this question, although a "best guess" can certainly be made on the basis of the anatomy of the cerebellar system. The cerebellum has a unique computational architecture (Houk, 2005; Houk et al., 2007). During evolution, the cerebellum developed different types of excitatory and inhibitory neurons and connections (Azizi, 2007; Middleton & Strick, 1994, 2000). The purpose of these neurons is to "fine-tune" the behaviors that have been selected by the cortico-striatal-pallidal-thalamic system (Houk et al., 2007). The refinement of behaviors to meet environmental perturbations or changes is such a specialized process that it requires its own system, residing outside of the cerebral cortex.

Three different functional regions of the cerebellum can be identified. First, there is the archicerebellum which has also been referred to as the vestibulocerebellum. Its main structures comprise the flocculus and the nodulus which are commonly termed the flocculonodular lobe. This is the phylogenetically oldest region of the cerebellum. The paleocerebellum is the next in evolutionary age, sometimes called the spinocerebellum. This region is located within the vermis and the intermediate regions of the cerebellum. The neocerebellum forms the rest of the cerebellum and includes the lateral cerebellar hemispheres proper (Guzzetta, Mercuri, & Spano, 2000). The phylogenetic age of these regions correlates with behavioral complexity. The most basic adaptive functions are mediated by the oldest regions, while higher-order functions are subsumed by the phylogenetically newest regions. This neuroanatomy will be reviewed in detail in Chapter 5.

As with the cortex, the cerebellum can be divided into anterior and posterior lobes. The posterior lobes demonstrate a dramatic increase in size along with the evolutionary enlargement of the cerebral cortex. While there are four deep cerebellar nuclei, the phylogenetically newest and most lateral, the dentate, has demonstrated the most increase in size along with the posterior cerebellar hemispheres (Middleton & Strick, 2000). Its specialization will be discussed in Chapter 5. It will suffice to say for now that higher-order motor and cognitive cortical regions project to specific target areas of this nucleus. The inferior posterior regions of the cerebellum make contributions to cognitive functioning, while the phylogenetically older vermal region is important for regulating the amplification of affective responding (Schmahmann, 1997). Cerebellar cortex is homogeneous, not at all like heterogeneous cerebral cortex which is specialized to perform a variety of different sensory and motor functions. Because of this homogeneity, it is accepted (although this is somewhat of an overgeneralization) that the cerebellum performs one operation, but it performs that operation on a wide variety of different kinds of specialized cortical information.

The cerebellum does not generate movement, cognition, or emotion. Instead, it performs computations on the neural signals of behaviors that have been selected by the cortical–basal ganglia system. The cerebellum makes "online" adjustments to behaviors that have been selected and are in the process of execution. These adjustments provide the appropriate amplification of the behavior in an ongoing way. The "fine-tuning" of behavioral units during their execution requires a unique interplay and timing of excitatory versus inhibitory processes. The "one function" of the cerebellum is to perform these computations, and in this way, the cerebellum supports the purpose of the selected behavior.

Summary

Throughout the 20th century, brain research expanded exponentially. From early understanding of electricity and chemistry in the brain to sophisticated mapping of neural connections throughout highly specialized regions of the cortex, we have learned an enormous amount about how the brain allows us to act and think in the way we do. These higher-cortical functions have always been complimented from an understanding of movement involving key subcortical structures. However, it is only relatively recently that neuroscience has begun to understand the intricate relationship between cortex and subcortex for functions other than movement. We can now understand cognition and emotion as extensions of the motor control system.

Neuropsychology is now presented with the challenge and opportunity of adapting to this changing neuroscientific landscape. Cortex is an amazing structure that allows us to reach new heights, interact in important ways, and remember incredible amounts of information. However, it cannot act alone, in isolation. Cortex is composed of complex circuitry that supports higher-order behavior. However, the networks of the cortex are regulated by "loops" of interaction that run through the basal ganglia and cerebellum. These subcortical regions modify the information received from cortex and, therefore, play a significant role in "deciding" what information is and is not returned to cortex. The cortex, basal ganglia, and cerebellum are three brain systems that run in parallel. Each region makes a unique contribution to behavior, whether that behavior is motor, cognitive, or affective. These systems actually operate within a dual-layered model of behavioral control comprising both stimulus-based responding and higher-order control. This functional neuroanatomy has dramatic implications for neuropsychological assessment and opens up tremendous opportunity to provide more comprehensive, relevant evaluation. We consider this book an early adaptational step in response to this changing landscape, and to the extent this early movement has under or overshot its mark, it is to be refined through further loops of interaction through continued research and clinical application.

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Chapter 2
The Basal Ganglia: Beyond the Motor System—From Movement to Thought

Everything should be made as simple as possible, but not simpler.

Albert Einstein

In studying and practising a cortico-centric model of neuropsychology, few students or clinicians likely pay much attention to or fully understand the functions of the basal ganglia, a set of interconnected subcortical nuclei arising from the mammalian forebrain. This is, in part, due to the fact that the anatomical subdivisions of the basal ganglia can seem confusing. Some regions of the basal ganglia can be broken down into multiple components. Several basal ganglia structures feature further subdivisions, and some components of the basal ganglia can have more than one name, based on which structures are grouped together. There are reasons for these differences, which will be described in the course of this chapter. Figures 2.1 and 2.2 illustrate lateral and antero-lateral views of the basal ganglia. Figure 2.3 illustrates horizontal and coronal views of major structures of the basal ganglia.

The basal ganglia are not solely a processor of movement. The basal ganglia have been implicated in a diverse array of motor, cognitive, and affective symptoms and are involved in the pathology of a variety of psychiatric disturbances. For example, Parkinson's disease, Huntington's disease, Dystonia, Tourette Syndrome, and obsessive-compulsive disorder are five different pathologies that can all be considered neurologic conditions resulting from abnormal functioning within the basal ganglia (Utter & Basso, 2008).

This chapter has three purposes. The first purpose is to review all of the structures of the basal ganglia, including their important subdivisions and groupings. Second, this chapter will discuss the basal ganglia in terms of function, based upon the roles of the input, intermediate, and output structures. Clarifying this basic organization facilitates an understanding of what the basal ganglia do and how they work. Third, the functions of the basal ganglia will be illustrated by reviewing two movement disorders commonly associated with basal ganglia dysfunction, namely, Parkinson's disease and Huntington's disease.

L.F. Koziol, D.E. Budding, *Subcortical Structures and Cognition*,
DOI 10.1007/978-0-387-84868-6_2, © Springer Science+Business Media, LLC 2009

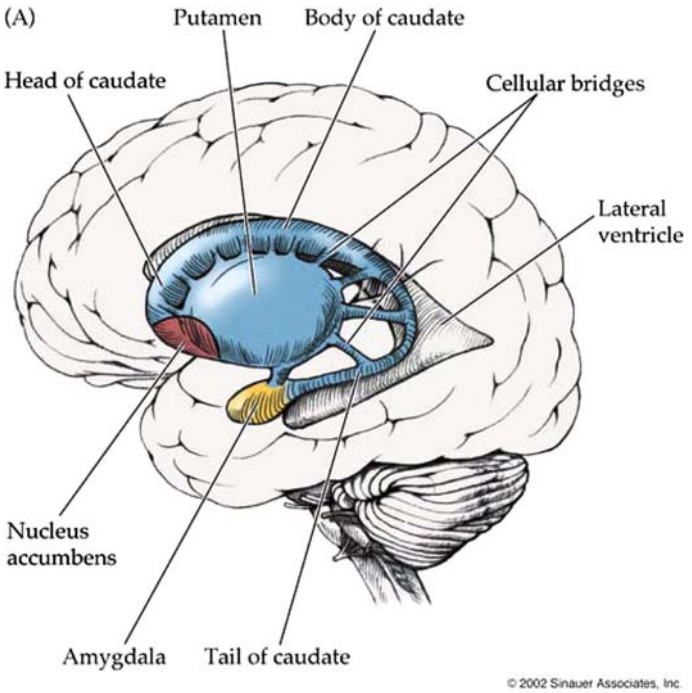

Fig. 2.1 Lateral view of the basal ganglia, reprinted by permission of Sinauer Associates, Inc., 2002

A clear understanding of how the basal ganglia can "go wrong" in these disorders provides important clues about the roles of the basal ganglia in cognitive and emotional functioning. The main premise of this book is that the basal ganglia perform the same functions for cognition that they perform for movement. This principle will be used to provide an organizational framework for understanding behavior and for conceptualizing neuropsychological testing. Examples of ways the basal ganglia influence cognition and behavior will be presented.

Anatomical Structures and Subdivisions of the Basal Ganglia

The basal ganglia are a collection of bilaterally represented gray matter nuclei located deep within the white matter of the brain. They lie at the core of the cerebral hemispheres and are central to the basal forebrain. The term "basal ganglia" most commonly refers to four structures (Middleton, 2003). These structures are the striatum, the pallidum, the substantia nigra, and the subthalamic nucleus. Three of these structures—the striatum, the pallidum, and the

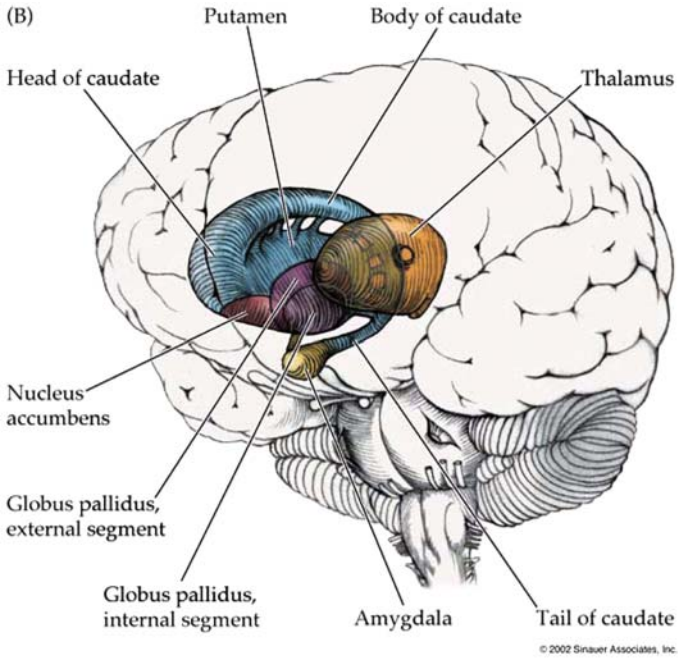

Fig. 2.2 Anterolateral view of the basal ganglia, reprinted by permission of Sinauer Associates, Inc., 2002

substantia nigra—have important subdivisions. Divisions of the basal ganglia are illustrated in Table 2.1.

The striatum is the primary region of all sensory input into the basal ganglia. Therefore, all of the structures comprising the striatum are considered input structures. The striatum can be broken down into two primary subdivisions, the dorsal striatum and the ventral striatum. The dorsal striatum consists of the caudate nucleus and the putamen. The ventral striatum consists of the nucleus accumbens, the septum, and the olfactory tubercle. The nucleus accumbens has two additional divisions, namely, the medial core region and the lateral shell region. "Striatum" is the term used when referring to all of these structures together.

The pallidum can be divided into three primary subdivisions. The most ventral and anterior region of the pallidum is called the ventral pallidum. The two largest regions of the pallidum are the internal segment of the globus pallidus (Gpi) and the external segment of the globus pallidus (Gpe). The Gpe is the lateral division and the Gpi is the medial region. The ventral pallidum and Gpi are considered output structures. The Gpe is considered an intermediate structure. All intermediate structures of the basal ganglia send projections to other regions within the basal ganglia, modulating their function or output. All output structures of the basal ganglia project to various thalamic nuclei. Output structures also project to brainstem nuclei.

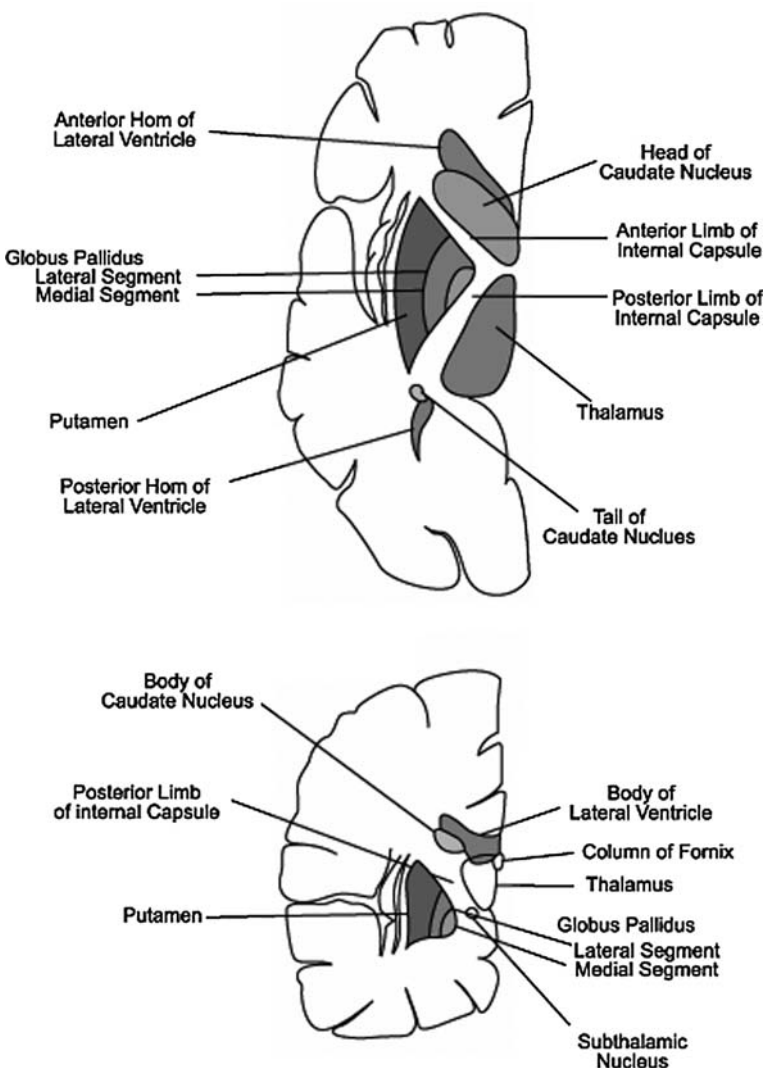

Fig. 2.3 Drawings of horizontal and coronal sections through the basal ganglia, reprinted by permission of Guilford Press, 1992

The substantia nigra has several subdivisions. The two most obvious and most studied subdivisions are the substantia nigra pars compacta (SNpc) and the substantia nigra pars reticulata (SNpr). The SNpc is a black pigmented region which is an important source of dopamine synthesis. Cellular deterioration in this region results in the hypokinetic movement disorder of Parkinson's disease. The SNpc is considered an intermediate structure that projects to most other regions

Table 2.1 Basal ganglia subdivisions

Basal ganglia structure	Primary subdivision	Secondary subdivision	Tertiary subdivision
Striatum	Dorsal striatum	Caudate	Core
	Ventral striatum	Putamen	Shell
		Nucleus accumbens	
		Septum	
		Olfactory tubercle	
Globus pallidus	External segment	Outer portion	
	Internal segment	Inner portion	
	Ventral pallidum		
Substantia nigra	Pars compacta	Pars lateralis	
	Pars reticulata		
Subthalamic nucleus			

(a) input structures
- Caudate
- Putamen
- Nucleus Accumbens
- These input structures receive direct projections from nearly the entire cerebral cortex

(b) intermediate structures
- Subthalamic Nucleus
- Globus Pallidus Externa
- Substantia Nigra Pars Compacta
- These nuclei project most heavily to other basal ganglia nuclei

(c) output structures
- Globus Pallidus Interna
- Substantia Nigra Pars Reticulata
- Ventral Pallidum
- These output nuclei send projections to the thalamus (VA/VL/DM/IL), which project back upon cerebral cortex

of the basal ganglia, supplying the basal ganglia with the neurotransmitter dopamine. The SNpr is considered an output structure. It projects to the medial dorsal nucleus of the thalamus and to the superior colliculus which is a mid-brain structure important for the control of eye movements.

Combining these various regions according to function, the basal ganglia have three output structures. These structures are the Gpi, the ventral pallidum, and the SNpr. These structures project to different regions of the thalamus, either the ventral anterior nucleus (VA), the ventral lateral nucleus (VL), the medial dorsal nucleus (MD), or the intralaminar nuclei (IL). The simplified, general pattern of basal ganglia circuitry projects from cortex to striatum, from striatum to pallidum, from pallidum to thalamus, and from thalamus back to cortex (Alexander,

DeLong, & Strick, 1986). Through the cortical-striatal-pallidal-thalamic-cortical connectional system, the basal ganglia output nuclei are in an anatomic position to influence a very wide, diverse range of cortical regions. The basal ganglia are the target of input from all cortical areas, while these subcortical nuclei project back to those same regions, potentially influencing a wide range of behaviors. Similarly, the segregation of these circuits implies that specific regions of the basal ganglia are involved in the modulation of highly specific, specialized functions. As will be discussed in the following chapter, motor, cognitive, affective, and motivational modules are represented within separate channels of basal ganglia circuitry. Resting state fMRI has mapped these multiple distinct circuits,

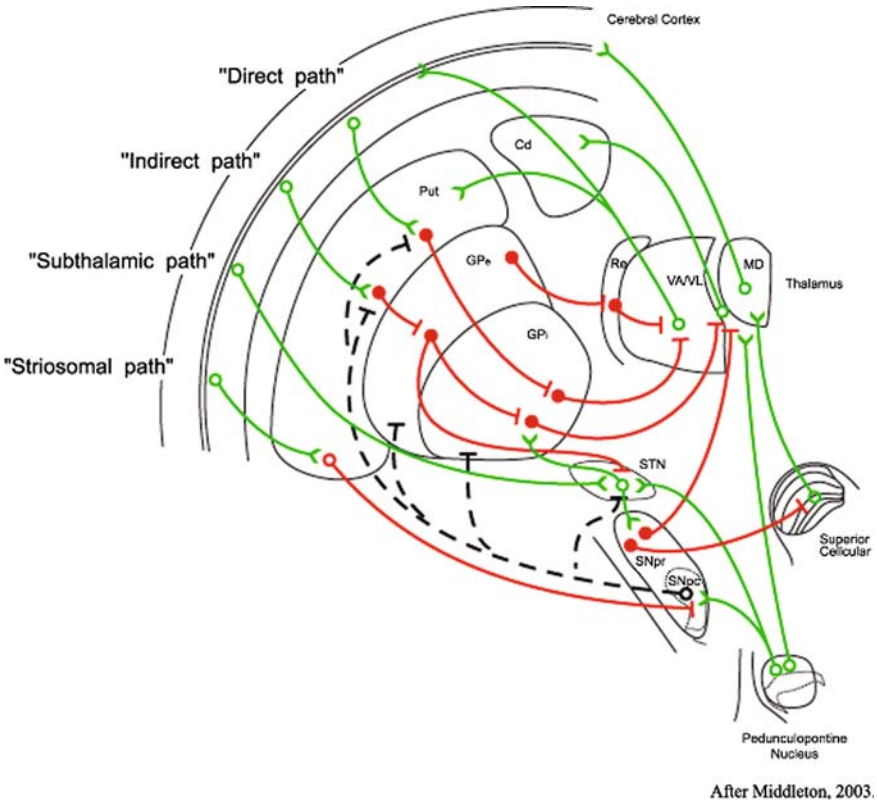

Fig. 2.4 Basic cortico-basal ganglia circuitry. This drawing illustrates the organization of connections between different components of the basal ganglia and the cerebral cortex, the thalamus, and certain lower-level brain stem nuclei. Excitatory connections are shown in *green*. Inhibitory connections are shown in *red*. The *broken line* illustrates inputs from the SNpc to regions in the striatum, and these inputs can be either excitatory or inhibitory. Abbreviations are as follows: Put = putamen, Cd = caudate, Gpe, Gpi, STN, SNpr, SNpc, and thalamic nuclei as described in text. Note that all projections from Cd are not illustrated. Printed with permission from Middleton (2003) (See online version for color details)

substantiating the hypothesized motor, cognitive, and affective divisions within striatal subregions (Di Martino et al., 2008). Therefore, localized involvement can theoretically impact upon a single functional domain.

The final important structure of the basal ganglia is the subthalamic nucleus (STN). Some people consider this an intermediate structure because it projects to another basal ganglia structure, specifically, the Gpi. However, there are good grounds for considering the STN an input structure, since it receives direct projections from areas of the frontal lobes (Mink, 2003). All of the structures of the basal ganglia are listed in Table 2.1. Tables 2.1 (a–c) lists the input, intermediate, and output structures of the basal ganglia. Figure 2.4 reveals the primary basal ganglia connections. Understanding the circuitry in this figure enables one to understand a great deal of behavior and pathology. This circuitry should be central to current neuropsychological thinking about brain–behavior relationships. The following sections explain this circuitry in detail. See Fig. 2.4 for an illustration of this circuitry.

Basal Ganglia Circuitry

There are two sets of cortical input into the striatum, namely, the direct and indirect pathways. These two pathways comprise most of the cortical input into the striatum. These are excitatory inputs which use the neurotransmitter glutamate, and project into a region called the striatal matrix (Graybiel, 2001, 2005). Because the projections from the cortex are excitatory, they are active only when required, dependent upon the nature of the activity. This means that these projections are activated according to the circumstances or needs of the organism. Projections into the striatum arrive at very specific regions, while there is some overlap based upon the function of the striatal region (Mink, 2003). For example, within the putamen, input from sensory regions that mediate the movement of one finger can overlap with input that mediates the movement of other fingers and even the wrist. This makes some sense, since the hand is a functional unit that is usually used as a whole. In this way, the strictly organized homunculus seen within sensory and motor cortices is not evident within the striatum. One region of cerebral cortex might project to more than one striatal zone, and one striatal zone might receive projections from more than one cortical region. This pattern of neural connections supports functional integration.

The striatum is primarily composed of medium spiny cells and interneurons (Middleton, 2003), but the basal ganglia are not a laminated structure like the neocortex, which has six layers, or the cerebellum which has three layers. The basal ganglia are groups of nuclei comprising a single layer. As a result, the structure and organization of the basal ganglia can appear more straightforward than the organization of the cortex or cerebellum.

Specific Projections into the Striatum

The dorsal lateral head of the caudate receives input from the dorsolateral prefrontal cortex, the ventral striatum receives projections from the orbitofrontal cortex, and the nucleus accumbens receives inputs from the anterior cingulate regions. Therefore, prefrontal and anterior frontal cortices primarily project to the head of the caudate. The body or lateral region of the caudate primarily receives projections from the inferior temporal lobes. The tail of the caudate receives projections from the parietal lobes (Middleton & Strick, 1996, 2001). The entire projection input system is reasonably systematic, subdivided and segregated. The body and tail of the caudate receive projections from the ventral and dorsal, or object identification and object location information-processing streams of the cerebral cortex, respectively (Lawrence, Watkins, Sahakian, Hodges, & Robbins, 2000).

The putamen receives input from the motor cortex, from the premotor cortex, from the supplementary motor cortex, and from the frontal eye fields. Projections also arrive from the somatosensory cortex. The individual parts of the body that play the most active roles in movement appear to be organized or represented somatotopically (Middleton & Strick, 2000). However, at the level of the basal ganglia, the strictly organized homunculus found in the motor cortex is lost, as described above.

As we have seen, the striatum receives input from all major cortical regions. These regions include perceptual and association regions, motor regions, affective and motivational regions, and prefrontal executive regions. In addition, these inputs are not only direct, they are also extremely compressed. The ratio of inputs has been estimated at 10,000 cortical neurons to 1 medium spiny cell neuron, while other estimates are as high as 20,000 to 1 (Houk, 2005). The input ratio from the striatum to the GP is estimated at 300 to 1 (Bar-Gad, Morris, & Bergman, 2003). This aspect of basal ganglia anatomy is extremely significant, and has several implications that should be discussed before we return to the description of direct and indirect pathways.

The input anatomy of the basal ganglia provides a substrate for a wide variety of contextual information to be made available to the striatum. This fact implies that the striatum would be extremely sensitive to environmental context. The striatum constantly receives a broad sampling of sensory data providing information about object identification, object location, and external environmental states. The striatum receives information about internal states as well, including information about the goals and purposes of the organism as a whole (Saint-Cyr, 2003a). This latter information is critical if the basal ganglia are to play a role in attention and action selection. The basal ganglia would need to be aware of *both* sensory data *and* the purposes of the organism as a whole in order to contribute to executive decision making. This input anatomy is thus part of the neural substrate that allows for participation in executive control.

The high input compression ratio lays the anatomical groundwork for the striatum to be able to generalize. This means that the basal ganglia are able to determine the similarity between one context and another similar context. The basal ganglia are able to see patterns between one situation and a similar set of circumstances. This pattern recognition function is implied by the fact that 10,000 or more cortical neurons can project to a single spiny cell neuron. At the level of the cortex, numerous "bits and pieces" of information are represented individually. At the level of the striatum, common features of sensory information are extracted and treated as equivalent (Bar-Gad et al., 2003). It would follow that if the basal ganglia play an active role in selecting procedures and behaviors based upon context, the basal ganglia would have to be able to recognize patterns and be able to generalize (Seger, 2008). For example, if stimulus A has many elements in common with stimulus B or C, while at the same time featuring minor differences, extracting those features that are common to similar situations while eliminating redundant features would be biologically economical. This type of ability to generalize provides an efficient representation of stimuli. Acting on this representation would be of adaptive value if the same behavior would "work" in all three situations. Therefore, the basal ganglia would be able to mobilize the same adaptive behavior in all situations when appropriate, which conserves adaptive resources.

Finally, "sensitive to context" is another way of saying that the basal ganglia are sensitive to the reward characteristics of the environment (Delgado, 2007). Sensitivity to reward is an essential element of reward-driven association learning. In this way, the basal ganglia are positioned to function as an instrumental learning mechanism. It has been demonstrated that specific pathways within the basal ganglia are differentially sensitive to positive and negative reward characteristics (Frank, 2005). For example, un-medicated Parkinson's disease patients, with basal ganglia pathology that primarily affects the direct pathway, are more sensitive to negative reinforcement than they are to positive rewards, and these reward-learning characteristics can be manipulated depending upon medication status (see Chapter 4 for a description of the roles of the basal ganglia in learning). Different regions of the basal ganglia are involved in different types of learning tasks. The direct pathway learns desired responses and the indirect pathway learns to avoid unwanted behavioral responses (Joel & Weiner, 2000).

The Gpi and SNpr are composed of a relatively small number of neurons, and as indicated above, receive relatively few projections. This must mean that the Gpi is receiving very compressed information. Similarly, since the Gpi and SNpr project to thalamic nuclei (which in turn projects back to cortex), whatever information that is encoded within these neurons must be vastly compressed (Frank, Loughry, & O'Reilly, 2001). While this pattern of compression of information might at first seem like a constraint, this is consistent with the basal ganglia acting as a selection mechanism or "gate," rather than as a sensory or motor processor. The basal ganglia, through the re-entrant projection system, need to convey information to the cortex about "when" to become active. This affects initiation, but the details of the activity to be executed remain

stored, or represented, in cortex, as will be explained by many examples to follow (Frank et al., 2001; Houk et al., 2007).

Direct and Indirect Pathways

The direct pathway projects from the striatum to the Gpi. The medium spiny cells in the striatum are inhibitory. They use GABA as a neurotransmitter, and they have a very low spontaneous firing rate. In order to fire, they must be stimulated by the cortex (Miller, 2008). The Gpi projects to the thalamus, and the thalamus sends excitatory projections to the cortex. This completes the "loop."

Neurons in the Gpi have a very high spontaneous firing rate. Therefore, the Gpi is considered to be tonically active. Their neurons are almost always firing. This activity comprises the default condition of the Gpi. The activity serves to tonically inhibit the thalamus, resulting in the thalamus being unable to excite the cortex. In this way, the basal ganglia can be considered to function as a type of "brake" upon the cortex. By stimulating the striatum, the cortex releases the brake (Mink, 1996). This occurs because cortical activation of the direct pathway causes the medium spiny cells of the striatum to inhibit the firing of cells in the Gpi. This releases the thalamus from its tonic inhibition. As a result, the thalamus excites the cortex so that behavior is released.

The indirect pathway involves inhibitory connections of the striatum to the Gpe. The Gpe has inhibitory connections to the STN. The STN has excitatory connections to the internal segment of the Gpi. Therefore, the activity of the indirect pathway causes the STN to actually increase the tonic inhibitory activity of the Gpi, which suppresses behavior.

The two pathways presumably operate in opposite directions and in balance. Activity in the direct pathway causes the Gpi to release inhibition on the thalamus and to release behavior. Normal activity in the indirect pathway causes the STN to activate the Gpi. This activation of the Gpi suppresses thalamic activity, which of course, prevents the release of behavior. The direct pathway mediates behavioral release and the indirect pathway mediates behavioral suppression. The direct pathway is thus believed to be important for releasing wanted movement and the indirect pathway is believed to be important for inhibiting closely related unwanted movement. This is the most common explanation of this circuitry. It remains useful in understanding the basic basal ganglia mechanisms involved in the starting, facilitating, and stopping of behaviors. In fact, this represents the original theory that has become very popular over the past 20 years in explaining the pathologies of Parkinson's and Huntington's diseases. More simply put, the direct pathway starts activity and keeps it going. The indirect pathway inhibits or stops activity. However, these ideas warrant modification in view of additional theories which are more encompassing in explaining the release and inhibition of behaviors.

In Parkinson's disease, the projections from the SNpc to the striatum are lost. As a result, the direct pathway "loop" is not able to function normally

(Parent & Cicchetti, 1998). The direct pathway can no longer perform its function of inhibiting the Gpi, so that the active Gpi continues to tonically inhibit the thalamus. At the same time, activity within the indirect pathway results in even further inhibition of the thalamus. Because of this massive inhibition on the thalamus, behavior cannot be released. As a result, it becomes very difficult to start a movement. Because starting and stopping movements are slow, it is difficult to "shift" or switch from one movement or activity to another. In this way, the brain's intention programs are disrupted.

In Huntington's disease, the striatum itself deteriorates, resulting in GABA and neuropeptide enkephalin (ENK) changes in the Gpe (Miller, 2008). In the earlier stages of the disease, this results in abnormal activity within the indirect pathway. Activity within the Gpe is altered, so that inhibition can no longer be removed from the STN. The internal segment of the globus pallidus can no longer be activated. Because the Gpi can no longer suppress thalamic activity, fragments of purposeful, unwanted movements are released. Once again, this can be understood as a disturbance in the brain's motor intention programs.

Therefore, an essential point to note is that basal ganglia circuitry is centrally involved in the "when" of behavior (Denckla & Reiss, 1997). Abnormal activity in the regions that have just been described does not result in the loss of movement programs. Instead, there is a loss of voluntary control over movement and behavior. The brain loses its ability to translate sensory "what" into motor "when." In this way, the basal ganglia are not primarily about "movement" per se. The basal ganglia are about "intention." This has important implications not only for understanding the neurologic movement disorders, but also for understanding psychological and psychiatric disturbances and developmental disorders, which will be discussed later.

The Subthalamic Pathway

Certain regions of the motor, pre-motor, supplementary motor cortices, and frontal eye fields also project directly to the STN (Mink, 2003). These direct projections have been termed the subthalamic, or the hyperdirect pathway (Nambu et al., 2000). Because this pathway excites the STN, activity in the internal segment of the GP increases. Increasing or stimulating activity within the Gpi increases the tonic inhibition on the thalamus, which suppresses behavior. This pathway functions two to two and one half times faster than the indirect pathway because this hyperdirect route has fewer synapses than the indirect pathway (Mink, 2003). When this pathway is active, it suppresses all behavior. It is the quickest way to terminate a behavior in process of execution. It stops behavior. In addition, this pathway is important for preventing premature responding (Frank, 2006). This pathway enables the organism to "not respond" when a new behavioral program must be devised.

In a problem-solving situation, the best thing to do initially is nothing. For example, consider the Wisconsin Card Sorting Test (WCST). The best

approach is to "not respond" with behavior, but instead, to think, and hopefully discover at least one of the stimulus-based categories of color, form, and number. In the Tower of London Test, the subject can impulsively rush into random responding or the subject can first inhibit responding, not engaging in "behavior" while first thinking things through. Stimulating the STN pathway applies the "brake," allowing the individual to think before responding. Therefore, this pathway is important for impulse control.

The Striosomal Pathway

The final route in this circuitry is the striosomal pathway. Certain regions of the cortex project to regions of the striatum called "patches" or striosomes (Middleton, 2003). Input into the striosomes originate in certain orbitofrontal regions and from cortico-limbic or paralimbic regions (Middleton, 2003). This includes input from motivational centers such as the amygdala and hypothalamus. This pathway does not follow the routes and principles of the direct and indirect pathways. Instead, these striosomal connections project directly to the SNpc. Recent data also reveal that striosomal cells additionally project to the SNpr (Miller, 2008). This constitutes a "limbic"-basal ganglia circuit. The SNpc is considered a dopamine synthesizing region. This pathway allows information about rewards and behavioral states to be integrated within the basal ganglia. This pathway provides the basal ganglia with information of motivational importance (Miller, 2008). The limbic regions evaluate the motivational significance of sensory input. Information about the outcome of this evaluation is projected to the SNpc to control the dopamine system in reward-driven association learning. The basal ganglia are thus closely involved in instrumental conditioning—the behavior to be executed now depends upon instrumental conditioning in the past. (see Chapter 4 for a description of the role of dopamine in instrumental learning). This plays an important role in executive functions in the sense that "decisions" made in the present depend upon the instrumental learning that occurred previously. When the striatum "reads" an environmental context and "disinhibits" a behavior, the behavior released is the one that was adaptive before under similar circumstances.

Basal Ganglia–Subcortical Loops

Most neuroscientific efforts toward understanding the basal ganglia have focused upon the unidirectional flow of information from the cortex to basal ganglia to thalamus and back to cortex. However, certain thalamic neurons project back upon the striatum. Although little attention has been directed toward understanding this projection system, these additional recurrent

thalamic loops likely modulate basal ganglia function in a way analogous to the way thalamic projections modulate sensory information processing.

However, the striatum also receives thalamic projections that originate in brainstem sensorimotor structures. These regions of origin include the superior and inferior colliculi and the pedunculopontine nucleus (McHaffie, Stanford, Stein, Coizet, & Redgrave, 2005; Miller, 2008). The output structures of the basal ganglia (Gpi and SNpr) also project back to these brainstem nuclei. Although this is not a topic that will be covered in detail in this book, subcortical loops through the basal ganglia are very similar in structure and architecture to cortical–basal ganglia loops. These circuitries have several implications. The phylogenetic age of these regions seems to reveal the basal ganglia's longstanding evolutionary role in attention and behavior selections. The basal ganglia originally mediated the attention and action selections of lower level sensory and motor systems. With the evolution of neocortical–basal ganglia circuits, a hierarchical organization of action selection can be envisioned. The basal ganglia can be conceived of as an interface between subcortical and cortical systems. This linkage is depicted in Fig. 2.5. It can be

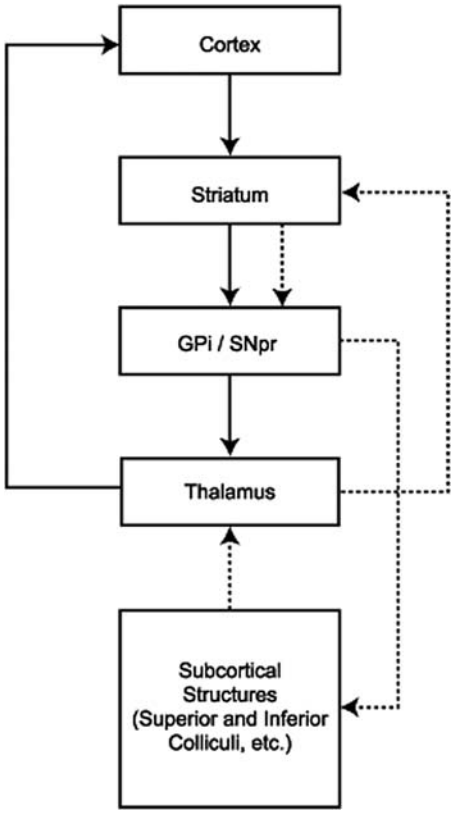

Fig. 2.5 Illustration of cortico-basal ganglia and basal ganglia–subcortical circuitry. The striatum receives input from both cortical and brain stem systems. Cortical inputs are direct as described in text. Subcortical inputs are by way of the thalamus, after Mcttaffie, et al., 2005.

hypothesized that cortical and subcortical inputs into the basal ganglia can act independently, cooperatively, or competitively in influencing behavioral selection (Heimer, Van Hoesen, Trimble, & Zahm, 2008; McHaffie et al., 2005). This is the case because some of the organism's decisions and behavioral choices could stem from lower level subcortical inputs. Considering the basal ganglia as an interface between higher and lower-level systems only emphasizes the role of the basal ganglia in executive functions. In this way, the basal ganglia can be understood as the brain's original executive unit.

For example, while the cortical–basal ganglia circuitry described above focuses on the thalamus as a target structure, output from certain regions of the basal ganglia also target the brainstem nuclei. Orienting responses to visual, auditory, and even tactile stimuli are mediated through basal ganglia–subcortical loops or circuitries (McHaffie et al., 2005). In some novel situations, the release of an orienting response is quite appropriate. If an individual was engaging in an activity in which circumstances suddenly changed that made the situation threatening, it would be adaptive to interrupt the behavior and orient to the novel stimuli. In higher-level problem-solving situations or in some situations which engage automatic processing, it might be appropriate to suppress lower level orienting responses. During the performance of an activity, the inability to inhibit responses to sensory information would actually generate distractions. Therefore, output nuclei of the basal ganglia can serve to disinhibit targets in both the thalamus and the brainstem, thus influencing most of behavior. These systems working cooperatively generate efficient adaptation, but when working competitively or independently, can result in pathological behavior.

Many psychopathologies can be understood as manifestations of abnormal basal ganglia gating functions (see Chapter 7). We even view anomalous functioning of basal ganglia circuitry as one of the primary neurodynamic events in a condition referred to by some professions as "sensory integration disorder." This is a diagnosis typically made by occupational therapists, but professionals in other disciplines also identify this condition. As an aspect of this condition, the patient can demonstrate hypersensitivities to multiple sensations, including visual, auditory, and tactile stimuli. The individual understandably becomes quite distractible. These distracting sensations likely represent basal ganglia failures in the process of selective inhibition–disinhibition (additionally, the abnormal intensity of these stimuli is likely a manifestation of anomalous sensory amplification mediated by the cerebellum, see Chapter 5).

For the sake of simplicity, this book will minimize the attention it pays to the SNpr. The SNpr is primarily the basal ganglia output region for eye movements (Hikosaka, Takikawa, & Kawagoe, 2000; Hikosaka & Wurtz, 1985; Wurtz & Hikosaka, 1986), although recent anatomic evidence implicates the SNpr in a type of "limbic circuit" (Miller, 2008). In many ways, the SNpr is very similar to the Gpi. Cell size, histochemistry, and connectional anatomy are all comparable (Mink, 2003). For a brief review of how the Gpi and SNpr might coordinate output between cortical and subcortical regions as related to the frontal eye fields, see McHaffie et al. (2005).

What Does the Cortico-striatal System Do?

The cerebral cortex is a six-layered structure that performs a wide range of highly specialized operations. These operations can be divided into two broad categories. First, posterior cortices are involved in sensory-perceptual information processing and storage. These cortical areas are the occipital, parietal, and temporal lobes. Second, the anterior cortices, or the frontal lobes, are involved in the processing or programming and retention of movement and action patterns. Therefore, the entire cortex can be considered a highly specialized information-processing "machine." The products of the information-processing computations performed by the cortex remain represented within the cortex (Squire, Clark, & Bayley, 2004; Squire, Stark, & Clark, 2004).

The basal ganglia do not directly participate in the computations performed by the cortex. The basal ganglia do not comprise a laminated information-processing structure. The basal ganglia are groups of nuclei that are involved in gating or selecting the representations that are processed by the cortex so that these representations become active or can be expressed (Frank et al., 2001; Houk et al., 2007; Mink, 1996; Redgrave, Prescott, & Gurney, 1999).

The cortico-striatal system modulates cognition and behavior. It does this through the loops of interaction that have been described, projecting from cortex to basal ganglia to thalamus and back to cortex. This circuitry enables the selection or gating of a subset of movements or representations that have been activated by the cortex. The potential behaviors and the cognitions and goals of the individual are stored or represented in various areas of the frontal lobes, for example, the prefrontal cortex and premotor regions. One of the roles of the basal ganglia within the frontostriatal system lies in selecting which of these numerous possible behaviors to execute. This very important role of the basal ganglia can be referred to as action selection (Seger, 2008). Inhibitory projections from the Gpi/SNpr to the thalamus exert a tonic inhibition on the thalamus. This keeps all potential behaviors suppressed. When an appropriate behavior has been identified within the striatum through cortical activation, tonic inhibition is reduced, but only for that selected action, which is then executed.

The basal ganglia perform an analogous operation on representations in other cortical areas that are not necessarily associated with overt behavior. For example, visual and auditory association areas also project to the striatum, while the flow of information through the basal ganglia is processed through the same intrinsic connectional pattern, from cortex to basal ganglia to thalamus and back to cortex. When the appropriate "perception" or "cognition" has been identified after being activated by parietal, temporal, or prefrontal cortices, inhibition for that selected perception/cognition is reduced, resulting in the focus of attention being directed to that perception or cognition. In this way, the basal ganglia play a role in the selection of attention (Frank, Santamaria, O'Reilly, & Willcutt, 2007). Given the gating or selection operations performed

by the basal ganglia in both attention and action functions, it can even be stated that the cortex is dependent upon the basal ganglia (Heimer et al., 2008).

Three Selection Pathways—An Interim Summary

The basal ganglia are involved in these selection processes by way of three distinct pathways: the direct, indirect, and subthalamic (hyperdirect) pathways. The direct route functions in the process of selection by selectively reducing inhibition from the Gpi on the thalamus. This releases behavior. The indirect pathway increases inhibition on the thalamus by activating the Gpi. This reduces behavioral activity. As discussed, these two pathways exert specific effects on functionally related behaviors or particular responses. The projection pattern into the striatum is characterized by a high compression ratio and by some functional overlap. Therefore, when a behavior or response is selected, there are potentially competing aspects of responses or behavioral patterns. When these pathways operate in concert, the net result is the release of the desired response and inhibition of unwanted competing patterns (Mink, 2003). Deficient inhibition–disinhibition in this system is seen in Parkinson's disease with the inability to initiate movement and in Huntington's disease with the release of adventitious movement.

Application of Motor Behavior to Cognition

If we apply our knowledge of the direct, indirect, and subthalamic pathways that were just reviewed to a cognitive circuit, we can see that this might result in an impairment in focused concentration during the performance of cognitive tasks, with an individual exhibiting distractibility in ideation because unwanted ideas are released or disinhibited (it is also assumed that there are many forms of concentration problems, while different types of concentration difficulties suggest multiple etiologies). If we apply this type of deficit to a perceptual circuit, we might find an inability to focus sustained attention on a perceptual task. Applying the concept to a cognitive–expressive language circuit might result in a behavior resembling tangentiality in conversational speech. The purpose of the discussion is not to explain the etiologies of clinical behaviors in an absolute sense. Rather, the goal is to demonstrate how failures in selection processes/inhibition can contribute to a range of abnormal behaviors.

In this regard, the Gpi needs to be understood as a highly specialized nucleus. Symptoms of dementia, such as impaired executive functioning and memory disturbance can result from focal, acute cerebral infarction of the globus pallidus (Kim et al., 2008). It is true that ventral and posterior regions of the Gpi serve primarily motor-related functions. However, rostral, dorsal, and medial regions are involved in cognitive and perceptual operations, as suggested

by following the trail of the circuitry. For example, dorsolateral prefrontal cortex projects to dorsolateral regions of the caudate. These regions of the caudate project to the medial dorsal region of the Gpi. This region of the Gpi projects to the medial dorsal nucleus of the thalamus, which projects to the prefrontal cortex. Therefore, the Gpi is an integral node in the distributed circuitry of the prefrontal cortex, since the prefrontal lobe is defined as that region of frontal cortex that receives projections from the medial dorsal nucleus of the thalamus (Fuster, 1997).

Surgical pallidotomy for treating Parkinson's disease has demonstrated the involvement of the Gpi in cognitive and emotional functioning. Surgical lesions in dorsomedial regions of the Gpi generate the types of cognitive deficits seen in the dysexecutive syndrome, while surgical lesions confined to ventral and posterior regions of the Gpi (which through the striatum, receives projections from and eventually, through thalamus, projects back to motor regions of cortex) have their primary effect on motor symptoms (Lombardi et al., 2000). Selective cognitive and emotional changes in pallidotomy (PVP) and deep brain stimulation (DBS) of the STN in the treatment of Parkinson's have also been described (Saint-Cyr, 2003a). After PVP, patients experience both executive dysfunction and hemisphere-specific cognitive disturbances. Lesion location in pallidotomy has been demonstrated as critical in determining both motor and cognitive outcome in Parkinson's patients (Obwegeser et al., 2000; Yokochi et al., 2001). While posterior and ventral lesions influence motor control, dorsal and rostral lesions impact cognitive and emotional functioning. Bilateral lesions of the GP often result in a full-blown frontal lobe syndrome characterized by cognitive executive deficits, affective, and personality changes (Bedard, Agid, Chouinard, Fahn, & Korczyn, 2003; Miller, 2008).

The third basal ganglia pathway influencing attention and action selection is the STN route. In this hyperdirect path, diffuse projections from the cortex pass through the STN, bypassing the striatum. Activation of this pathway blocks behavior. Therefore, the STN pathway is critical for general impulse control. This pathway can be important in stopping behaviors that have already begun execution. Similarly, this is an important mechanism in discontinuing one behavior for the purpose of switching to another. Since this route blocks all responding, it is implicated in executive impulse control, allowing advantageous problem-solving and cognitive operations before engaging in a response (Winstanley, Baunez, Theobald, & Robbins, 2005). It has recently been demonstrated that DBS of the STN specifically interferes with the normal ability to inhibit in conflictual decision-making circumstances, selectively causing impulsivity, in other words, cognitive/executive dysfunction (Frank, Samanta, Moustafa, & Sherman, 2007). Although DBS can dramatically improve motor symptoms in Parkinson's disease, patients also speed-up decision making under conflictual circumstances, making choices very quickly. This finding was interpreted as an inability to self-modulate decision making under conditions of conflict. DBS of the STN has also been reported to generate mood alterations, ranging from apathy to

euphoria (Saint-Cyr, 2003b). Bilateral stimulation of the STN has been reported to disturb negative emotional information processing in Parkinson's disease (Dujardin et al., 2004). The STN route can be thought of as a mechanism that adjusts the magnitude of inhibitory Gpi discharge for the purpose of increasing or decreasing a range of behavioral output (Geday, Ostergaard, Johnsen, & Gjedde, 2007).

Examples of the Frontostriatal System in Operation

The information described in previous sections establishes the basic principles of the role of the basal ganglia in movement. The basal ganglia and frontal cortices interact through the elaborate connections of the frontal-striatal-pallidal-thalamic-cortical circuits. When we talk about movement, we understand these frontal-basal ganglia connections as selectively "disinhibiting" the action/motor plans that are stored or represented in frontal cortex. The basal ganglia "release the brake" on these motor plans to generate movement. The basal ganglia detects the appropriate context for performing motor actions and the basal ganglia enable the frontal cortex to execute the appropriate motor plan at the appropriate time (Frank et al., 2001). A fundamental premise of this book is that the basal ganglia do the same things for cognition that they do for movement. The following sections develop these ideas.

The basal ganglia do not comprise a sensory perceptual processing mechanism, nor do they function as a primary behavioral programming mechanism. The basal ganglia function as a selection or gating mechanism (Redgrave et al., 1999). Neuroanatomically, if the basal ganglia select and gate movement, it is presumed that they also select and gate cognitions. The basal ganglia "tell" different regions of the cortex "when" to become active. This section will thus use the principles involved in basal ganglia movement selection to demonstrate how these structures also select attention, cognition, and action. Some of this information is heuristic. However, the application of all of this information clearly flows from what is currently understood about cortical–basal ganglia circuitry. The examples to be reviewed can readily be translated into testable hypotheses that would increase our understanding of the role of the basal ganglia in non-motor behavior. Applying the concepts of this circuitry to cognition and instrumental learning has already received considerable support in computational models (Frank, Samanta et al., 2007; Houk et al., 2007; Frank, Santamaria et al., 2007, Frank et al., 2001).

With this in mind, different facets or aspects of the frontostriatal system will be illustrated by reviewing four essential features of basal ganglia functioning. The basal ganglia's sensitivity to context will be discussed first. Second, we will examine the basal ganglia's involvement in higher-order cognitive functioning through their regulation of working memory processes. We believe this is an absolutely critical function of the basal ganglia because this is the underpinning of self-directed, controlled behavior. In other words, this underlies much of

executive function and self-control. Third, we will consider the role of the basal ganglia in habit execution. Finally, we will examine a behavioral example of the interplay between cortical and basal ganglia functions. These examples will serve to help illustrate the functions of the frontostriatal system as seen in practice.

Sensitivity to Context: The Basal Ganglia in Learning

Numerous problem-solving tasks that activate the prefrontal cortex also activate the basal ganglia (Middleton, 2003). This is particularly true for rule-based category learning tasks, which activate both the prefrontal cortex and the striatum (Filoteo et al., 2005; Rao et al., 1997). In these tasks, categories are learned via some explicit reasoning process (Ashby, Alfonso-Reese, Turken, & Waldron, 1998). The learning occurs as a result of hypothesis testing during which the subject is provided with reinforcement/feedback after each trial. A rule is learned through this process of trial and error feedback. The Wisconsin Card Sorting Test is an example of this type of rule-based category learning test (Heaton, Chelune, Talley, Kay & Curtis, 1993). However, the WCST is cognitively complex, or multifactorial, so caution needs to be exercised for studies in the experimental investigation of the basal ganglia (Stuss, 2007). Therefore, experimental paradigms often use simpler versions of categorization tasks that allow for greater specificity in identifying and isolating various cognitive processes.

In one study employing a categorization task, a single principle ran throughout the task, and after the rule for that task was learned, subjects were given a task with another rule, and they were then required to learn this new rule. In this study, activity in the head of the caudate was seen to peak early after the initial presentation of each problem and then to decrease rapidly. Activity in the prefrontal cortex reached peak values later than activity in the head of the caudate and decreased slowly with the progression of the task, as the task was learned (Seger & Cincotta, 2006). The authors interpreted these results as demonstrating that the striatum participates in the executive aspects of the learning of the task. The striatum identifies the behavioral context necessary for the prefrontal cortex to generate hypothesis and decide upon an appropriate response strategy. According to this study, the head of the caudate appears to play an important role early in the learning process. It recognizes the context of the situation, and biases the prefrontal cortex to choose or select and implement the proper learning and response strategy (Houk et al., 2007; Houk & Wise, 1995; Frank & Claus, 2006 Frank, Seeberger & O'Reilly, 2004). In this way, the striatum puts the prefrontal cortex "in the ballpark" for developing more detailed hypotheses and algorithms to guide behavior (Frank & Claus, 2006; Houk & Wise, 1995; Saint-Cyr & Taylor, 1992).

This type of sensitivity to context demonstrates a central role for the basal ganglia in cognition, specifically, through the process of categorization.

Categorization is important because it allows us to classify properties and characteristics of the environment. This is essential for successful adaptation. Categorization allows an organism to recognize what is edible versus what is not food, it enables us to determine who is friend and who is foe, and allows us to recognize a safe environment versus a threatening or dangerous environment. From this perspective, category learning can be thought of as a type of instrumental conditioning. A response that was adaptive in response to a stimulus has been learned or categorized and allows for executive decision making. What we decide now is based upon what has been adaptive, or what has "worked" because of the conditioning of the past. However, all categorization learning is not alike. The head of the caudate is activated when conscious feedback processing is involved as just described, while the body and tail of the caudate and the putamen are involved in associative, implicit instrumental learning (Cincotta & Seger, 2007). Therefore, different regions of the basal ganglia are specialized for different types of learning (see Chapter 4 for additional information on categorization).

For a practical example of context sensitivity, consider that you are driving while thinking about something else, a common experience for most of us. You are in an unfamiliar neighborhood, having your mind on something other than the task of driving, when all of a sudden, you become aware that your surroundings are not only unfamiliar, but they are intuitively unsafe. This experience can be interpreted as demonstrating the interplay between cortex and basal ganglia. You are consciously aware of what you are thinking (which is mediated by cortex) while you are engaged in an adaptive behavior (driving), which is undergoing automatic processing (stimulus-based control). Your sudden awareness of danger reflects the sensitivity of the striatum to context. The striatum has recognized a changed context which has now biased the frontal lobe to think about other sensory evidence—in this case, the potential threat—and perhaps to choose and implement an alternative response, such as deciding whether you are lost and if you should drive toward a different neighborhood.

Higher-Order Cognition and Working Memory

Higher-order cognition has traditionally been considered to be mediated by the cortex. The literature to support this conclusion is voluminous, particularly if one's bias is cortico-centric. The regions of interest discussed in numerous brain imaging studies focus upon the activity of the cortex. For example, a vast literature demonstrates that working memory functions are dependent upon networks that include prefrontal, parietal, temporal, and occipital cortices (D'Esposito, 2008; Frith, Blakemore, & Wolpert, 2000; Habeck et al., 2005; Linden, 2007; Wager & Smith, 2003). Why is working memory so important? Working memory is most simply defined as the ability to hold information

cognitively "online" for a brief period of time, temporarily, but sufficiently long enough for task completion. This capacity is critical for a multitude of other abilities. It correlates with general intelligence and it predicts performance in a wide variety of real-world cognitive tasks (Richardson et al., 1996). It is a basic mechanism that allows for the higher-order control of behavior. For example, deficits in working memory interfere with the ability to plan behaviors to reach a goal, or even to keep a goal of behavior in mind. The inability to keep information adequately "online" impairs a person's ability to organize events and behaviors temporally. Working memory allows the individual to plan and organize a higher-order behavior instead of merely responding to the immediacy of the environment. Without working memory, the behavior of the individual is driven by immediate environmental stimuli, contributing both to problems with impulse control and environmental or structural dependency. In short, working memory is one of the abilities at the heart of executive function or self-control.

While there are different types of working memory, two divisions have been described in the functional neuro-anatomic literature. These two divisions are organized by the object recognition and object location, or "what" and "where" pathways of the cortex (Goldman-Rakic, 1992; Muller & Knight, 2006; Petrides, Alivisatos, Evans, & Meyer, 1993; Ungerleider & Haxby, 1994). The dorsolateral prefrontal cortex has reciprocal excitatory connections with parietal cortices, which has been identified as the anatomic substrate for spatial location working memory tasks (Leung, Oh, Ferri, & Yi, 2007; Ricciardi et al., 2006). This circuitry allows us to keep information about spatial location "online." Second, more ventral lateral regions of the prefrontal cortex have reciprocal excitatory connections with ventrally localized object recognition pathways in the temporal lobes. This anatomy subserves working memory for object identity (Ranganath, 2006).

Therefore, prefrontal–cortical connections are specialized for the mediation of different tasks that require the maintenance of information "online" as the task is performed (Goldman-Rakic, 1996; Smith & Jonides, 1999; Ungerleider, 1995). Many tasks require the simultaneous operation of both dorsal and ventral working memory information-processing streams (Buchsbaum, Olsen, Koch, & Berman, 2005; Lawrence et al., 2000). For example, many tasks in life are composed of multiple components and require information about object identity and location derived from different sensory modalities. In the sections below, the digit span backwards task will be reviewed as a theoretical example to illustrate the participation of both the dorsolateral and lateral ventral systems.

These aspects of neuroanatomy imply that working memory is a multiple component system that mediates the temporary storage of the internal representations guiding behavior (Baddeley, 1998, 2003). Verbal and visuospatial working memory functions, presumably mediated by left and right hemisphere processes respectively, are postulated to be guided by a "central executive" (Baddeley, 2003). Since the reader of this book is likely familiar with this

conceptualization of working memory function, the specific details of this model will not be reviewed here. The anatomical localization of this system is considered cortico-centric in nature. Baddeley's (2003) elegant model of working memory function has nevertheless encountered some difficulties developing testable hypotheses related to what drives the system. Even when attempting to differentiate between storage and updating working memory functions, it is not possible to identify specific cortical mechanisms that control these processes (Smith & Jonides, 2003). Is the central executive a homunculus residing in the Prefrontal Cortex (PFC)? How does the PFC know what plans and behaviors to select? Is there anything going on behind the scene of cortical operations to support working memory functions? The answer to this last question is an unequivocal "yes," and understanding this answer helps explain the central executive and its selection of plans and actions.

The mechanisms that maintain multiple representations online, the mechanisms that manipulate these representations, the mechanisms that prevent the intrusion of distractions, and the mechanisms that update the contents of working memory are easily envisioned as mediated by interactions between the cortex and the basal ganglia. The basal ganglia perform various selection operations by interacting with prefrontal cortex in a way analogous to the role of a doorman or bouncer in a nightclub (Awh & Vogel, 2008; McNab & Klingberg, 2008). Prefrontal–cortical connections maintain information "online," while the basal ganglia "gate" manipulations of information and prevent the intrusion of distractions through basal ganglia–cortical interactions. The direct and indirect pathways comprise an important anatomic underpinning for these interactions. Output from the Gpi, because of its influence over thalamus, appears to be a "key player" in updating functions (McNab & Klingberg, 2008). The basal ganglia "let in" the desired information through the direct pathway and "keep out" the distracting information by way of the indirect pathway. Therefore, working memory is characterized by a division of labor between maintaining information online, which is a function of cortex, and updating information, which is gated by the basal ganglia. It is very possible to have a selective impairment in a specific aspect of working memory. For example, patients with Parkinson's disease appear to be more impaired in manipulation and updating functions than in maintenance functions of working memory (Lewis, Slabosz, Robbins, Barker, & Owen, 2005).

Superimposing cortical networks upon the BG gating system provides a fairly straightforward method to approach the development of testable hypotheses in this area.

Working memory's dependence upon cortical processing is well-documented (Wager et al., 2003; D'Esposito, 2008). However, this ability or capacity is easily disrupted by any condition that affects the frontostriatal system. For example, patients with Parkinson's disease, without dementia and without depression, exhibit reduced working memory span (Gabrieli, 1996). Deficient working memory capacity is seen in Huntington's disease (Lawrence et al., 2000).

Neuropsychiatric disorders such as Tourette's syndrome, attention deficit disorder, and schizophrenia all include disturbances in working memory function (Keri, 2008; Ross, Harris, Olincy, & Radant, 2000). Working memory dysfunction has been described in patients with disturbances within the basal ganglia (Brass, Benedict, Weinstock-Guttman, Munschauer, & Bakshi, 2006; Salmon, Heindel, & Hamilton, 2001). Basal ganglia activity during working memory tasks is reported in healthy control subjects, and the temporal dynamics of regional basal ganglia participation have been mapped for different phases of a working memory task (Chang, Crottaz-Herbette, & Menon, 2007). Significant increases in activation have been observed in the caudate nucleus, particularly when tasks emphasize the manipulation of information within working memory (Lewis, Dove, Robbins, Barker, & Owen, 2004). These findings very clearly indicate that the basal ganglia comprise an essential nodule within the brain's higher-order executive function system. Working memory requires interacting networks that include cortical and subcortical regions (Schlosser, Wagner, & Sauer, 2006).

Many studies of working memory focus upon cortical regions of interest. A PET investigation of the digit span task revealed activation of the dorsolateral prefrontal cortex, the bilateral inferior parietal lobe, the medial occipital cortex, the anterior cingulate, and the cerebellum (Gerton et al., 2004). In general, the caudate is often activated along with frontal areas in this type of study, implying involvement of cortico-striatal circuitry, although there was no mention of this area as a region of interest. The findings were interpreted from a cortico-centric framework, and in this regard, little attention was paid to the high degree of cerebellar activation.

An fMRI investigation focusing on differentiating working memory functions revealed virtually identical patterns of prefrontal and parietal activation during processes of maintenance and manipulation. The authors concluded that these distinctions are functional rather than neuroanatomical, but it is not at all clear that subcortical areas were ever regions of interest (Veltman, Rombouts, & Dolan, 2003). Because different types of inhibitory and excitatory cells can fire simultaneously, with opposite patterns of firing within certain regions of the basal ganglia, it is unclear how this would affect rCBF and/or BOLD fMRI signals (Frank, M., personal communication, May, 2008). However, when studies are designed specifically to examine basal ganglia activity along with specific aspects of working memory function, basal ganglia participation is readily evident. For example, McNab and Klingberg (2008) specifically linked the activation of output of the Gpi to the filtering of working memory updating, identifying the Gpi as an essential nodule in working memory gating functions. Similarly, Chang and colleagues linked the temporal dynamics of specific regions of basal ganglia recruitment during the encoding, maintenance, and response phases of a working memory task (Chang et al., 2007).

How Does Working Memory Work?

How can an activity that seems so uniquely cognitive be analogous to motor behavior in any way? *The cognitive control system is likely an evolutionary extension of the frontal–basal ganglia motor control system* (Hazy, Frank, & O'Reilly, 2007). For the business of the basal ganglia, motor functioning and cognition are similar or even parallel processes. For example, we can think of motor "plans" or behaviors as represented or maintained in cortex, specifically, within premotor and supplementary motor regions. In this context, the frontal cortices are maintaining a motor control plan to "guide" a sequence or ordering of motor movements (Frank et al., 2001). This can be considered a "motor working memory" representation. This is the plan of the motor activity that the brain wants to accomplish. The basal ganglia, through the direct and indirect pathways, "gate," or disinhibit these representations when appropriate by interacting with these representations that reside in cortex (Menon, Anagnoson, Glover, & Pfefferbaum, 2000). Essentially, this is serial-order processing. The unique "looped" architecture of the basal ganglia is well suited for this function.

Serial order processing is made possible by the re-entrant projections that "loop back" to the same areas of cortex from which they originated. The basal ganglia, by interacting with the cortex in the proper sequence, release the proper order of behavior. As the behavior is released, the "sequence" needs to be updated, while the remaining elements of the motor sequence need to be maintained as representations "online" until the program is completed. We believe that the basal ganglia interact in the same way with the representations of plans and goals that reside in the prefrontal cortex. In this way, the processes that guide motor functioning have much in common with the cognition of working memory that ultimately guides behavior. The processes that guide movement manage many of the same requirements that are essential for manipulating the contents of working memory.

As described above, a variety of functional demands underlie working memory. Since different tasks require different functional components, the working memory system needs to be able to manage multiple and separate representations. In fact, even a single task can require multiple cortical representations. The online maintenance of information needs to be robust enough to withstand competing or distracting influences. Since the representations being held online actually change during the performance of the task, the system needs to include a mechanism for updating the status of the representations. The demands of robust maintenance and flexible updating appear to represent contradictory processes (Hazy et al., 2007). However, prefrontal–cortical and frontostriatal connections allow the working memory system to fulfill these characteristics (D'Esposito, 2008; Gruber, Dayan, Gutkin, & Solla, 2006). There is a "division of labor" within the working memory system as related to information maintenance and manipulation/updating functions.

Object and location representations are stored or maintained in the cortex, in inferotemporal and parietal regions. Activation in these regions actually correlates with the amount of information undergoing temporary storage (Todd & Marois, 2004; Vogel & Machizawa, 2004). These regions project to the prefrontal cortices. Neurons of the dorsolateral PFC have a unique intrinsic property for "firing" in a manner that keeps information "online" (Fuster, 1997). The striatum receives projections from these same areas of the prefrontal lobes to which the temporal and parietal cortices project. Prefrontal–cortical connections are excitatory, so that a vast amount of processed information is potentially in competition to be considered in "working memory" or to intrude upon its functions. However, the same PFC regions that have reciprocal projections with cortical areas also activate the head of the caudate through the direct pathway. This activation of the striatum selectively reduces Gpi inhibition on the thalamus, so that the PFC-posterior cortical working memory loops can be selectively identified, chosen, and maintained. This "selection" function performed by the striatum (through its interactions with the Gpi) allows the information in prefrontal–cortical circuitry to be kept "online" for the purpose of thinking about the information or representations (Ashby, Ell, Valentin, & Casale, 2005; Ashby & Spiering, 2004; Ponzi, 2008).

At the same time, activity of the indirect pathway, through Gpe and STN connections, activates surrounding areas of the Gpi in order to inhibit all other cortical representations. The indirect pathway serves to prevent distractions during working memory activation. This helps to keep representations online while inhibiting the intrusion of competing influences. In this way, the basal ganglia are actively participating in a network of brain activity supporting working memory. The basal ganglia are selecting prefrontal–cortical representations so that they can remain active, while at the same time inhibiting other prefrontal–cortical activity in order to prevent responding to competing or distracting influences. We can thus see that information to be kept online is actually distributed throughout the cortex in the same regions where it is or was initially processed, while "working memory" is actually the controlled activation of these representations under the mediation of the basal ganglia's selection mechanisms.

Selective disinhibition of the thalamus by the Gpi allows for cortex to interact with the striatum in selecting and updating the content of working memory functions just as this mechanism of inhibition–disinhibition allows for cortical–striatal interactions to "release" motor sequences. Computational models of these processes have been developed and corroborated by several important empirical studies (Hazy, Frank, & O'Reilly, 2006; Hazy et al., 2007; McNab & Klingberg, 2008). Clinical studies with patient populations also demonstrate that the striatum is critical in the manipulation and updating functions of working memory (Lewis et al., 2005, 2004). These types of activities might even be considered to represent the *default condition* of the basal ganglia.

The recitation of digits backwards is regarded as a traditional working memory task. However, we would like to note that it is not clear how this

task translates to "real world" working memory function. We have decided to review a theoretical neuroanatomy of this task, since the task is familiar to most readers. However, in our view, this is a task that emphasizes higher-order control, requiring very significant "working memory" demands. Therefore, it is unlike the episodes of brief and less effortful working memory tasks that occur during the course of practical daily living. For example, "working memory" tasks that are practiced have been demonstrated to recruit less brain activation (Garavan, Kelley, Rosen, Rao, & Stein, 2000). Nevertheless, since all higher-order control requires working memory function, the performance of this task can be examined in order to demonstrate the properties of working memory within this cortical–basal ganglia model.

For this purpose, consider the recitation of the digit series, 8-5-3-9-7, in reverse order of presentation. First, this information needs to be represented within the cortex. This representation includes both the identity and the position of the individual numbers. Theoretically, both inferotemporal and parietal-prefrontal working memory loops would need to be activated. The individual representation of each number, in its proper position, thus requires a multiple, distributed cortical network. The identity of each number is presumably represented in the lateral ventral PFC and the position of each digit is presumably represented in the dorsolateral PFC.

The prefrontal cortex would need to excite the direct pathway within the striatum in order for the Gpi to selectively release inhibition on the thalamus to activate the representation of the string of digits within the appropriate prefrontal-temporal (identity or "what") and prefrontal-parietal (position or "where") cortical networks. This allows the information to be maintained or held cognitively "online." Tonic pallidal inhibition of other non-task related thalamic regions prevents the cortical representations of potentially distracting information in the environment from becoming active. The STN sets the tonic inhibitory tone of the pallidum. Additionally, it might be argued that the standard, over-learned, numerical sequence (1-2-3-4-, etc.) would also need to be inhibited (Valera, Faraone, Biederman, Poldrack, & Seidman, 2005). This inhibition would presumably be accomplished through activation of appropriate Gpi regions through the indirect pathway. Therefore, selective pallidal inhibition of the thalamus, through the direct and indirect pathways, would be required to keep the 8-5-3-9-7 stimulus "online" while inhibiting all other potentially competing and distracting information.

The reversed sequence consists of the recitation, "7-9-3-5-8." To recite this sequence, the number 7 would be released through striatal activation of the direct pathway, while all the remaining numbers in the sequence would be maintained. Next, the number 9 would be selectively "disinhibited," while the remaining sequence of 3-5-8 would be inhibited, and so on and so forth. Therefore, through this process of selective disinhibition and inhibition, (from PFC to striatum to globus pallidus to thalamus to cortex), the contents of working memory would be appropriately updated as the task of recitation is performed and completed. In this regard, the basal ganglia functions of attention and

action selections are very well suited to meet the requirements of the general working memory system. Prefrontal–cortical connections keep information maintained, while the basal ganglia act as a "switch" that allows for the selective gating of information.

In this proposed system, it can be argued that there is no need for an abstract concept of a "central executive." In our proposal, the updating mechanisms serve the role of central executive and are inherent in the model. There is no need for a central executive to function as a homunculus. For example, let's review the initial example of comparing working memory to the execution of a motor plan. The question was asked about how a cognitive activity such as working memory can be compared to a motor behavior. In executing a sequence of movements, it is not so much necessary to "monitor" the activity consciously as it is important to keep track of the sequence through appropriate updating of the motor plan. In learning a new sequence, more monitoring is required. After an element of the sequence is completed, the movement goes forward to the next element. Although the element is "stored" in cortex, it is no longer maintained in the current "working memory" of the movement because that element was completed. In other words, as the motor plan unfolds, elements of the organized movement that were completed simply "drop out" of the motor working memory sequence. Through pallidal inhibition of the thalamus, the completed element no longer occupies "working memory." The element can remain as a representation in cortex, but it is no longer "active." The activity is updated through Gpi output and only the remaining elements of the plan are maintained "online"(McNab & Klingberg, 2008). In fact, keeping completed elements in "working memory" would again reveal a failure of the "bouncer" to keep unnecessary information out of working memory (Awh & Vogel, 2008).

This same issue can be argued in regard to cognitive working memory. In reciting the letter sequence, "b-g-c-b," "b" drops out of the sequence after its repetition through selective pallidal inhibition–disinhibition. The temporary memory is updated. After "g" is recited, the working memory is again updated through frontal-basal ganglia interactions so that now, only "c-b" remains in working memory. The updating mechanisms—namely, the prefrontal-basal ganglia interactions—serve the function of the central executive in managing the content of working memory. In this way, a "central executive" or updating mechanism has a dynamic locus of control, depending upon the nature of the working memory task being performed, although prefrontal-striatal interactions are always involved. Thus, the additional abstract idea of a separate "central executive" is not necessary to control the process. The theory of "threaded cognition" in explaining multitasking proposes a similar mechanism, without the need for specialized executive processes (Salvucci & Taatgen, 2008).

To be sure, the necessity of an abstract "central executive" in working memory remains controversial. Higher-level executive management processes depend upon the degree of "higher-order" control necessary to perform the task, which often depends upon the degree of familiarity versus novelty. For

example, in perceptual decision-making tasks, there is evidence for a system that is involved in performance monitoring (Heekeren, Marrett, & Ungerleider, 2008). This is presumably an "error-detection" system that adjusts responding in order to maximize performance, particularly under conditions of uncertainty. The prefrontal cortex is an essential nodule in this system. Heekeren and colleagues believe this system runs in parallel to circuitries necessary to perform the given task.

The cerebellum also plays an important role in the online maintenance of representations in working memory. This may be through error-detection/correction, through timing functions, or by modulating the strength of neural signals/memory traces (Hayter, Langdon, & Ramnani, 2007; Ravizza et al., 2006; Valera et al., 2005). However, this will be discussed in sections specifically related to the cerebellum and to neuropsychological testing. An additional important implication of this "digits backwards" example concerns its lack of sensitivity to locus of cognitive control. Data from PET imaging reveal that digit span tasks recruit the dorsolateral prefrontal cortex, the anterior cingulate, inferior parietal lobe regions and medial occipital lobes, as well as anterior and posterior lobes of the cerebellum (Gerton et al., 2004). If an individual is unable to perform this task, the performance failure in itself says little about the localization of the anatomic deficit, since the pathology could conceivably be found within anterior or posterior cortices or within subcortical brain regions.

Context and Higher-Order Control in Combination

The Wisconsin Card Sorting Test provides an example of how cortical–subcortical networks operate in problem-solving. The cards in this task are to be sorted according to the rules of color, form, and number. Initial activity in the striatum "biases" the prefrontal cortex to attend to the various characteristics of the cards. These characteristics of color, form, and number are represented in inferotemporal and parietal regions. For the sake of this example, assume that color is the bias "guessed" as an initial response, and receives feedback indicating that this reply is correct. This reduces working memory demand, and the subject replies automatically to color for the next 10 presentations. Suddenly, the next such automatic response receives negative feedback. The task has now generated a high working memory demand, as the automatic response does not work and the individual needs to figure out what to do. With this negative feedback (sensitivity to context), activity in the head of the caudate increases (Monchi, Petrides, Petre, Worsley, & Dagher, 2001). This activity reduces inhibition on the thalamus so that the PFC-posterior cortex working memory loops can again be activated and maintained for the purpose of strategy generation and hypothesis testing about the characteristics of color, form, and number.

Let's say form is the next response and it is positively reinforced. After 10 correct sorts, negative feedback occurs, again initiating working memory and the choice of number, and so on. Now let's say during the second sequence of sorting by color, the subject "loses set" after five or more trials. According to our proposed model, this occurred due to insufficient pallidal inhibition on the thalamus—the "bouncer" failed to "throw out" or inhibit responses to distracting stimulus features. In this way, a theory of frontostriatal functioning can be directly applied to a clinical neuropsychological testing situation. Although it needs to be kept in mind that subjects can perform poorly on the WCST for reasons other than frontostriatal involvement, the example remains useful for illustrating frontal-basal ganglia interactions. Furthermore, these dynamic interactions are not easily summarized by test "scores."

The Basal Ganglia and Automatic Processing

The basal ganglia are involved in a variety of tasks requiring automatic processing. These tasks include motor skill learning, perceptual-motor learning, cognitive skill learning, category learning, and sequence learning (Knowlton, 2002; Seger, 2006; Seger & Cincotta, 2005). These seemingly disparate tasks have several features in common. One important element of these tasks involves the gradual learning of associations. With repetition, an individual acquires a habit or a procedure, defined as a characteristic way of responding to a stimulus (Albin & Mink, 2006). Additionally, although higher-order control can at times be useful in the learning of these tasks, they do not require conscious mediation in order to be learned. After these tasks are learned, they are best executed without conscious mediation. In fact, it has been suggested that cortical and subcortical learning systems do not interact in a synergistic way, and under certain circumstances, may actually operate antagonistically in relationship with one another (Seger & Cincotta, 2005; Seger, 2006; Knowlton, 2002). Finally, these tasks are all acquired instrumentally. Execution of these types of tasks is based upon the principle that current actions depend upon the "procedural" or instrumental knowledge of what actions in the past have led to favorable or unfavorable outcomes (Miller, 2008). The fact that these tasks do not require higher-level conscious and cognitive control does not relegate them to a secondary class. To the contrary, the performance of these "unconscious" or automatic tasks ensures adaptation and thus survival (Toates, 2006). These are elegant automatic routines that accomplish goals with little or no conscious mediation.

The performance of these tasks comprises a bonus of the frontostriatal system, and provides further evidence that the basal ganglia are involved in executive decision making and control. Although the acquisition of these instrumental tasks requires rehearsal or repetition, learning these types of tasks allows us to benefit from experience. Behavioral solutions to problems

with interacting with the environment can then be acquired to the extent that in the future, these behaviors can be executed automatically, quickly, and without time-consuming deliberation. This level of functioning actually conserves adaptive resources by simultaneously allowing for adaptive responding and freeing cortical systems for attending to those processes requiring effort.

This principle is readily observed in any "first-responder" profession. Firemen, policemen, medical crises personnel, and hospital emergency room staff participate in training that essentially focuses upon making "familiar" that which is initially "unfamiliar." In a crisis or emergency situation where time and proper decision making are of the essence in managing a problem, it is essential to know how to respond immediately, without giving the situation a second "cognitive" thought. In fact, responding quickly and automatically allows cortex to "think" about other aspects of the emergency situation that might require unique attention. Airplane pilots undergo frequent simulation training in order to anticipate a proper automatic response to whatever crises might occur during a flight. Cortex works slowly, and in most crises situations there is literally no time to think.

Instrumental learning and behavior is not only important in times of emergency. All participants in various sports constantly train on the fundamentals to make these behaviors automatic—a competent golfer or baseball batter does not think about his/her swing, a quarterback or pitcher does not think about how to throw a ball, a football player does not think about the tackle, a hockey player does not think about skating. All of these behaviors are engaged instrumentally so that attention can be allocated elsewhere.

Instrumental behaviors are also essential to everyday life. All of us are creatures of habit. We all do many of the same things, in the same way, every day, without thinking about them. These routines include dressing, bathing, and personal hygiene tasks. Additionally, important aspects of higher-level tasks such as reading, writing, using a keyboard, and calculating depend upon instrumental learning. We have all acquired instrumental procedures for automatically interacting with our environment. The acquisition of these procedures is not an option. We must learn these according to "habit," or else these routine tasks must be performed deliberately, by cortex, which by necessity slows performance. Most of our basic "activities of daily living" rely on these procedures and, not surprisingly, performance of these tasks is often impaired among individuals with dysfunction in frontostriatal function. All of these "routine" tasks provide examples of behavior under frontostriatal–basal ganglia control. As we have repeatedly seen, projections form cortical—sensory information-processing regions allow the basal ganglia to be sensitive to context. This sensitivity to context allows for stimulus generalization and for establishment of stimulus-response associations. Dopaminergic instrumental conditioning allows for the binding of sequences that are represented in sensory and motor cortices. The appropriate stimulus excites the striatum, which reduces Gpi inhibition over the thalamus, allowing release of the cognitive or behavioral sequence or "habit."

Alternating Episodes of Automatic Versus Higher-Order Control

As we have seen, many or even most tasks in life are accomplished through habit. Most tasks are accomplished automatically. Little cognitive control is required because we have habitual ways of responding to most situations. Therefore, the frontostriatal system is involved in most of life's tasks, or "activities of daily living." Imaging studies demonstrate that cortical activity is accompanied by basal ganglia activity in the performance of instrumental and problem-solving tasks (Dagher, Owen, Boecker, & Brooks, 1999; Vogel, McCollough, & Machizawa, 2005; Vogel & Machizawa, 2004; Knowlton, 2002; Monchi et al., 2001). As we have also seen, a number of circumstances require higher-order control. These circumstances require either the modification of an existing behavioral sequence or the development of a new behavioral program. Perhaps automatic behaviors should not be considered as variations of "motor" or procedural learning in terms of a defining characteristic. Instead, it is important to consider the daily flow of behavior as patterned, organized, and as directed towards accomplishing goals (Joel & Weiner, 2000). In an environment that presents novelty and change, flexibility is required in selecting and executing motor programs in order to achieve goals. Therefore, frontostriatal interplay can easily be envisioned, going back and forth between controlled and automatic responding.

Consider another everyday example. You are driving along a familiar route to a familiar location, which we can term a basal ganglia routine. This is a habitual behavior which likely consists of driving (a procedural activity) while you are thinking about something else (a cortical activity). You notice that up ahead, the road is flooded and cannot be traveled. In a plausible neuroanatomic scenario, this change in context would activate the striatum. This striatal activity would bias the prefrontal cortex to attend to the change in circumstances. Activity would be gated from whatever we were thinking about towards selecting those cortical regions that recognize the novel problem. The prefrontal cortex would exert control through the STN pathway to activate the posterior and ventral Gpi in order to slow down the behavior of driving to provide time to think. The PFC would further stimulate the head of the caudate to reduce inhibition on the specific dorsal regions of Gpi. This would release activity in the MD nucleus of the thalamus, in order to activate dorsolateral–cortical working memory excitatory loops.

The working memory loops would recruit declarative knowledge about the geography of the area in order to devise the appropriate detour. The PFC would develop a detour strategy based upon that knowledge, and stimulate the striatum to select the appropriate right and left turns through the direct and indirect pathways. After this was accomplished, the striatum would recognize the change in context back to familiar surroundings, would bias the PFC, and the PFC would stimulate the original direct and indirect pathways to resume driving to the familiar location along the once again familiar route.

The point of the example is to demonstrate that the cortex and basal ganglia interact continuously during the performance of most activities. While organisms prefer automatic responding, circumstances arise that require modifications in behaviors. Most circumstances require alternating episodes of automatic and higher-order controlled responding. Therefore, the frontostriatal system evolved so that both automatic and higher-order control coexist and interact in order to make behaviors biologically adaptive.

An Integrated Cortical–Subcortical Model of Behavioral Selection

How does the brain actually select a behavior? How do we decide what to do? What is the striatal contribution to these selections? The frontal cortex and the basal ganglia operate in tandem to generate adaptive behavioral output. In a sense, the relationship between the cortex and the basal ganglia is like the relationship between the front rider and the back rider on a bicycle built for two. When both riders are functioning at the optimal or proper level, the bicycle moves smoothly. There is appropriate speed and balance, while during the course of the ride, the front rider makes appropriate adjustments in steering in order to stay on proper course (interaction between automatic and controlled responding). With both people pedaling, the ride is coordinated, economical, and occurs with appropriate speed.

If there is no back rider on this bicycle, the front rider can still get from point A to point B. However, the bicycle moves much more slowly and considerably more effort is required to accomplish the task. The front rider gets no help from the "absent" back rider. This is analogous to frontal cortex functioning without basal ganglia—task accomplishment becomes deliberate, slow, and effortful. On the other hand, if there is just a back rider, with no front rider, it becomes difficult if not impossible to make fine adjustments in the movement of the bicycle. Driving straight might work, but changes in steering to accommodate changing road conditions cannot be accomplished. In fact, imagine that the bicycle will hit every bump in the road that is in front of it. This is analogous to basal ganglia functioning without cortex, resulting in the organism becoming environmentally dependent or "stimulus bound" without flexibility in behavioral programs.

The Striatum Learns and Mobilizes Procedures

The striatum selects behaviors or motor routines. Because the striatum is sensitive to context, it performs these selections according to current environmental circumstances and motivational states, based upon instrumental associations to internal and external stimuli. The striatal selection is based upon reward-driven instrumental learning—what worked in the past should work

now, given the similarity in stimulus characteristics, and as a result, the behavior should benefit the whole organism, just as it did previously. The striatum is able to subserve this function because of its neuroanatomy. The striatum receives input from perceptual, limbic, cognitive, and motoric cortical brain regions. In this way, the striatum is very well suited to detect specific cortical, or environmental, contexts, since it is inherently sensitive to patterns of cortical activity. The limbic, striosomal input mechanisms of the basal ganglia allow for the formation of associations between inputs and outputs.

Learning occurs when, in a specific situation that generates a pattern of cortical activity, a set of striatal neurons is activated and the resultant behavior leads to a favorable outcome. (see Chapter 4 for a description of basal ganglia learning mechanisms.) In the case of positive outcome or "reward," the corticostriatal synapses that were activated are strengthened. Therefore, that same set of neurons is likely to be activated in the future, under similar stimulus circumstances. As a result, the same behavior is likely to be selected and executed. If it worked before, it should work again. This is an instrumental learning mechanism. It ensures that the most appropriate behavior will be selected according to past experience. This maximizes reward possibilities. Under similar stimulus conditions, the striatum is highly sensitive to the context that generated that behavior and the striatum, therefore, biases the frontal cortex with information about the most appropriate behavior given the current perceptual, cognitive, and motivational pattern or context that it detects (see Joel & Weiner, 2000, for further description). The instrumental behavioral mechanism includes learning to anticipate or expect reward based upon prior experience with similar situations.

While this represents how the striatum selects a behavior, "habit" or procedure based upon a pattern of cortical activity, this does not necessarily translate into a behavioral product. This is because the frontal cortex is receiving input from other cortical regions as well. In addition to information about the current pattern from the striatum, the frontal lobes receive information about the current context from other regions of cerebral cortex. This additional input or "sensory evidence" might contain information that is more specific, or information that needs to be analyzed because of perceptual differences and even subtle characteristics that were eliminated in the generalization that emerged from the striatal pattern. Under conditions of novelty or uncertainty, a specific medial frontal–striatal–thalamic network is activated, which signals that more attentional resources are required to process a task accurately (Heekeren et al., 2008).

The Prefrontal Cortex Decides upon Behavior

Therefore, the prefrontal cortex is biased by two sets of inputs. One set of inputs is based upon the selection from the striatum, which is based upon the pattern of cortical activity that it "reads." The other set of inputs comes from the cortical

cell assemblies that are specifically activated by the current situation. Two factors determine if the behavior selected by the striatum is the one that will be signaled for release by the PFC. First, the strength of the striatal biasing effect upon the cortex is likely a determining factor. Second, the degree of consistency or congruency between the biasing effects of the striatum and the biasing effects of other cortical regions upon the PFC also plays a role in determining behavioral output (as described by Joel & Weiner, 2000).

In a well-learned, routine, or highly familiar situation, one would expect the striatum to be strongly activated. This should lead to a strong biasing effect from the striatum upon the PFC to signal the release of the automatic behavior. At the same time, in familiar situations, other cortical regions would bias the activity pattern in the PFC in the same direction, to release the same behavior. Therefore, under highly familiar circumstances, there is a strong striatal biasing effect upon the PFC and there is congruency with the biasing effect of other cortical input upon the PFC. The result is that the PFC signals the striatum to release the automatic behavior, which is executed in an effortless fashion.

In a novel or new situation, striatal neurons associated with a particular behavior would be activated only weakly because the context of the situation is not associated with any particular behavioral pattern. Similarly, input to the PFC from other cortical regions characterizes the situation as not stimulus-based. Therefore, the PFC stimulates the head of the caudate to maintain activation of PFC–cortical working memory loops so that a new behavior can be devised or programmed, since there is no automatic or stimulus-based behavior that works under those novel conditions.

Many situations can be characterized as intermediate because the cortical context is partly familiar while it contains some new components or some components that are slightly different. Striatal neurons associated with the learned behavior for that partly familiar context are, therefore, activated, but not as strongly as they would be activated in a completely familiar situation. This biases the PFC to signal the release of the behavior selected by the striatum. The biasing effect upon PFC from other cortical regions is similar, but it contains elements of novelty. These biasing effects can be strong enough to release the automatic behavior, while at the same time, maintaining activation of PFC-cortical working memory circuits that provide on-line modifications of the released behavior. This allows for alternating episodes of stimulus-based behavior with appropriate adjustments from PFC supervisory higher-order control mechanisms. In particular, the anterior cingulate (medial prefrontal) circuitry plays a critical role in the monitoring of performance, in detecting performance deviations, and in signaling the need for behavioral adjustments (Heekeren et al., 2008).

According to this model, higher-order control comes "online" when routine behavior is not possible. This occurs when stimulus-based responding does not immediately work or when it needs modification. The frontal supervisory process is often not necessary for adaptive behavior and under routine, familiar conditions it participates in behavior only in a relatively limited way. The

prefrontal cortex is responsible for releasing the execution of routine behavior through activation of the striatum via the direct and indirect pathways. The execution of these behaviors does not require frontal control or supervision. The striatum can notify the PFC of a change in context during the course of execution of a behavior. Changes in sensory evidence from cortical information-processing areas can also signal changes in perceptual context. This allows for behavioral modification or adjustment.

Non-routine or novel problem-solving behavior requires interaction of the PFC with other cortical brain regions and with the basal ganglia. Even when the basal ganglia are not recruited to execute a routine behavioral pattern, the basal ganglia continue to play a role in higher-order behavioral control. This is at least the case because the basal ganglia assist in establishing the context for problem-solving while also participating in the division of labor of working memory functions by gating cognitive activity through the direct and indirect pathways. The basal ganglia guide the frontal lobes into a "ballpark" behavior that is appropriate for the context, and provide the mechanisms that are necessary for regulating working memory functions (Houk et al., 2007). Therefore, the basal ganglia play an essential role in higher-order cognitive-behavioral control.

Pathology/Developmental Disorders

Basal ganglia circuitry has been implicated in a variety of psychiatric and developmental disorders (Bradshaw, 2001). Attention deficit disorder, obsessive-compulsive disorder, and schizophrenia are but a few of these conditions. Attention deficit disorder can be considered a disorder of intention. Children with this condition primarily demonstrate a disturbance in gating appropriate action selections (Frank, Scheres, & Sherman, 2007). As a result of a deficit in gating sensory "what" into motor "when"—a function of the frontostriatal system—people with this condition experience a disturbance in intention programs. This is manifest by deficits in knowing when to start a behavior, knowing when not to start a behavior, knowing when to persist with a behavior, and knowing when to stop a behavior. These deficits are manifest in premature responding or impulsivity, distractibility, difficulties in making behavioral transitions, and general disinhibition or behavioral dysregulation. This is consistent with brain imaging data which reveal multiple regions of abnormality, including involvement of the frontostriatal system.

Obsessive-compulsive disorder is another executive function disturbance involving this circuitry (An et al., 2008; Cavedini, Gorini, & Bellodi, 2006). It has been proposed that hyperactivity in the orbitofrontal region and caudate nucleus leads to decreased Gpi inhibition of the thalamus and, therefore, cortical excitation, releasing the same idea, over and over again, dependent upon the focal area of involvement. The specific cortical and subcortical correlates of checking, washing, and hoarding behaviors will be discussed in a

subsequent chapter. One of the roles of the striatum is to act as a filter or switch, to process information automatically and without conscious representation, particularly for stereotyped, rule-governed, or routine behaviors. Hyperactivity within the OFC/caudate over-runs the switch, so that behaviors cannot be turned-off, despite the conscious intention to do so.

It has been demonstrated that in schizophrenia, with medication-naïve subjects, the Gpi is underactive (Spinks et al., 2005). This could conceivably result in the release of fragmented perceptions and ideas, representing the underpinnings of psychosis. This would be analogous to the release of fragments of purposeful movements observed in Huntington's disease, where the indirect route in unable to activate the Gpi regions that govern motor nuclei. These disorders will be reviewed further in a section specifically considering subcortical contributions to pathology.

Summary

The basal ganglia and its subdivisions can be classified according to input, intermediate, and output structures. These structures are connected to cortex through a circuitry that grossly runs from cortex to striatum, from striatum to globus pallidus, from globus pallidus to thalamus, and from thalamus back to cortex. The connections of the basal ganglia are organized so that input into the system can selectively decrease or increase the inhibitory effect of output nuclei on their specific target structures in the thalamus or the brainstem. Selective disinhibition/inhibition on these target structures releases the desired behaviors. This chapter emphasized the role of the basal ganglia in attention and action selection. Observations about movement from patients with Parkinson's and Huntington's disease were used to clarify the functions of the basal ganglia. These same mechanisms were applied to cognition and behavior in order to demonstrate that the basal ganglia perform the same functions for cognition that they perform for movement. The circuitry of the frontostriatal system was applied to a variety of practical behaviors and pathologies in order to illustrate the roles of this system in the ongoing interaction between stimulus-based responding and higher-order control.

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Chapter 3
Frontal–Subcortical Real Estate: Location, Location, Location

Not everything that can be counted counts, and not everything that counts can be counted.

Albert Einstein

The previous chapter described the functional neuroanatomy of the basal ganglia. This chapter describes the functions of the separate prototypical circuits that connect the basal ganglia with the cortex. It also describes the current role of neuropsychological testing in evaluating this circuitry. The original conceptualization of these cortical–subcortical loops consisted of five parallel, segregated circuits between the frontal cortex and the basal ganglia (Alexander, DeLong, & Strick, 1986). These circuits were the skeletomotor, oculomotor, dorsolateral prefrontal, orbitofrontal, and anterior cingulate circuits. However, it is now evident that the basal ganglia receive afferents from nearly all cortical regions while sending efferents back to the diverse thalamic nuclei that project to those same cortical areas (Middleton & Strick, 2002). The original conceptualization has thus been modified to include two additional circuits: the inferotemporal and posterior parietal loops. These two additional circuits will be discussed in the next chapter. This circuitry is depicted in Fig. 3.1.

All of these circuits can now be broadly classified into two different categories, specifically, anterior and posterior circuitries, although this represents our classification and not an established nomenclature. We justify this classification on the basis of a simple anatomic distinction. The central sulcus separates the anterior from the posterior regions of the brain. The frontal lobes and basal forebrain constitute anterior regions, and the temporal, parietal, and occipital lobes that are posterior to the central sulcus are considered posterior brain regions. Therefore, we call the inferotemporal and parietal loops posterior circuitries based upon their points of origin relative to the central sulcus. In any event, multiple closed loops connecting the basal ganglia with sensory and motor cortical regions characterize the interactions between the cerebral cortex and the basal ganglia. These additional "sensory" circuits further constitute "cortico-cortical" loops because the cortical points of origin of these circuits also project to frontal

L.F. Koziol, D.E. Budding, *Subcortical Structures and Cognition*,
DOI 10.1007/978-0-387-84868-6_3, © Springer Science+Business Media, LLC 2009

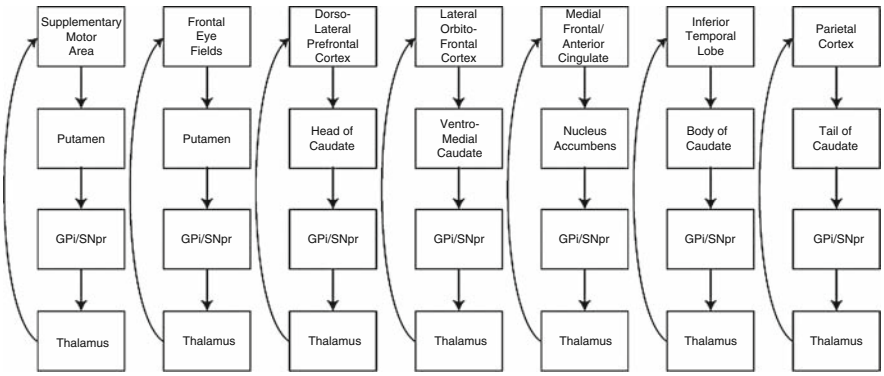

Fig. 3.1 Diagram of prototypical cortico-striatal–pallidal–thalamic circuits

brain regions. The cortical–subcortical loops of interaction form the anatomic substrate for the basal ganglia's roles in attentional and action selection. Understanding the functions of the regions of origin of these circuits provides an important key to understanding these behavioral selections.

Divisions of the Frontal Cortex and the Anterior Circuits

The frontal lobes can be divided into many regions. There are several different systems for classifying the various areas of the frontal lobes. A practical behavioral description of the frontal lobes divides regions according to function and comprises the motor, premotor, and supplementary motor corticies, as well as the frontal and supplementary eye fields. These regions are not believed to be primary participants in cognitive functions. Instead, these areas represent a substantial part of the frontal convexity that mediates motor functions. Therefore, much of the frontal lobe does not directly participate in cognitive activity. Anterior to these regions lies the prefrontal cortex (PFC). This region is often considered primary in mediating higher-order cognitive control. The PFC, like the frontal motor cortices, is not a monolithic or unitary entity. The prefrontal cortex is divided into three areas. These areas are the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC), and the anterior cingulate or medial frontal cortex (MFC). All of these regions feature points of origin in the segregated, parallel "looped" circuitry described in the previous chapter (Chow & Cummings, 2007). Focal impairment in these regions can generate very specific behavioral syndromes. Generally speaking, disrupting the circuit at any point within the loop will generate the cognitive or behavioral deficit specific to that particular circuit.

More recently, Ardila (2008) has divided the frontal lobes according to an alternative functional system. He proposes "metacognitive executive functions"

which include the classic cognitive control behaviors of problem solving, planning and strategy development, and working memory. These functions are primarily mediated by dorsolateral prefrontal circuitry and are the functions that are typically measured by neuropsychological tests of executive capacity. Second, he proposes "emotional/motivational executive functions" which he describes as responsible for coordinating cognition with emotion. These functions are mediated by the orbitofrontal and anterior cingulate/medial circuits, and are not easily measured by traditional neuropsychological and personality tests. All of these classification systems are well justified on the basis of anatomical and functional distinctions.

The Dorsolateral Prefrontal Circuit (DLPFC)

The DLPF circuit originates on the lateral surface/convexity of the prefrontal lobes. Neurons in this region project to the dorsolateral head of the caudate nucleus. Fibers from this region of the caudate project to the lateral aspect of the mediodorsal Gpi and to the rostrolateral SNpr as part of the direct pathway. The indirect route projects from the caudate to the dorsal Gpe, which projects to the lateral STN. Output of the DLPF circuit from the basal ganglia projects to the ventral anterior and to the mediodorsal thalamus. The circuit is closed by the mediodorsal thalamus projecting back to the region of origin of the circuit (Lichter & Cummings, 2001). This thalamic projection defines the prefrontal lobe (Fuster, 1997).

The DLPFC is responsible for executive cognitive activity. Executive function can be described as the capacity to generate adaptive behavior autonomously, in the absence of external direction, support, or guidance. The capacities necessary to accomplish the behavior include the ability to focus attention, inhibit inappropriate responses, to provide the working memory required for the frontal lobe's planning and organizational functions, and the actual programming of behaviors in order to solve problems that do not have an immediate, stimulus-based solution. When affect is disturbed in patients with damage to this circuit, the most common presentations are apathy and depression. *Most neuropsychological and cognitive tests access or go through this specific circuit* (Ardila, 2008; Malloy & Richardson, 2001; Stewart, 2006).

Lesions within the dorsolateral prefrontal circuit result in a presentation that typically includes deficits in attention. Attention needs to be conceptualized as a multiple component process in order to understand its role in the dysexecutive syndrome (Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991; Mirsky & Duncan, 2001). At its core, attention includes both perceptual and inhibitory processes—when one attends to one thing, one is refraining from attending to other things (Kinsbourne, 1993). From this perspective, attentional selection and inhibition can readily be seen as related functions. Attention is also characterized by an element of maintenance. Attention needs to be sustained for a

sufficient period of time in order to fulfill the goals of the organism. These dimensions have also been referred to as selective, intensive (maintenance), and exclusionary (inhibition) attention (Fuster, 1997). In the DLPF syndrome, attention is typically primarily disturbed within the dimensions of selection and maintenance. Patients demonstrating this syndrome often display a lack of interest—they can appear apathetic. This is because of their notable aspontaniety, not only cognitively but also motorically. This lack of initiation gives the impression that patients are apathetic or unconcerned. They are also often perseverative in their behavior because they have difficulty in shifting their attention and thinking from one thing to another.

The DLPF syndrome is further characterized by deficits in working memory, planning, and organization (Lichter & Cummings, 2001). These patients have trouble keeping several things in mind simultaneously and they have difficulty mentally manipulating and reorganizing information. In other words, they demonstrate a deficit in the ability to maintain information "online" and to sustain attention on internal representations or ideas. Planning functions are likely affected for multiple reasons. The aforementioned lack of interest and working memory deficits are contributing factors. These deficits can result in an inability to set goals, which in turn diminishes deliberate action, resulting in a lack of spontaneous initiation of activities. Patients with the dysexecutive syndrome can thus have great difficulty managing the cognitive activities necessary for autonomous daily living.

As the primary deficits demonstrated in DLPF syndrome are considered to be executive/cognitive, a variety of specific deficits are demonstrated on neuropsychological testing. Unlike the executive activities of daily living, the cognitive tests used to measure executive functions are inherently emotionally neutral (Ardila, 2008). People with deficits in executive functions generally perform poorly on formal tests of working memory that require the ability to hold several things in mind at one time and to mentally track test performance. Given the deficits in cognitive functions underlying working memory, it should not be surprising that neuropsychological tests requiring complex working memory functions such as repeating digits in reverse order of their presentation or Auditory Consonant Trigrams (ACT)/ the Brown-Peterson Technique (Lezak, Howieson, & Loring, 2004) are often performed poorly.

The ACT test requires the subject to keep information actively in mind while directing thinking towards some other activity and then recalling the status of the original information. This test has repeatedly been described as sensitive to frontal lobe/dorsolateral involvement (Kapur, Turner, & King, 1988; Leng & Parkin, 1989). Poor performance on this test is also reported among Parkinson's and Huntington's disease patients (Graceffa, Carlesimo, Peppe, & Caltagirone, 1999; Myers, 1983). This is significant because these patient populations demonstrate subcortical pathology, either directly or indirectly affecting the striatum. As pointed out by Mega and Cummings (2001) and Stewart (2006), similar cognitive and behavioral changes are observed with lesions of the dorsolateral prefrontal cortex and the subcortical

structures linked to this region, or from lesions in white matter tracts that essentially disconnect circuit members of the circuit.

Because planning and organizational functions are affected in the dysexecutive syndrome, patients often exhibit deficits when performing tasks that require the development of cognitive strategies to solve problems. These patients therefore often appear inflexible and perseverative in their behaviors. They are unproductive on tasks that require self-organization and self-generation of responses. They have difficulties on tasks that require the generation of multiple responses. Performances on rule-based category learning tasks such as the Wisconsin Card Sorting Test are often characterized by high rates of perseverative responding (Grafman, Jonas, & Salazar, 1990; Robinson, Heaton, Lehman, & Stilson, 1980). Perseverative responding on this test can result from difficulties with concept formation, problems incorporating new information in order to change thinking patterns which is essentially a problem with hypothesis generation, or because of insensitivity to feedback.

While Parkinson's disease patients with primary basal ganglia pathology perform poorly on this test (Owen et al., 1993), it has also been suggested that conventional "frontal" tasks correlate with both frontal lobe and parietal lobe function, so that posterior brain system involvement can contribute to executive dysfunction as well (Matsui et al., 2007).

Problems in mentally tracking performance on the WCST are often evidenced by failures to maintain cognitive set, which can be understood as either a failure in working memory or a susceptibility to distraction. In any event, performance deficits on the WCST do not appear to be specific to frontostriatal involvement, although impairment in frontostriatal function is perhaps the most common reason for poor performance.

Patients with dorsolateral prefrontal pathology also typically perform poorly on planning tasks such as the Tower of London or the Tower of Hanoi. In both of these tasks, the patient is required to look ahead to determine move order to solve the problems. However, the tasks do not measure identical skills (Goel & Grafman, 1995). The Tower of London emphasizes planning, while the Tower of Hanoi is weighted towards inhibiting prepotent or "obvious" responses. Nevertheless, both tasks do require planning, inhibition, and working memory functions, particularly as problems increase in level of difficulty. Frontal lobe patients generally perform poorly relative to normal controls on these tasks (Carlin et al., 2000; Shallice, 1982; Shallice & Burgess, 1991). These patient groups take more moves to solve problems, they use random or trial-and-error strategies, and they make more rule violations than normal controls in completing the tasks. Patients with basal ganglia pathology demonstrate similar performances (Dagher, Owen, Boecker, & Brooks, 1999, 2001; Middleton, 2003; Saint-Cyr & Taylor, 1992; Watkins et al., 2000). However, these are all multiple component tasks that require a variety of cognitive functions and multiple executive skills. In order to think ahead and solve the problems of these planning tasks, working memory, inhibition, and visuospatial skills are all necessary.

Within this population, speech fluency is very often diminished, and depending upon the location of the lesion when it occurs within the left hemisphere, expressive aphasic symptoms are usually evident. In this way, the DLPF syndrome can often include language disorder in its presentation. As might be expected, a lack of response productivity is often evident on tasks of verbal fluency, especially when retrieving words according to starting letter. This is because words are stored semantically, according to the meaning they convey or the way they are used, while retrieving words according to starting letter requires the generation of a novel response strategy. Language is essentially a categorizer, and letter-word fluency tasks by-pass this categorization function, requiring subjects to develop novel organizational and response strategies in order to be appropriately productive. However, it is not at all uncommon for DLFC lesions to generate diminished levels of productivity on all spontaneous fluency tasks.

While it has been reported that deficits in verbal fluency occur with left frontal lobe involvement (Butler, Rorsman, Hill, & Tuma, 1993), it has also been reported that patients with left DLFC and/or lesions within the striatum were the most impaired on letter fluency tasks (Stuss et al., 1998). Patients with basal ganglia pathology routinely demonstrate deficits on word retrieval tasks (Salmon & Chan, 1994). However, performance on word fluency tasks can also be affected by level of vocabulary. Comparable productivity deficiencies are observed on tasks of design fluency in patients with frontal involvement, particularly in the right hemisphere (Baldo, Shimamura, Delis, Kramer, & Kaplan, 2001).

Performance on tests of learning and memory is often impaired. On word list learning tasks, learning slopes are typically flat to shallow. This is generally due to difficulties in developing mental strategies to aid the learning process (Baldo, Delis, Kramer, & Shimamura, 2002). Voluntary or free recall is often incomplete, and voluntary delayed recall is often poor, but there is usually significant improvement in recognition conditions (Yener & Zaffos, 1999). This pattern shows that memory storage is intact but that there is a difficulty with the effortful reproduction of newly acquired material. The patient has difficulty in organizing the complex mental activity necessary for efficient memorization and recall. This pattern is also common in relation to subcortical dementias with primary basal ganglia pathology (Stewart, 2006).

Deficits in programming new motor movements or behaviors are also often evident. For example, deficits are reported in motor sequence learning. These patients have trouble in acquiring novel motor patterns or programs. They have trouble learning new motor sequences (Mega & Cummings, 2001). Deficits in learning motor programs that require bimanual coordination are very common. However, these deficits are not unique to damage to the dorsolateral prefrontal cortex. Deficits is motor sequence learning very commonly occur in patients with basal ganglia pathology. It has been demonstrated that lesions in those areas to which the dorsolateral prefrontal cortex projects generate impairment in sequence learning as well (Middleton, 2003).

While neuropsychology has a number of tests to identify, measure, and characterize executive function deficits, neuropsychological tests alone can generate false positive findings when the individual has instrumental cognitive impairment (Stuss, 2007).

Neuropsychological tests are often multifactorial or multiply determined. This means that language, memory, visual-perceptual-spatial, and praxic functions can potentially affect performance on the tasks used to evaluate executive cognitive functions. Therefore, making the inference of executive functioning deficit as a manifestation of dorsolateral frontal involvement requires that instrumental cognitive domains are intact. Many tasks require working memory, inhibition, planning, and shifting functions for successful performance on the specific single task, so that poor test performance does not necessarily identify or isolate the specific type of cognitive executive deficit.

For example, the WCST is a task that requires multiple aspects of executive skill. Prefrontal lesions as well as subcortical lesions such as involvement of the caudate nucleus can generate comparable if not identical test results (Cummings & Miller, 2007; Mega & Cummings, 2001). As noted previously as well, individuals with subcortical involvement routinely perform poorly on planning tasks, tests of working memory, category learning tasks, word list learning tasks, and motor programming tasks as subcortical pathology mimics the pattern of test performance seen in patients with prefrontal lesions (Cummings & Miller, 2007; Denckla & Reiss, 1997). Therefore, as is evident, cognitive and neuropsychological tests as generally used are often not sufficient for differential diagnostic purposes.

Orbitofrontal Circuit (OFC)

The OFC circuit has two divisions that can be thought of as two circuitries based upon their projection patterns. These are the lateral and medial divisions. The medial OFC originates in ventromedial prefrontal cortex and projects to the medial nucleus accumbens, ventral regions of the pallidum, and back to medialdorsal thalamus and medial OFC. This region of the OFC has reciprocal connections with the limbic system and insula. The medial OFC circuitry is believed to integrate and modulate visceral drives and the internal milieu (Lichter & Cummings, 2001). This circuitry is not directly assessed through neuropsychological and/or psychological testing. Aspects of this circuitry would be evaluated informally, through history and observation, in regards to alimentary, gustatory, and olfactory behavior. These functions could play roles in areas of adaptation more traditionally understood as related to personality functioning. Changes in eating patterns or in the sense of smell can betray involvement of medial circuitry. Personality changes include anergy and anhedonia (Mega & Cummings, 2001).

The lateral OFC also originates in the ventromedial prefrontal cortex, sending projections to the ventromedial striatum/caudate. This region projects to the most medial region of the mediodorsal Gpi and to rostromedial SNpr. The ventral anterior and mediodorsal are the thalamic targets which project back to OFC (Lichter & Cummings, 2001). Involvement of the lateral OFC circuit results in the "Phineas Gage" syndrome. The primary deficits are related to personality changes. These changes include disinhibition, impulsivity, irritability, and emotional lability. In terms of social behavior, tactlessness and undue familiarity are often described (Ardila, 2008; Chow & Cummings, 2007; Mega & Cummings, 2001). This circuitry is important for the temporal ordering of behavior in determining the proper time and place for expressing behaviors (Fuster, 1997). As a result, damage to this circuit often results in socially inappropriate behavior.

This circuit plays an important role in sustaining motivated behaviors in the absence of external cues or contingencies. It assists in allowing the individual to maintain behavior without immediate, tangible reinforcement, or environmental influence. It is involved in inhibiting responding to external distractions and other interfering influences. Therefore, attention is disturbed as manifest by impairment in inhibitory/exclusionary functions (Fuster, 1997). Deficits involving this region often result in social disinhibition and socially inappropriate behaviors because instincts are disinhibited. Patients with OFC involvement are often "stimulus bound." This has been termed the "environmental dependency syndrome" or "utilization behavior" (Lhermitte, Pillon, & Serdaru, 1986; Lhermitte, 1986). Involvement within this circuit is often broadly characterized by dysregulation of affect, judgment, and social behavior. The affective tone is often characterized by euphoria or mania (Cummings & Miller, 2007).

Few neuropsychological test measures of orbitofrontal functions in humans exist (Malloy & Richardson, 2001). Inferences about the integrity of this circuitry are frequently drawn from observation or report instead of from administering direct, interactive neuropsychological testing instruments that identify and quantify the deficit. Therefore, the methodologies for evaluating involvement of this region are vulnerable to all the biases that can affect self-report and observational report instruments.

Patients with focal OFC pathology can perform adequately on many neuropsychological tests since discrete lesions in this region do not necessarily affect cognitive function (Ardila, 2008). Some studies do report dysnomia in people with ventral/orbitofrontal pathology, and this has been linked to psychopathy as well (Lapierre, Braun, & Hodgins, 1995). When neuropsychological function is affected, it is likely the manifestation of deficits within mechanisms of inhibitory control. Although the functioning of this region is not easily measured through formal cognitive testing in a direct way, competing programs go-no go tasks have demonstrated utility in evaluating involvement of this region (Malloy & Richardson, 2001).

Certain types of continuous performance test (CPT) paradigms featuring alerting and target stimuli tax the inhibitory functions of this area, although

once again, deficits on these tasks can be observed in individuals with pathology in other frontal system regions as well, including the caudate nucleus (Hager et al., 1998). Sometimes patients with OFC pathology demonstrate vulnerability to interference on word list learning tasks, and this can be associated with difficulties in the temporal sequencing or ordering of newly presented material (Schnider & Gutbrod, 1999; Yener & Zaffos, 1999). All of these deficits do not occur in each and every patient with OFC involvement. Therefore, the absence of these findings does not rule out pathology of this area. By and large, the orbitofrontal syndrome is characterized by changes in personality functioning.

The deficits associated with involvement of this circuit emphasize the problems that traditional neuropsychology encounters in offering interpretations of behavior in the absence of obvious cognitive pathology on neuropsychological tests. When the presenting symptoms are related to personality functioning such as irritability, emotional lability, or social deficits, the inclination is to interpret the behavior within a strict "psychological" framework. The observations that are made about patients are attributed to psychological and emotional factors, instead of considering the behavior as a possible manifestation of a disturbance of OFC–subcortical circuitry. This can easily occur within the spectrum of developmental disorders such as obsessive-compulsive disorder and attention deficit disorder, which are essentially developmental disorders of the frontostriatal system (Bradshaw, 2001).

The Medial Frontal Circuit (MFC)/Anterior Cingulate Circuit

The medial frontal circuit originates in the anterior cingulate, which projects primarily to the nucleus accumbens and related regions of the ventral striatum, including the olfactory tubercle. These regions can be thought of as the "limbic striatum" (Heimer, Van Hoesen, Trimble, & Zahm, 2008). This circuit returns near its point of origin through the rostrolateral globus pallidus and the dorsomedial nucleus of the thalamus to the anterior cingulate area.

Involvement in this circuit is characterized primarily by apathy. Patients appear indifferent. They appear to lack interest, but these patients typically do not demonstrate the lack of motor spontaneity seen in dorsolateral patients (E. Goldberg, personal communication, 2008). The deficits are not primarily cognitive as they are in the dorsolateral syndrome. Involvement of the MFC circuit results in what is known as an amotivational syndrome. In its most extreme form, this is characterized by akinetic mutism (Mega & Cummings, 2001). Patients with this condition are literally mute and show no response to those stimuli that were previously sources of reward and reinforcement. In less extreme forms, spontaneous speech is diminished, verbalizations are brief, and there is little drive and motivation.

Because of these aspects of the presentation, cognitively capable patients with reasonably intact cognitive profiles can escape detection through traditional

neuropsychological tests, while the presenting difficulties might be attributed to "psychological" or "emotional" variables. This helps to foster the misleading notion that "cognitive" and "emotional" functions are separate, and that these problems with motivation and drive are not brain-related. In brain– behavior relationship reality, these types of "executive" deficits result from interactions between brain circuitries, although neuropsychological test psychometric "scores" are not particularly useful for identifying and characterizing these possible interactions. In this regard, deficits in executive functioning can and do occur for reasons other than cognitive pathology (Ardila, 2008; Chow & Cummings, 2007).

As indicated in Chapter 1, the nucleus accumbens is very old phylogenetically and it is one of the brain's important motivational centers. Perhaps this region underpins the simple notion that vertebrates are driven by seeking reward and avoiding pain, which is a topic that has interested psychologists, psychiatrists, and neurologists for centuries. Dopaminergic activity in the nucleus accumbens, particularly within the shell division, is associated with pleasurable feelings (Higgins & George, 2007). Addictive behaviors are conceptualized as manifestations of a lack of activity in this region (Bowirrat & Oscar-Berman, 2005; Koob & Le, 2008). Drugs of abuse like cocaine, alcohol, and nicotine all generate enhanced activity within the nucleus accumbens (Pizzagalli et al., 2008; Thomas, Kalivas, & Shaham,, 2008). Many people have difficulties with motivation as part of their clinical presentation. These problems can be manifest as lack of initiation, procrastination, lack of behavioral persistence, and/or lack of sustained interests.

Traditional clinical psychology often conceptualizes these issues with theoretical psychological explanations. However, these types of motivational problems can all be understood as manifestations of medial circuitry involvement (Delgado, 2007). There really are no neuropsychological tests specific to the problems of this circuitry, and in a neuropsychological test profile without cognitive pathology, it becomes tempting to dichotomize thinking and diagnostic formulations, viewing these motivational problems as resulting from "emotional" instead of neuroanatomic etiology. Certain data imply the IOWA Gambling Task might be of use in identifying pathology within this brain region (Nakaaki et al., 2007; Passetti, Clark, Mehta, Joyce, & King, 2008; Tanabe et al., 2007). Although this task is also multifactorial, is has been reported to identify pathology within medial/cingulate circuitry.

Patients with involvement in this region often demonstrate disinhibited responses on competing programs tasks, but just as with the orbitofrontal circuitries, involvement of this circuit can be elusive to direct measurement for identification and characterization. Observations of behavior represent one methodology that guides diagnostic considerations, and self-report is another method of assessment. The observational methodology, or indirect method of assessment, has never been a central focus of American neuropsychology which tends to focus upon formal test scores. In addition, self-report inventories are only as "good" as the subject's self-monitoring skills, so that when frontal

system pathology is part of the clinical presentation, this only adds to difficulties in diagnosing involvement of medial circuitry. An absence of positive findings on self-report inventories does not necessarily imply "psychological denial" as much as it reflects the lack of integrity of frontal system functions. On the other hand, concepts such as "denial" can lose their tinge of judgment if considered within the context of brain-related circuitry.

The Motor Circuits

The skeletomotor circuitries originate in the motor, premotor, supplementary motor, and somatosensory cortices. The circuitry passes through the putamen, through posterior and ventral regions of the pallidum, and on to the ventrolateral nucleus of the thalamus. The circuit then projects back to the supplementary motor cortex.

Involvement of this circuitry results in the classic symptoms of movement disorders. For example, the hypokinetic movement disorders are characterized by the akinesia and bradykinesia of Parkinsonian syndromes, while the chorea and release of fragments of purposeful movement sequences are seen in the hyperkinetic syndrome of Huntington's disease. Both of these disease processes provide important clues to one of the functions of the basal ganglia, since these disorders can be loosely characterized as disturbances in the voluntary control of movement. This characterization implies that intentionality is related to cortical–subcortical circuitry. However, at the cortical level, disturbances in the origins of this circuitry are manifest by deficits in motor programming. Unless a neuropsychological evaluation includes a comprehensive assessment of motor functioning, specifically examining the programming of new motor tasks, the intricacies of this circuit are neglected. This area of function is essential, because the motor circuitries are also involved in various procedural learning tasks. The acquisition of procedures and routines is absolutely critical to adaptation, yet this area of functioning is typically overlooked in traditional and contemporary neuropsychological assessment. This topic will be addressed in the following chapter.

Neuropsychology tends to parcel out and emphasize cognitive over motor functions. This is unfortunate, since an important feature of successful adaptation is the ability to learn and automate new behaviors. In fact, early motor development has been related to later cognitive development (Piek, Dawson, Smith, & Gasson, 2008; Sillitoe & Vogel, 2008; von Hofsten, 2007). Hallmark contributions of the frontostriatal system include determining the stimulus-based characteristics of novel situations and automating behaviors for future adaptation. Many clinical presentations, especially those found in developmental disorders, are characterized by difficulty or even an inability to learn a new "routine," which implies involvement of the instrumental or procedural learning system mediated by the frontostriatal axis. Automatic behaviors are often

considered non-cognitive, not higher-order, and, therefore, as non-essential. However, numerous cognitive and emotional predispositions are just as "automatic" as a motor routine or habit.

Automatic behavior is economical, it is elegant in that it is very efficient and reliable while requiring little if any conscious control, and it is qualitatively different than higher-order control in terms of processing characteristics (Saling & Phillips, 2007). Its elegance is observed in that it requires less brain activation, arguing for the efficiency of its representation (Poldrack et al., 2005). Automatic processing dependent upon basal ganglia systems has been demonstrated to operate within cognitive skills such as language and arithmetic computation (Saling & Phillips, 2007). Therefore, not all "cognitive" processing is always cortically mediated.

The frontal and supplementary eye fields are the regions of origin for the oculomotor circuits. These circuits pass through the striatum, primarily the putamen, and on to the substantia nigra pars reticulata, to thalamic nuclei, and then re-entering the respective frontal eye fields. Involvement in the circuitry results in problems in voluntary fixational control, abnormal saccades, and disturbances in visual search strategies. Again, little attention is paid to this regional and functional circuitry during the course of a routine neuropsychological evaluation. However, Malloy and Richardson (2001) have described methods for making inferences about the functioning of this circuitry. This circuitry would necessarily be recruited in the performance of planning tasks with a component of visual searching, so that deficits in the voluntary control of visual search strategies can impact performance on a variety of popular neuropsychological tests. For example, trailmaking test paradigms, cancellation tasks, judgment of line and angle orientation, navigating through mazes, and even complex pencil-and-paper copying tasks such as the Rey Complex Figure (Knight & Kaplan, 2003), all require systematic voluntary visual searching and sustained oculomotor control, so that voluntary oculomotor regulation can be expected to impact performance on these tasks. Similarly, involvement of this circuitry would by its nature affect the acquisition of skills in which procedural learning is required. Certain developmental disorders, such as attention deficit/hyperactivity disorder, also exhibit deficits in this circuitry (Feifel, Farber, Clementz, Perry, & nllo-Vento, 2004).

Motor, Cognitive, Motivational, and Affective Analogues

The circuits that were reviewed are all organized in parallel. This means that all of these circuits are organized in the same manner in which movement is organized. From this, we hypothesize that what the basal ganglia do for movement, they also do for cognition, emotion, and motivation. The basal ganglia are not really all about movement. Instead, the basal ganglia are about intention. Therefore, if we can understand how intention is manifest in movement,

we should be able to recognize or observe how disturbances in intention are manifest or expressed within the other parallel and segregated circuitries.

When the motor circuitries are involved in a disease process, the resultant movement disorders—or disorders of movement intention—can be ranked along a dimension of speed (Blumenfeld, 2002). Along this continuum, movements range from slow (bradykinesia/hypokinesia) to fast (myoclonus). The same concepts can be applied to cognition. Slowed cognition, frequently seen in patients with Parkinson's disease, is termed bradyphrenia. Fast cognition, for which we propose the term hyperphrenia, would refer to racing thoughts, which is observed in different psychiatric disorders. This could imply involvement of the dorsolateral circuit. This concept can also be applied to the medial circuit that regulates motivation. Lack of activity would be seen in an a-motivational syndrome in which nothing interests the patient. Excessive activity in this circuitry would be manifest by increased motivation and energy that also can be characteristic of manic or hypomanic patients (Mega & Cummings, 2001).

Finally, this continuum can be applied to emotional and/or social circuitries mediated by the orbitofrontal–subcortical circuits. Hypoactivity within an affective channel would result in lack of emotional responsiveness. When a more specific social circuit would be involved, we can imagine social withdrawal. Excessive activity within an emotional circuit would result in hyper-emotional responsiveness, or perhaps an embellishment of affect in response to what is pedestrian. Excessive activity within a social circuit might result in the behavior of the "social butterfly" in which social dependence might be the psychological observation. We can also imagine interactions of these circuits that would constitute an individual's predispositions or personality traits and characteristics.

We can also characterize these behaviors in terms of more specific disturbances in intention programs. We can think of intention programs as falling into four categories. These categories comprise:

1. Knowing when to start a behavior.
2. Knowing when not to start a behavior.
3. Knowing when to persist with a behavior.
4. Knowing when to stop a behavior.

Let's start with the concept of inability to start a movement. This easily translates to an inability to concentrate in order to start a cognitive activity when there is a disturbance within a dorsolateral circuit. An example of this would be the inability to retrieve words spontaneously, either in initiating conversation, in generating words on a fluency task, or in retrieving words on a word list learning task (see Chapter 8 for a description of this aspect of the functional neuroanatomy of the frontostriatal system). Translating this to an emotional circuit, one would find a difficulty or an inability to generate an emotional response to a situation. In a motivational circuit, there would be a lack of motivation or interest in an activity.

Knowing when not to start a movement is equivalent to a dyskinesia. We can place choreo-athetoid movements and tics in this category. In a cognitive circuit, this type of disinhibition might be manifest by blurting-out ideas or statements. It might also be manifest as the intrusion of irrelevant ideation or intrusive thoughts often observed in obsessive-compulsive disorder. In an emotional circuit, affective dyskinesia would look like sudden changes in mood or feeling, and even irritability. In a motivational circuit, this might be manifest by changes in interest levels in activity.

Within the motor realm, behavioral impersistence provides an example of not knowing when to persist with a behavior. We see this cognitively when people cannot maintain an idea or train of thought, which we describe as "distractible," and we can see this socially or interpersonally in superficiality in interpersonal relationships when ties with others are not maintained. Not knowing when to stop a behavior is also known as perseveration. In a cognitive circuit, this is manifest by repetitive ideation, thinking about the same thing, over and over again. In an affective circuit, this is seen as the inability to terminate an emotional reaction, being unable to "let go." In an interpersonal situation, perseveration would be observed as an inability to separate from another, as in a child with separation anxiety or school phobia.

Our purpose is not to examine every imaginable behavior or to force every behavior into the processes of the frontostriatal system. Rather, our point is to understand that motor behavior has cognitive, affective, and motivational predispositions and analogues. We believe that it is important to recognize behavioral observations and symptoms as potential products of the frontostriatal system and to recognize that circuitry interactions generate complex behavioral presentations. This assists us in understanding that what the basal ganglia do for movement, they also do for numerous other adaptive processes. We feel that this is an approach that should assist in both differential diagnosis and treatment formulation.

Frontal System Syndromes

These circuitries demonstrate that there is no one, single, "frontal lobe syndrome." Instead, there are frontal lobe syndromes. Each broad type of frontal lobe syndrome is characterized by the specific behavior patterns described above. Especially at the level of the cortical convexity, lesions can be very discrete and can result in distinct cognitive and behavioral presentations. However, it is not unusual for more than one circuit to be involved in a patient's presentation, and this is manifest by a mixture of behaviors that would characterize the functions of several circuits (Chow & Cummings, 2007; Malloy & Richardson, 2001). While more than one circuit can be involved in a patient's presentation, the functioning of every circuit cannot be approached through using the same assessment methodologies.

On the other hand, if dorsolateral pathology in particular is not involved, it can be very difficult and sometimes impossible to identify deficits upon

neuropsychological testing. When this occurs, a neuropsychologist might conclude that the patient's executive functioning is perfectly normal. This conclusion is not necessarily justified. Instead, it may very well be that the testing procedures did not tap those regions in which there was pathology. This fact contributes significantly to the problems with "ecological validity" noted in relation to neuropsychological evaluation (Odhuba, van, & Johns, 2005; Sbordone, 2001; Silver, 2000). Simply put, as they exist today, neuropsychological tests do not measure every possible brain-related function. In addition, an important principle of this circuitry concerns the fact that lesions in areas to which these circuits project have a strikingly similar (if not the same) observable presentation (Mega & Cummings, 2001). The psychometric properties of neuropsychological tests are simply not sensitive to making these differential localization discriminations. For example, lesions of the dorsolateral prefrontal cortex, a lesion within the dorsolateral head of the caudate, or a lesion in the medial dorsal region of the internal section of the globus pallidus can all generate a very similar symptom picture (Bombois et al., 2007; Cummings & Miller, 2007; Grau-Olivares, Bartres-Faz et al., 2007; Grau-Olivares, Arboix, Bartres-Faz, & Junque, 2007; Lee & Chui, 2007; Su, Chen, Kwan, Lin, & Guo, 2007). In this regard, single neuropsychological tests or even most test batteries are not sensitive to discriminating involvement at different levels of the circuitry. Similarly, simple behavioral observations might not be particularly discriminating in identifying the level of pathology in other related frontal–basal ganglionic circuits.

These frontal-basal ganglionic circuits are organized around different channels or modules of function. Despite the fact that these circuits originate in widespread regions of the frontal cortices, and project deep inside the basal forebrain to a spatially restricted region, the integrity and segregation of each of these circuits is maintained. However, because of the spatial extant of the convexity, lesions in very circumscribed cortical regions can result in very specific frontal lobe syndromes, with fairly well-delineated cognitive, affective, and behavioral manifestations. As lesions descend deeper into anterior brain regions towards the basal forebrain, however, the spatial constriction of the area increases the likelihood that one "lesion" would impact on more than one circuit. At this deeper level, behavioral manifestations become more mixed, with one lesion generating the effects and features of multiple circuitries (Su et al., 2007; Lee & Chui, 2007; Bombois et al., 2007). In fact, descending deep into the brain, it becomes difficult to imagine a single lesion impacting upon a single circuit only (Middleton, 2003). The involvement of multiple circuits, with mixed cognitive, affective, and motivational features becomes the rule rather than the exception because the spatial geography or territory is shared.

This fact becomes particularly important for understanding developmental and psychiatric disorders. Conditions such as attention deficit disorder, obsessive-compulsive disorder, Tourette's syndrome, autism, depression, and schizophrenia have all demonstrated neurologic and behavioral abnormalities characteristic of involvement of the frontostriatal system (Bradshaw, 2001).

All of these conditions present with cognitive and behavioral variability implicating the involvement of multiple circuitries, and all have proven vexing to neuropsychologists seeking to find common localizing "patterns" of test results based on traditional psychometric and cortico-centric approaches to neuropsychological evaluation and test data.

Another important point is that the behavioral symptoms of frontostriatal circuitry can interact. For example, a patient might have many cognitive complaints that are characteristic of the dysexecutive syndrome. These complaints might include problems with planning, difficulties with organization, and procrastination or trouble with initiation. A patient with these complaints can perform perfectly adequately on the appropriate neuropsychological tests that assess the integrity of dorsolateral frontostriatal circuitry. The complaints of executive function deficits can be a manifestation of compromised functioning within medial and/or orbitofrontal circuits. Apathy or diminished motivation as a result of a compromised reward center can easily result in behaviors that imply a lack of executive control. While this might not be detectable upon neuropsychological testing, it would be erroneous to conclude that the patient's problem was purely "psychological" or "emotional."

An example of the vulnerability of neuropsychological testing in cases that do not present with obvious cognitive pathology is presented in the following set of test results. These are from a standard flexible battery of tests that included Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983); the California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 2000); Wechsler Intelligence and Memory Tests (Wechsler, 1999; Wechsler, 2001); Rey Complex Figure Test and Recognition Trial (Meyers & Meyers, 1995); Tower of London (Culbertson & Zillmer, 2001); Personality Assessment Inventory (Morey, 1991); Stroop Color and Word Test (Golden, 1978); Wisconsin Card Sorting Technique (Heaton, Chelune, Talley, Kay, & Curtis, 1993); Gordon Diagnostic System (Gordon, 1983); Benton Finger Localization (Benton, Sivan, des Hamsher, Varney & Spreen, 1994); Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001); Grooved Pegboard (Trites, 1977); and Behavior Rating Inventory of Executive Function (Gioia, Isquith, Guy, & Kenworthy, 2000). Tests such as Auditory Consonant Trigrams (Brown-Peterson Technique) and Trail Making Tests are featured, with norms, in Spreen and Strauss (1998); Strauss, Sherman, & Spreen (2006), Table 3.1.

Table 3.1 Wechsler Abbreviated Scale of Intelligence (WASI)

Scale	Raw scale	T score	%ile rank	Qualitative description
Vocabulary	80	75	99	Very superior
Block design	70	69	97	Superior
Similarities	48	72	99	Very superior
Matrix reasoning	34	68	97	Superior
Sums of T scores	Verbal 147	Performance 137	4-Subtest 284	2-Subtest 143

Table 3.1 (Continued)

	Sum of T-scores	IQ	Percentile	90% confidence interval
Verbal	147	143	99.8	137–146
Performance	137	134	99	128–137
Full-4	284	144	99.8	140–147

California Verbal Learning Test-II (CVLT-II)

Subtest	Raw score	Z score
Trial 1	9	1
Trial 2	11	0.5
Trial 3	14	1
Trial 4	16	1.5
Trial 5	16	1
Total	66	64 T-Score
Interference	8	0.5
Short delay-free	16	1.5
Short delay-cued	15	1
Long delay-free	16	1.5
Long delay-cued	16	1
Recognition	16	0
Semantic cluster ratio	–0.4	–1
Serial clustering bidirectional	2.5	1.5
Learning slope	1.9	0.5

Wechsler Memory Scale-III Abbreviated (WMS-III)

	Raw score	Scaled score	Scaled score
Logical memory I	61	16	
Logical memory II	55		18

Rey Complex Figure Test (RCFT) >16 = Normal Range

Copy Trial:
Raw score = 35
%ile range = >16
Time to copy = 295 s: 6–10th %ile

Immediate recall	raw score = 30	T-score = 63	%ile score = 90
Delayed recall	Raw score = 29	T-score = 60	%ile score = 84
Recognition	Raw score = 24	T-score = 68	%ile score = 96
Recognition true pos.	Raw score = 12		%ile range = >16
Recognition false pos.	Raw score = 0		%ile range = >16
Recognition true neg.	Raw score = 12		%ile range = >16
Recognition false neg.	Raw score = 0		%ile range = >16

Wisconsin card sorting test

WCST scores	Raw scores	Standard scores	T scores	%iles
Trials administered	70			
Total correct	63			
Total errors	7	112	58	79%
% errors	10%	113	59	81%
Perseverative responses	4	114	59	82%
% perseverative responses	6%	113	59	81%
Perseverative errors	4	114	59	82%
% perseverative errors	6%	113	59	81%
Non-perseverative errors	3	110	57	75%
% Non-perseverative errors	4%	112	58	79%
Conceptual level responses	63			
% conceptual level responses	90%	114	59	82%
Categories completed	6			>16 = Normal
Trials to complete 1st category	11			>16 = Normal
Failure to maintain set	0			>16 = Normal
Learning to learn	0.15			>16 = Normal

Benton judgment of line orientation – Form H = 30 correct out of 30 100% superior range

Tower of London, 2nd edition – Adult record form		
Total sove score:	SS = 118	Raw score = 8
Total correct score:	SS = 122	Raw score = 8
Total rule violation score:	SS = 106	Raw score = 0
Total time violation score:	SS = 108	Raw score = 0
Total initiation time:	SS = 134	Raw score = 94
Total execution time:	SS = 94	Raw score = 210
Total problem-solving time:	SS = 78	Raw score = 404

Stroop color and Word test

Scale	Raw score	Predicted score	Residual	T-score
Word	132	109	23	66.1
Color	100	81	19	65.7
Color–Word	68	48	20	69.4
Interference	68	57	11	61.1

Lateralized sensorimotor/psychomotor comparisons Right-hand dominant

Grooved Pegboard
Dominant mean = 51 s
SS = 15; T = 61; above average
Non-dominant mean = 54 s
SS = 15; T = 61; above average
5.9% faster expected dom. hand

Finger localization test

	Dominant	Non-ominant
One finger (visible)	10/10	10/10
One finger (hidden)	10/10	10/10
Two finger (hidden)	10/10	10/10

Trail Making Tests (Heaton)

Trial A				
Raw score	Scaled score	T-score	Descriptive classification	Deficit
20	12	49	Average	0
Trail B				
17	19	78	Above average	0

Letter fluency—FAS

Raw score	Scaled score	T-score	Descriptive classification	Deficit score
Total correct				
54	14	56	Above average	

(Expanded norms: Heaton)

Category fluency

– Animals			
50	19	76	Above average

(Expanded norms: Heaton)

The Gordon diagnostic system

Vigilance tasks				
Summary data		Tracking data		
Total correct	30	00	19X	
Block 1 correct	10	00	XX9	Errors of commission
Omission	00	00	XX1	
Commission	00	00	X1X	
Block 2 correct	10	00	X9X	
Omission	00	00	XXX	
Commission	00	.50	Block 1	
Block 3 correct	10	.47	Block 2	Latency
Omission	00	.45	Block 3	
Commission	00	.47	Total	
Total omission:	000			
Total commission:	000 Normal			

Latency: block 1 = .50; block 2 = .47; block 3 = .45; total = .47 Vigilance = Mean latency (ms) = 382 (SD = 87.44)

Distractibility task

Summary data		Tracking data	
Total correct	29	00 19X	
Block 1 correct	10	00 XX9	Errors of commission
Omission	00	00 XX1	
Commission	00	00 X1X	
Block 2 correct	09	00 X9X	
Omission	01	00 XXX	
Commission	00	.47 Block 1	
Block 3 correct	10	.45 Block 2	Latency
Omission	00	.48 Block 3	
Commission	00	.47 Total	
Total omission: 001			
Total commission: 000 Normal			
Latency: block 1 = .47; block 2 = .45; block 3 = .48; total = .47			
Distractibility = mean latency(ms) = 405.08 (SD = 77.47)			

BRIEF-A	
	T-scores (percentile)
Inhibit	T40 (19th)
Shift	T47 (51st)
Emotional control	T38 (15th)
Self-monitor	T42 (31st)
Initiate	T66 (93rd)
Working memory	T46 (50th)
Plan organize	T62 (86th)
Task monitor	T63 (95th)
Organization of materials	T58 (82nd)
Metacognition index	T61 (83rd)
Global executive composite	T52 (56th)

Personality assessment inventory (PAI)

Validity			
	Raw score	T-score	%
ICN	5	49	100
INF	0	40	100
NIM	0	44	100
PIM	17	54	100

Full scales

Raw	T-score	%	Raw	T-score	%
SOM 0	39	100	ANX 5	39	100
ARD 18	48	100	DEP 3	38	100
MAN 20	47	100	PAR 16	47	100
SCZ 7	41	100	BOR 10	42	100
ANT 2	38	96	ALC 0	41	100
DRG 4	50	100	AGG 3	36	100

Table 3.1 (Continued)

SUI 0	43	100	STR 3	44	100
NON 0	37	100	RXR 5	31	100
DOM 11	33	92	WRM 27	56	100

The interpretation of this case can seem straightforward. This college-age female patient's scores on most cognitive tests are very strong. There is little test evidence of neuropsychological impairment, aside from initially slow and variable latency times on the GDS vigilance task. Variable reaction time has been associated with motivational deficits (Frank, Santamaria, O'Reilly, & Willcutt, 2007). List learning performance features a semantic clustering score that falls a full standard deviation below the mean, suggesting possible executive deficits and a passive approach to learning material. However, this patient presents with a variety of "executive-like" complaints which do not readily emerge from these neuropsychological test data. She complains of procrastination. She has difficulties in getting things started. In school, she cannot initiate projects. She typically puts things off to the last minute and then finds herself rushing through projects and assignments just to get things done. As a result, she is dissatisfied with her work product, and she believes that she does not work up to her potential. Her lifestyle is not extraordinary. She goes to class, she fills her free time in passive ways by watching television or reading about current events, and she occasionally socializes with friends and visits family. Her behavior does not stand out in any way. Although she enjoys her academic major, she continues to find it very difficult to initiate activities. She has no trouble in taking tests or in comprehending the content of her academic subjects.

It is tempting to interpret this patient's complaints and presentation as purely "psychological." However, her symptoms can also be understood a manifestation of executive dysfunction with symptoms that are the result of something other than cognitive factors. The clinical presentation can be understood as representative of dysfunctional medial circuitry. In this regard, the elevation on the Initiation and Planning/Organization scales of the BRIEF (Gioia et al., 2000) serve as "red flag" findings. This case demonstrates that prefrontal-subcortical circuitries can and do interact, and that executive-like deficits occur for other than purely cognitive reasons. Neuropsychological tests simply do not measure "everything" that might be relevant to a patient's presentation. This patient's complaints are actually chronic and have been characteristic throughout the course of her development. Her behaviors do not necessarily meet criteria for any particular DSM diagnosis aside from possible ADHD/Inattentive type, but she does not convincingly demonstrate "executive" deficits on cognitive tests. Nevertheless, she demonstrates a developmental disorder of the frontostriatal system, with an anatomic focus that is not easily identified through tests that primarily access dorsolateral channels.

Summary

This chapter described the anterior circuitries of the basal ganglia and cortex. Five prototypical frontal-basal ganglia circuits were defined, as well as their characteristic behavioral presentations. Neuropsychological testing primarily taps the dorsolateral-prefrontal cognitive circuit. While tasks that specifically access inhibitory control can be useful in detecting pathology within the orbitofrontal and medial–frontal circuits, pathology in these regions is most often inferred from behavioral observation. These circuits function interactively, so that neuropsychological test results need to be combined with history and behavioral observations for the purpose of clinically meaningful diagnostic evaluation. Neuropsychological testing has a "blind spot" since certain brain regions are not easily evaluated objectively by using traditional psychometric and cortico-centric methodologies.

It is important to frame behavioral observations in a neuroanatomic way. It can be very tempting to assume that a patient's problems are all "psychological" when the patient's cognitive profile appears to be intact. However, what the basal ganglia do for movement, they also do for cognition, affect, and motivation. It is important to frame patient complaints and to consider behavioral observations within the context of circuitry predispositions and analogues to movement. In this regard, the basal ganglia are not so much about movement as they are about motor, cognitive, emotional, and motivational *intention*. When certain circuitries are affected and others are spared, inconsistencies can be observed within the patient's pattern of presentation.

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Chapter 4
Learning and the Basal Ganglia: Benefiting from Action and Reinforcement

If you hold a cat by the tail you learn things you cannot learn any other way.

Mark Twain

Tell me and I'll forget; show me and I may remember; involve me and I'll understand.

Chinese Proverb

Many—if not most—of our daily activities should really be considered organized patterns of behavior that we implement in order to achieve specific goals. This would include activities such as hygiene, dressing, eating, and driving, and would encompass almost any behavior performed the same way every time it is performed because it accomplishes goals when interacting with a "predictable" environment. These are the things that "need" to be done, and in this regard, they are repetitive and predictable. The significance of these behaviors cannot be overemphasized because they are essential to adaptation. The fact that these behaviors are performed easily by most people does not mean that they are "mindless," or unimportant (Saling & Phillips, 2007). Instead, the ease with which they are performed by most people reveals that these behaviors are highly efficient. In fact, it is the inability to acquire and perform these habitual behaviors efficiently that often brings both children and adults to clinical attention. Impaired "activities of daily living" underpin many of our patients' presenting complaints and symptoms. Therefore, it is important to understand the neuroanatomy that drives these learning systems.

The basal ganglia are important for performing tasks automatically. Doing something automatically is typically associated with little need for conscious, effortful control over task performance. A working definition of "automaticity" is the ability to perform this primary task when it is not affected by the performance of some other task that is typically under conscious control. Thus, doing one thing while thinking about something different is a very broad example of automaticity. Others have referred to this type of multitasking as "threaded cognition," a cognitive resource mechanism that allows for the completion of simultaneous tasks without the need for specialized executive processes (Salvucci & Taatgen, 2008). Sequence, motor skill, and habit and categorization

L.F. Koziol, D.E. Budding, *Subcortical Structures and Cognition*,
DOI 10.1007/978-0-387-84868-6_4, © Springer Science+Business Media, LLC 2009

learning are types of instrumental, procedural learning tasks that are performed automatically once they are acquired. When a task is under conscious control, it is likely that prefrontal–subcortical circuits are always involved. However, as we learn procedures and engage in instrumental and procedural behaviors, the anatomical network changes within this circuitry. Different classes of tasks demonstrate different dynamic changes. This chapter reviews the various regions of the basal ganglia that are involved in different types of learning.

The Basal Ganglia and Learning

The executive, motor, inferotemporal, and posterior parietal circuits are involved in sequence learning, motor skill learning, habit learning, and category learning. Although these tasks have many things in common, they are not all equivalent. The basal ganglia are always recruited in the learning and performance of these types of tasks, although different tasks have different requirements, and, therefore, recruit somewhat different neuroanatomic networks (Poldrack et al., 2005; Saling & Phillips, 2007; Seger, 2008; Shohamy et al., 2004; Shohamy, Myers, Kalanithi, & Gluck, 2008).

Sequence learning can be defined as the learning or acquisition of a sequence of events over time (Seger, 2006). Learning different sequences can consist of cognitive or motor content, or even a combination of both. Learning sequences of behaviors is common to motor skill and habit learning. Therefore, even though it might seem overly simplistic, we will consider sequence learning and motor skill learning within the same over-arching category for general anatomic reasons. The neostriatum is activated during the learning and performance of these tasks (Dominey & Jeannerod, 1997; Knowlton, 2002). Sequence learning occurs incrementally. Acquisition occurs relatively slowly over multiple trials, in contrast to the very quick acquisition of the medial temporal lobe memory system. The individual learns a "habit" of responding in a certain way. In motor skill learning, the "habit" essentially comprises a sequence of movements. The "habit system" of the neostriatum appears to be specialized for gradual learning across many trials, as stimulus-response connections or associations are slowly formed. This type of learning is critical to adaptive functioning because it is involved in a wide range of activities.

This type of learning might be considered a form of instrumental conditioning. By instrumental conditioning, we mean that the behavior is performed because it works; it gets the job done. If the behavior got the job done before, it should get the job done again in the same or similar circumstances. For example, learning novel movement sequences in complex motor plans such as in manual occupations, sports, dance, and various routine and recreational activities all involve acquisition of new instrumental motor sequences. Many of the things that we do on a daily, routine basis can thus readily be recognized

as organized patterns of behavior rooted in sequence learning and instrumental conditioning. However, based upon this very broad definition, all instrumental learning is not alike.

Imaging studies have demonstrated that regions of the frontal lobes, the head of the caudate nucleus, and anterior regions of the putamen are activated during the course of sequence learning tasks. This implicates the executive and motor loops in the performance and acquisition of sequence learning tasks, including visuomotor learning tasks (Hazeltine, Poldrack, & Gabrieli, 2000; Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003; Loh, Pasupathy, Miller, & Deco, 2008). The prefrontal cortex is involved in the initial regulation, instead of direct participation in the execution of complex motor sequence tasks (Rao, Di et al., 2008). In addition, the striatum is also activated in motor skill and habit learning. Patients with Huntington's and Parkinson's diseases demonstrate impaired performance on these types of learning tasks, even when the motor response demands of the task have been minimized (Smith & McDowall, 2006).

It has been reported that when dopaminergic systems are dysfunctional within the basal ganglia, even cognitive sequence learning is affected, since stimulus-response associations are less efficiently acquired (Nagy et al., 2007). The basal ganglia appear to assist in the control of sequential or serial-order motor and cognitive learning through their unique looped connections with frontal cortices. The function of the basal ganglia appears to be to "chunk" together units of behavior or thought (Graybiel, 1998). The basal ganglia facilitate or promote the automated building-up of behavioral and cognitive units that need to be implemented in a particular temporal or sequential order (Bradshaw, 2001).

The development of motor skill automaticity features a dynamic neuroanatomy that changes over the time course of learning. Frontal, striatal, and parietal regions are activated during the initial performance of the sequential reaction time task (SRT). In this implicit learning task, subjects are required to quickly press a button when predetermined stimuli occur in a particular location. On some blocks of trials, the stimuli are presented in a particular sequence, while on other blocks of trials, the stimuli occur in a random order. Learning is measured by a decrease in reaction time. The supplementary area of the frontal cortex and the globus pallidus and putamen all demonstrate training-related decreases in reaction time, but for random trials, these decreases in activation as measured by fMRI are not observed (Poldrack et al., 2005).

These results provide direct evidence that these different brain regions are involved in the learning of motor sequence knowledge. The decrease in brain activity accompanying acquisition of the motor skill or sequence reveals that the representation within the brain becomes more efficient as automaticity occurs. The data also imply that higher-order control, which is initially required while learning a task, and automatic execution after task acquisition, are processed differently within the brain even though the task itself does not change and remains the same. These thus comprise different forms or types of

"information processing," and not just "faster" processing (Saling & Phillips, 2007).

In some ways, the anatomy of motor skill and sequence learning is analogous to conscious declarative learning and memory. For example, in declarative learning, the acquisition of information is dependent upon the hippocampus in a time-limited way. As information is stored over time in the distributed networks that were necessary to initially process the information, the resultant memory becomes independent of the hippocampal system (Squire, Stark, & Clark, 2004). In other words, declarative learning and memory represent a time dependent or changing neuroanatomy. Similarly, the acquisition of motor behaviors is mediated by a dynamically changing neuroanatomy. During the initial phases of the task, learning is dependent upon the dorsolateral prefrontal cortex and the head of the caudate, as well as the motor regions that are relevant for specific task performance. These specific motor cortical areas are the particular regions of supplementary motor and primary motor cortices that are necessary to perform the given task. Activation of the prefrontal anterior regions likely reflects the "executive" guidance necessary for the initial completion of the task. Practice is associated with automaticity, and this change is characterized by decreased activity within the PFC and caudate. The putamen and globus pallidus exhibit high activity initially, while training results in decreased activity for sequential trials but not for random or novel movement trials (Poldrack et al., 2005). However, the creation and maintenance of the longer-term motor representation requires at the very least continued contributions from both the motor and supplementary motor cortices (Doyon & Ungerleider, 2002).

In addition, both the striatum and hippocampus are important in procedural memory consolidation. Although the hippocampus does not appear to be involved in the initial learning of motor sequence tasks, over the longer period (24 h) a cooperative interaction is observed between these structures (Albouy et al., 2008). Therefore, the recruitment of various brain regions for motor skill and sequence acquisition is learning or time dependent across multiple practice trials, while later participation of the hippocampus is important for consolidation in order to optimize subsequent behavior.

This helps to explain why patients with basal ganglia disease do not "forget" how to perform previously acquired procedures. Instead, they have considerable difficulty in learning new procedures. After the procedure is acquired, it resides in supplementary and motor cortices. The basal ganglia seem to be necessary initially to "chunk" or "bind" the motor sequences and to later "select" them. The slowness that basal ganglia disease patients demonstrate in executing previously learned procedures has been interpreted as a manifestation of requiring more effortful control. In other words, the previously learned procedure is now being performed under cortical control, without the assistance of the basal ganglia. The basal ganglia are important for performing tasks automatically, and with basal ganglia impairment, tasks that were originally performed by habit must be performed in a deliberate fashion, under higher-order

cortical control (Knowlton, 2002). Motor skill and sequence learning are accompanied by a shift in brain activity as automaticity is achieved while slowness typically betrays higher-level cortical innervation.

In motor skill learning, the type of task to be acquired also greatly influences the pattern of brain activation. At the beginning stages of the learning process, motor tasks recruit the various motor cortical regions that are relevant for the task in addition to recruiting the striatum and the cerebellum. As the task becomes automatic, the representation of the acquired skill is distributed in a network of brain regions that involve either the cortico-striatal system or the cortico-cerebellar system. This shift in brain networks depends upon whether the task requires the acquisition of a new motor sequence or learning to adapt to environmental changes (Doyon et al., 2002; Doyon, Penhune, & Ungerleider, 2003; Doyon & Ungerleider, 2002). Implementing newly learned motor sequences recruits the cortico-striatal system. In an experimental paradigm, this would include the serial reaction time task described above. A task such as prism adaptation, in which an individual is required to adapt to wearing prism glasses and then must readjust his or her vision upon their removal, recruits the cortico-cerebellar system. Therefore, not all "skill" learning is alike.

The looped architecture of the basal ganglia (described in Chapter 2) is uniquely suited to learning the "timing" involved in the acquisition of motor sequences or the ordering of movements. The connections that project back to the same area of cortex from which they derived allow cortical–basal ganglia motor modules to perform serial order processing (Houk et al., 2007). We can imagine multiple cortico-striatal loops, firing in a sequential pattern, as mediating the movements necessary to perform a skilled motor task (Beiser & Houk, 1998). The amplification or refinement functions of the cerebellum (to be described in the next chapter) are suited to adapting to environmental perturbations (Houk et al., 2007).

The cerebellum functions to ensure "online" adaptation of behavior to a changing environment. This may explain why the cerebellum is always involved in at least the initial acquisition of motor learning tasks. Whenever a person is learning a new motor task, there is always some sort of accompanying adjustment to the environment. Although the independent functions of these motor learning systems can be investigated experimentally, nearly all real-world tasks require the interaction of both systems. In any case, these types of learning tasks are dependent upon subcortical systems. These types of learning also follow a time course. The initial phase of learning that involves executive control to guide the task comprises a slow acquisition phase. This is followed by a fast phase in which learning occurs quickly. For example, most improvement in skill acquisition is usually made during the course of the first practice session. Over a longer time period, with subsequent training sessions and consolidation in learning, additional improvement in learning occurs more slowly.

The Inferotemporal and Parietal Loops

In neuropsychiatry, most of the focus in evaluating cognition, emotion, and behavior has been placed on the five prefrontal–subcortical circuits (described in the previous chapter). The inferotemporal and parietal brain regions are primarily considered to provide sensory input to the frontal cortex, and particularly, to the dorsolateral prefrontal cortex for thinking and decision-making (Chow & Cummings, 2007; Mega & Cummings, 2001). This is how information about object identity and about object location arrives at the frontal lobes, providing prefrontal cortices the information it needs to think about.

When information to be thought about is retrieved by way of the medial temporal lobe memory system, this circuitry provides one of the avenues for this information to reach the prefrontal cortex. Therefore, this circuitry connects the frontal lobes with the rest of the brain. However, it is critical to understand that these posterior cortical regions also project to the basal ganglia (Seger, 2008). Information about object identity and about object location project directly to the striatum (Lawrence, 2000; Lawrence, Watkins, Sahakian, Hodges, & Robbins, 2000; Middleton & Strick, 1996, 2000). Thus, understanding this cortical–subcortical projection system is essential for understanding how the basal ganglia bias the frontal lobes in setting the context of an unfamiliar situation.

Information projected from these temporal and cortical regions to the basal ganglia is critical to the pattern recognition function of the striatum (see Chapter 2). Therefore, this is an essential "sensory nodule" in the striatum's ability to bias the frontal lobes, putting the prefrontal cortex "in the ballpark" for making hypotheses and decisions about problem solving. Just as importantly, this projection system plays a critical role in implicit and procedural learning. Circuits that project from temporal and parietal lobes to the basal ganglia are central to the brain's instrumental learning systems, allowing individuals to perform desired behaviors or to receive rewards (Seger, 2009). Procedural and instrumental behaviors are essential to adaptation and need to be recognized as aspects of executive function, since the "automatic" behaviors subserved by this circuitry act in the best interest of the organism and benefit the organism as a whole (Miller, 2008). As indicated, impairment in procedural or instrumental behaviors often brings a patient to clinical attention.

The inferotemporal and posterior parietal loops can be considered posterior circuitries because their points of origin lie posterior to the frontal lobes (see Chapter 3). Therefore, we have chosen to refer to this as the posterior anatomical circuitry system of the basal ganglia. While the temporal and parietal regions project to the body and tail of the caudate respectively, the temporal lobe cortex also projects to the ventrolateral prefrontal cortex and the parietal lobe also projects to the dorsolateral prefrontal cortex (Mega & Cummings, 2001). Therefore, these two posterior cortical regions project to

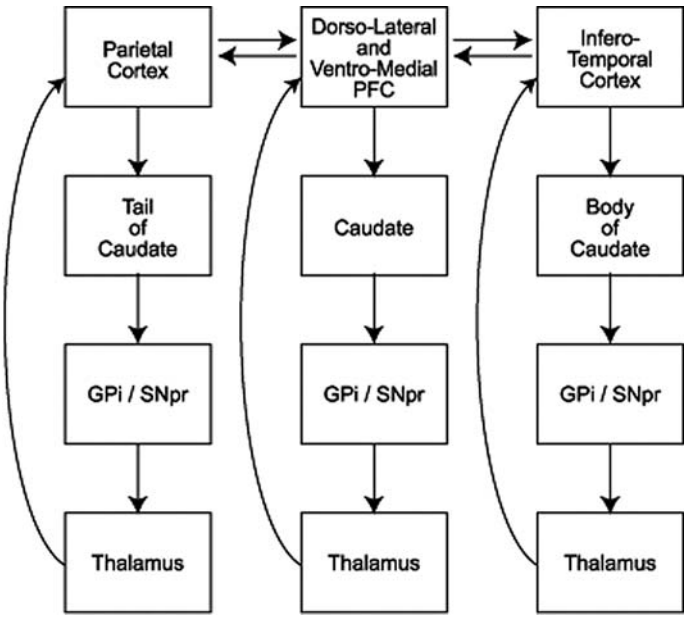

Fig. 4.1 Diagram of temporal and parietal lobe prefrontal and basal ganglia circuitries

the PFC in a cortico-cortical circuitry. In other words, the temporal and parietal points of origin project not only to the striatum, but also to the prefrontal cortex. Figure 4.1 depicts these anatomic relationships.

These posterior-prefrontal cortical projections are important for representations to be maintained in working memory (as described Chapter 2). In this regard, the parietal loop participates in the dorsolateral "executive" PFC circuit and the inferior temporal region participates in a ventrolateral "executive" PFC loop. These circuits can also be understood as participating in "metacognitive" and "emotional/motivational" executive functions, respectively (Ardila, 2008). In any case, these circuitries provide an anatomic substrate for interactions between executive, visual, and auditory systems. Similarly, this system of circuitry supports interactions between automatic processing and higher-order control.

Categorization and Classification

The ability to respond differently to objects or events that belong to separate classes or categories is termed categorization (Ashby & Ennis, 2006). This is an essential skill for adaptation and survival. For example, categorizing the environment as safe or dangerous, classifying a person as a friend or enemy, and classifying objects as edible or inedible are all necessary and fundamental skills

for successful adaptation and survival. This ability is really quite remarkable. For example, when we see a housecat, we immediately identify it as a "cat" and not a "tiger," even though there are notable perceptual similarities (with the exception of size). Further, we do not misidentify "wolf" when we see a "dog" or a "dog" when we see a "wolf," even though there are many visual-perceptual similarities that common sense might suggest would increase the probability of misclassification (Ashby, Ennis, & Spiering, 2007). Instead, a correct classification is instantaneous. The judgment or decision is made without conscious awareness of thinking. The evaluation is made very quickly and accurately.

These automatic evaluations would appear to extend to social cognition (see Chapter 6). We quickly make judgments about people. We sometimes do this on the basis of the way people "look," without further information. Often times, intuition or "hunch" seems to be involved, since we cannot easily verbalize a reason for the judgment. Social evaluations are often apprehended immediately, without any rational process or without any sense of higher-order conscious control. Our "scientific" intuition tells us that categorization of these types is a primitive skill that is phylogenetically very old. For instance, animals and certainly primates seem to make quick and accurate "category judgments" all the time, on a routine basis, which is of adaptive advantage and is necessary for survival. In this regard, perhaps it is not surprising that categorization ability is found in the basal ganglia, given the evolutionary age of this brain region (Ashby & Ennis, 2006; Lieberman, 2000).

In addition, these facts suggest a need for rethinking our definitions of executive functions. These categorical evaluations might not be under higher-order conscious control, but they clearly represent an "executive" decision that once again benefits the whole organism in successful adaptation. This also makes sense from an evolutionary point of view. A broader conceptualization of executive decision-making includes a division between "metacognitive executive functions" and "emotional/motivational executive functions" as proposed by Ardila (2008). This division allows for biological consistency in viewing "executive" functions throughout the phylogenetic scale, while allowing for interactions between higher-order control and automatic processing, which is one of the themes of this book.

In any event, experimental data in rodents and monkeys demonstrate that the tail of the caudate nucleus is necessary and sufficient for visual discrimination learning. This is very significant because discrimination learning is essentially categorization. A series of studies (reviewed by Ashby & Ennis, 2006; and Seger, 2008) have established the adequacy or sufficiency of the caudate nucleus for visual discrimination learning. All pathways out of the visual cortex were lesioned, including projections into the prefrontal cortex, leaving intact only those pathways that project to the tail of the caudate. Projections into the hippocampus and amygdala were also lesioned. These extensive lesions did not impair visual discrimination learning. Therefore, all visual discrimination learning or "judgments" do not appear to be mediated by the medial temporal lobe system or by the frontal lobes. Once again, this fact provides

an anatomic underpinning for the striatum's sensitivity to context. In addition, fMRI studies with humans routinely reveal activity within the body and the tail of the caudate nucleus during visual categorization tasks (Seger & Cincotta, 2006, 2005). These data give evidence that "executive" judgments can be made automatically.

The human brain has multiple and flexible coding mechanisms for making categorical decisions and judgments. A large network of cortical and subcortical areas process information about visual categories (Li, Ostwald, Giese, & Kourtzi, 2007). At the cortical level, temporal lobe regions are particularly sensitive to perceived form. Parietal regions are more sensitive to similarity in motion. Frontal brain regions and the striatum are critical for complex categorization tasks, and through the circuitry described above, modulate selections in temporal and parietal areas, therefore making "executive" judgments.

Not all complex category learning tasks are the same, and several different types of tasks have been identified in the literature (Ashby & O'Brien, 2005). In unstructured category learning tasks, the category exemplars lack any coherent relationship or structure that can be discovered. Unstructured categories such as "my passwords" or "my important phone numbers" are primarily acquired through explicit memorization. This type of associative learning is dependent upon interactions between cortex and the hippocampal system (Squire, Clark, & Bayley, 2004). This learning is accomplished through activation of the medial temporal lobe system. However, certain types of categorization tasks routinely recruit the basal ganglia. These tasks might be termed basal ganglia dependent, but this does not mean that the performance of these tasks relies solely on the basal ganglia (Seger, 2009). Just as in motor learning and sequence acquisition tasks, the basal ganglia interact with other brain regions in the performance of the categorization behavior. This is analogous to cortex interacting with medial temporal lobe structures within the declarative memory system.

One type of categorization task is probabilistic learning. The weather prediction task is a primary example (Knowlton, Squire, & Gluck, 1994). In this task, geometric shapes are printed on each stimulus card. On each trial, one to three cards are presented simultaneously, and the subject is required to guess if the outcome will be sunny or rainy weather. Each card is associated with one of these outcomes between 60 and 80 percent of the time. In the performance of this task, subjects feel they are guessing. Nevertheless, with trial-by-trial feedback, subjects gradually learn to select the most associated outcome for each combination of cards over all the trials. Other tasks of this type present a subject with abstract shapes (printed on cards) that cannot be verbalized while associating these stimuli with positive or negative reward a certain percentage of the time across many trials. These types of "guessing" or "intuition" tasks recruit the caudate nucleus, while the tail of the caudate is considered essential for optimal reward performance.

These probabilistic learning/decision-making tasks have been developed and employed to demonstrate specialization and dissociations between positive and negative reinforcement within the striatum (Frank, Seeberger, & O'Reilly,

2004; Frank, Samanta, Moustafa, & Sherman, 20072007; Frank & Claus, 2007). Other paradigms include the provision of reward incentives in card games, such as the Iowa Gambling Task or other video-based gambling tasks (Kobayakawa, Koyama, Mimura, & Kawamura, 2008; Perretta, Pari, & Beninger, 2005). These types of gambling tasks also recruit medial-frontal circuitry, including the ventral striatum/nucleus accumbens region. These brain regions represent one of the brain's experiential reward centers (Clark et al., 2008; Delgado, 2007; Dillon et al., 2008).

In information-integration learning tasks, maximum accuracy in performance requires the integration of information from at least two stimulus dimensions. However, the optimal strategy for successful performance is difficult or impossible to describe verbally. This task, like probabilistic category learning, is an implicit learning task. Learning is measured by gradually improved performance after trial-by-trial informational feedback. Information-integration learning presumably underlies experiential learning, a type of procedural learning (Ashby & Ennis, 2006; Poldrack & Foerde, 2008). Real-world examples of information-integration tasks are the seasoned and expert physician who makes an extremely accurate diagnosis but who is only partially able to describe the reasons for the conclusion because it was based upon "experience," or the expert radiologist who is only partially successful at explaining his/her categorization strategy in describing why an ambiguous radiologic image really is or is not a tumor (Ashby & Ennis, 2006).

These are clearly examples of "executive" ability, although experience seems to provide the basis for intuition contributing to that skill. These types of experiential learning skills can be dissociated from higher-order control processes. For example, in one case study, a physiotherapist who became severely amnestic as a result of herpes simplex viral encephalitis demonstrated relative sparing of implicit memory related to professional skills, while lacking the higher-order control processes necessary for flexible professional performance (Geffen, Isles, Preece, & Geffen, 2008). In any event, both probabilistic and information-integration tasks recruit the caudate and appear to be more specifically dependent upon the tail of the caudate nucleus for successful learning (Maddox, Ashby, & Bohil, 2003; Maddox, Ashby, Ing, & Pickering, 2004; Maddox, Bohil, & Ing, 2004).

In rule-based categorization tasks, the categories can be learned through an explicit reasoning process. An example of this type of task is the Wisconsin Card Sorting Test (WCST), in which the task is to sort cards according to the verbalizable dimensions or "rules" of color, form, and number. Positive or negative feedback is given after each trial to guide hypothesis testing. All of these categorization tasks that recruit the basal ganglia are characterized by three features (Seger, 2009). First, the individual is presented with a stimulus, second, the subject generates a response, and third, the subject receives information or feedback about the response being right or wrong. These three features of tasks are critical in recruiting the basal ganglia. Therefore, the provision of positive or negative reinforcement is important for activating the basal

ganglia in learning (Shohamy et al., 2004, 2008). This is consistent with the basal ganglia's sensitivity to context. In other words, the basal ganglia are sensitive to the reward characteristics of the environment.

Because the WCST is highly multi-factorial, simplified versions of this type of task are utilized in experimental studies. These studies attempt to isolate how specific regions of the basal ganglia might be specialized to perform specific roles in the process of categorization. Usually a single rule runs across the whole experimental task session. Studies have also been done that require subjects to learn different rules across groups of a number of trials. In this experimental paradigm, subjects see stimuli from one stimulus set and learn the rule for that set. Then, in a subsequent trial, subjects see stimuli from a new stimulus set and are required to learn a new rule for that set. In this way, the subjects are required to learn a new rule, but this is not the same type of switching or "shifting" that is an inherent feature of the WCST.

These types of experimental studies reveal a functional specialization of striatal regions during rule-based, explicit category learning. Various regions of the striatum are differentially activated over the time course of this type of learning, revealing a dynamically changing neuroanatomy. This neuroanatomy also includes interactions between the striatum and the cortex. An fMRI study has demonstrated that activity within the striatum precedes activity within frontal areas (Seger & Cincotta, 2006). With the presentation of each new stimulus categorization problem, activity within the head of the caudate rose quickly in the performance of the task, peaked early, and declined rapidly. Prefrontal lobe activity peaked significantly later and declined gradually over the course of the completion of the task. The body and the tail of the caudate were active during rule learning, while the highest levels of activity within these two regions of the caudate were evident with successful categorization. The body and tail of the caudate were the only regions that exhibited increased activity for fast rule learners as compared to slow rule-learners (Cincotta & Seger, 2007; Seger, 2006, 2008; Seger & Cincotta, 2005, 2006). Activity within the premotor cortex and putamen increases as task proficiency is achieved (Brasted & Wise, 2004). When subjects are required to "switch" to a new rule, basal ganglia activity again changes to the ventral striatum and head of the caudate nucleus.

The time course of rule-based category learning seems to consist of three phases, specifically, a starting phase in which the subject must first "guess" about category representation, a second learning phase which is governed by processing feedback which guides hypotheses generation, and a third phase which is characterized by automaticity. The authors (Seger & Cincotta, 2006) interepreted the dynamic fMRI findings as supporting the conclusion that the striatum is important for recognizing behavioral context and modulating cortical activity, placing the prefrontal cortex "in the ballpark" for developing appropriate problem-solving strategies. Therefore, the head of the caudate, which is an integral node of the dorsolateral loop, plays an important role in

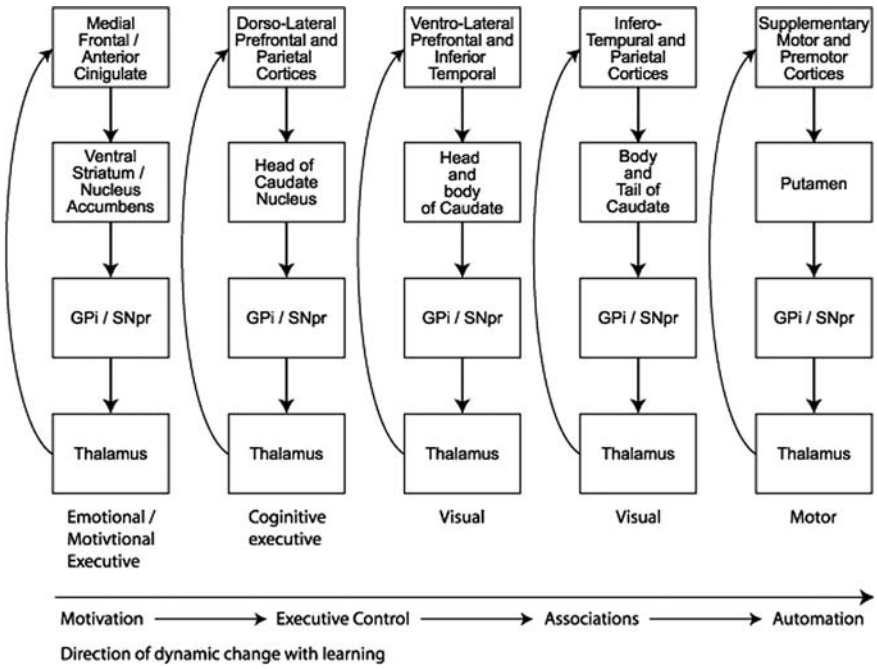

Fig. 4.2 Diagram of the direction of dynamic anatomic change during category learning, after Seger, 2008.

the initial "executive" phase of the learning task. The visual, inferotemporal and parietal loops are recruited during correct classification. As automaticity occurs, links between the visual and motor loops are established and activated, so that visual representations directly guide motor response. These anatomic relationships are depicted in Fig. 4.2.

Taken together, the data reveal a shift from the executive/visual interactive corticostriatal loops to the motor loop across the time course of learning. There are patterns of interaction between corticostriatal loops. This pattern follows a gradient from ventral, anterior, and medial regions (typically nucleus accumbens/ventral striatum) out to the most superior, posterior, and lateral portions (putamen). The visual loop is in the middle of the dynamically changing gradient. The visual loop receives feed forward information from motivational and executive loops, and it projects information to the motor loop. This anatomic "shift" to the motor loop is also observed in the sequence learning described above. Similarly, the data demonstrate interactions between the executive loop and the motor loop. The executive loop is involved in acquisition. The motor loop is involved in skilled execution. In these ways, sequence learning and categorization share a similar "procedural learning" anatomy. This subcortical anatomy has implications for executive functioning. This anatomy would appear to represent the neurologic substrate

for aspects of "emotional/motivational executive functions," the terminology applied by Ardila (2008).

The different basal ganglia category learning tasks described above also differ with regard to the timing of feedback. The critical feature of "timing" in rule-based category learning tasks relates to feedback being provided after each and every trial, although the timing of the feedback need not be immediate. This allows the explicit, executive system to decide if the current rule is correct, to hypothesize about and select a new rule if this is necessary based upon the feedback that was provided, and to then change the focus of attention and behavior to the new rule. This obviously implies conscious cognitive, executive input. In procedural and implicit probabilistic learning, timing is very sensitive and feedback needs to be delivered immediately following the response. This is because learning in the instrumental system is automatic. Time is not necessary to cognitively "process" the feedback or reinforcement signal. Instead, when a correct response is given, the appropriate synapses are automatically strengthened by the dopaminergic reward system. This is accomplished without conscious mediation. The individual essentially learns a "habit" of responding in a certain way because that behavior "worked," and was given a reward. This is the most basic type of instrumental conditioning in which learning is demonstrated through improved performance.

Improved performance is experience based, although this learning and performance is not necessarily accessible through conscious mediation or awareness. In fact, it has been suggested that the hippocampal learning and memory system might actually operate antagonistically with the striatal learning system during the course of acquisition on implicit learning tasks (Seger & Cincotta, 2006). Competition appears to exist between the implicit and explicit memory systems in learning. For example, severity of explicit memory impairment in Alzheimer's disease actually improves effectiveness of implicit learning in that condition (Klimkowicz-Mrowiec, Slowik, Krzywoszanski, Herzog-Krzywoszanska, & Szczudlik, 2008). While the striatum and hippocampus interact cooperatively in the consolidation of motor sequence learning (Albouy et al., 2008), it is not known whether or not a similar interaction occurs over a longer (24 h) period of time in category learning.

Differences are also observed between rule-based category learning and information-integration category learning dependent upon minimal versus full feedback. In minimal feedback conditions, subjects are given information only about whether their response was right or wrong. In full feedback conditions, subjects are told not only if their response was right or wrong, but they are also told correct category membership. Full feedback clearly facilitates rule-based category learning while it actually interferes with information-integration learning (Maddox, Love, Glass, & Filoteo, 2008). Therefore, the different types of category learning tasks are dissociable and dependent upon different learning systems.

Positive and Negative Reinforcement Learning

According to learning theory, positive reinforcement increases the likelihood of a behavior occurring in the future. Negative reinforcement decreases the likelihood of a behavior occurring under similar stimulus circumstances that initially evoked the behavior. But in "real life," it does not always work that way. Do positive and negative feedback have the same valence or meaning for the brain? We all know of people who seem dependent upon positive rewards. In fact, in pathological gambling, people will literally risk everything they have for the chance of receiving a positive reward. The chance of negative outcome or reward seems to mean little to them in the sense that it does not guide behavior. We also know people who will work significantly harder to avoid a negative outcome than they will work to increase their opportunity for a positive reward. In fact, some people seem driven by avoiding negative outcomes, while positive reward means little if anything to them because it does not seem to guide behavior.

In patient populations, children with Attention Deficit Hyperactivity Disorder (ADHD) are sometimes described as insensitive to rewards (Quay, 1998). Parents of these children report that their children do not seem to care if their behavior is reinforced positively or negatively. Sometimes rewards just do not seem to work at all. Why might these apparent reward preferences and contradictions exist? It is tempting to explain these preferences and differences on the basis of traditional psychological theories. However, we believe that the answers to these questions lie in the nature of the dopamine reward system which mediates or governs cortico-striatal reinforcement learning. The basal ganglia function as a reinforcement learning system (Doya, 1999).

There is absolutely no question that the role of dopamine within the prefrontal cortex and within the basal ganglia, is extremely complicated (Bonci & Jones, 2007). This is not a book about neurotransmitters or about psychopharmacology. This is not a book that addresses the neurochemical basis of learning and memory. However, we will introduce a few basic concepts. Within the brain, positive and negative reinforcement are not the same. This has implications for understanding instrumental learning, decision-making, and behavior, which certainly are some of the themes of this book.

The highest concentrations of dopamine within the brain are found in the basal ganglia and the prefrontal cortex. The nigrostriatal system is the source of dopaminergic input into the striatum (the caudate and the putamen). The ventral tegmental region is the source of two projection systems. The mesolimbic division primarily projects dopamine neurons to the nucleus accumbens—and to the olfactory tubercle, the septum, and the amygdala (Bonci & Jones, 2007). The mesocortical dopamine projections are mainly to the frontal cortices and the perirhinal cortex. These systems are illustrated in Fig. 4.3.

This extensive dopaminergic projection system is a critical reward circuitry. It has been hypothesized that the prefrontal cortex codes for the anticipation of

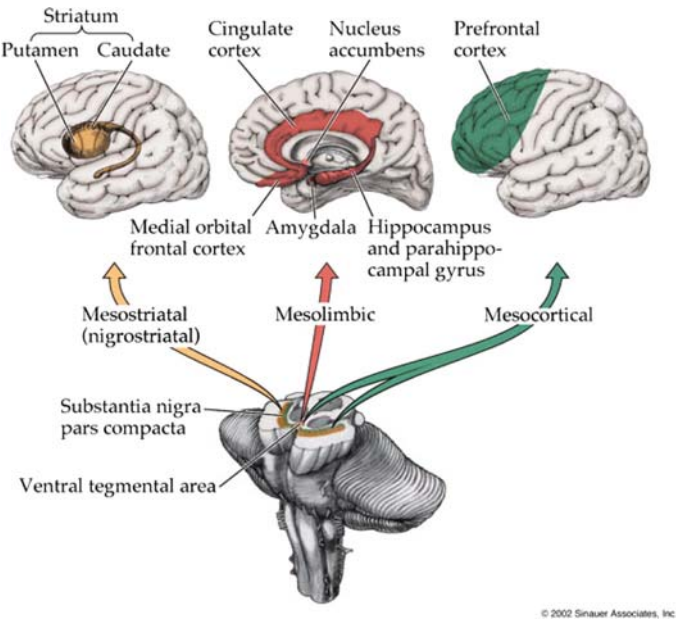

Fig. 4.3 Illustration of dopaminergic projection systems, reprinted by permission of Sinauer Associates, Inc., 2002.

reward, driving reward-seeking behavior. These specific circuitries include the anterior cingulate/ventral striatal regions. The orbitofrontal and medial frontal cortex projection systems are parts of the brain's circuitries related to certain types of *consummatory* reward or reinforcement. These regions become active with the actual enjoyment the individual receives (Dillon et al., 2008). The ventral striatum becomes highly active with the *anticipation* of reward, especially under conditions of high certainty, and remains active during periods of consumption (Heekeren et al., 2007). This "extended" basal forebrain region is extremely rich in dopamine (Heimer et al., 1997; Heimer, Van Hoesen, Trimble, & Zahm, 2008; Robbins & Everett, 2003). This system is believed to regulate a diverse set of behaviors, ranging from the control of movement to the modulation of desire, motivation and cognition (Sillitoe & Vogel, 2008). This system governs attention, different aspects of reward, mood, and certain appetitive drives. Disturbances within this system are associated with a wide variety of psychiatric and behavioral problems, from addiction to schizophrenia, and almost all disorders "in between."

What does this have to do with positive and negative reinforcement? The study of motivated behavior is an extremely complex topic. There are multiple reward centers mediating different types of behaviors. However, motivated behavior is controlled in part by learning (Robbins & Everett, 2003). Within the striatum, learning is mediated by dopamine. Dopamine acting on medium spiny neurons enhances or facilitates transmission along the direct

pathway (see Chapter 2). Dopamine receptors within this pathway are called D1 receptors. Dopaminergic activity within this pathway reduces the inhibitory output of the Gpi. This releases or increases thalamocortical output. This makes cortex active and generates behavior. In instrumental learning terms, this means a behavior is more likely to occur. This can be called a positive feedback effect within the striatum.

Dopamine inhibits neurotransmission within the indirect pathway. Dopamine receptors within this pathway are called D2 receptors. The indirect pathway acts as a "brake." Within this pathway, dopamine aids in releasing the brake, allowing the direct pathway to exert more influence over Gpi output. Therefore, dopaminergic activity has the overall effect of releasing behavior. Increases or "bursts" in dopaminergic activity should facilitate positive reinforcement learning (Frank, 2005).

Dopamine depletion has opposite effects. Decreased levels of dopamine increase neurotransmission within the indirect pathway, therefore increasing the inhibitory output of the Gpi, with the result of reducing or suppressing thalamocortical output. Without sufficient dopaminergic release within the direct pathway, the behavioral system is in a state of inactivity because the active indirect pathway results in excessive cortical inhibition. This suppresses behavior. In instrumental learning terms, this makes a behavior less likely to occur. Activity within the indirect pathway can be termed a negative feedback effect within the striatum (Frank et al., 2004) (see Chapter 2 for an explanation of the behavioral mechanisms associated the direct and indirect pathways.). Therefore, "dips" in dopaminergic activity should result in negative reinforcement learning. The behavior that was negatively reinforced should be avoided in the future. Learning, avoidance, and the extinction of responses all appear to be dependent upon dopaminergic activity (Sil'kis, 2008).

It can be hypothesized that every individual has a baseline level of dopamine within the dopaminergic system. This is called a "tonic" dopamine level. Based upon various biologic factors and neurochemical predispositions, this tonic level can be different from person to person. These tonic levels of dopamine can also be altered by "disease" processes such as Parkinson's disease and attention deficit disorder, to name just two conditions. There are also changes in dopamine levels based upon experiences that result from interacting with the environment. These are called "phasic" changes in dopamine levels. Certain interactions with the environment (positively rewarding experiences) result in phasic increases, "bursts" or "spikes" of activity above baseline levels, while other experiences (negatively reinforcing experiences) are associated with phasic decreases from tonic levels, called "dips" in activity below baseline levels (Niv, 2007). When the individual experiences an unanticipated reward, a phasic dopamine increase occurs. As a result of this "spike" or "burst" in activity, the individual learns about the behavior that led to the reinforcement. That behavior is more likely to occur in the future, under similar circumstances. However, when an expected or predicted reward is omitted or when it is negatively reinforced, there is a phasic "dip" in dopamine levels. As a result of this phasic

decrease, the behavior is avoided in the future. It drops out, or is extinguished (Pizzagalli et al., 2008). Positive reinforcement is associated with increases in dopaminergic activity and negative reinforcement is associated with "dips" in dopaminergic activity. In other words, dopamine "bursts" would increase synaptic plasticity within the direct pathway and decrease synaptic plasticity in the indirect pathway. In effect, this releases the "brake." This should support learning that reinforces a good choice. However, "dips" in dopamine would have the *opposite effect*, and this would underlie learning to avoid a bad choice. The individual learns to apply the "brake" (Frank et al., 2004.)

When a person is acquiring an instrumental behavior, positive feedback results in a dopaminergic "spike," "burst," or increase within the direct pathways relevant for the behavior in question. How does this happen? As might be recalled from Chapter 2, the striosomal pathway projects from paralimbic regions to the SNpc. These paralimbic regions are providing the SNpc with input of motivational significance. The SNpc, a dopamine systhesizing region, is therefore receiving information about the reward value of stimuli and about responses that are to be integrated within the basal ganglia. In other words, this pathway provides the basal ganglia with information of motivational importance. In circumstances with positive reinforcement, the SNpc sends a dopaminergic "burst" to the striatum to strengthen the synaptic connection. So the person "learns" the proper behavior, or more precisely, the correct behavioral sequences. Dopamine activity produces a positive feedback effect within the direct pathway. With repetition, this presumably strengthens synapses within the direct pathways responsible for that behavior. As a result, the individual acquires an instrumental behavior. This can be termed reward-driven association learning.

External positive reinforcement generates a dopamine "spike" in striatal activity and this facilitates learning in response to "good" choices. Negative feedback from the external environment generates a "dip" or decline in dopaminergic activity. Therefore, with negative feedback the individual learns to avoid the "bad" choice. Hypothetically, the direct and indirect pathways operate in balance, but in certain disorders and diseases, the two striatal pathways do not operate in concert, and when this occurs, differences are seen in instrumental learning in response to external positive and negative reinforcement effects (Frank, Scheres, & Sherman, 2007; Frank & O'Reilly, 2006). Thus, it could be theorized that if an expected response to a behavior occurs, even if not expressly "pleasant," this would lead to instrumental reinforcement.

Parkinson's disease is characterized by dopamine depletion, particularly within the direct pathway. Un-medicated Parkinson's disease patients have difficulty learning positive associations mediated by external rewards on probabilistic learning tasks. This presumably occurs because there is a lack of dopaminergic activity within the direct pathway. The SNpc connections that project to the head of the caudate and putamen are in effect dopamine depleted. Therefore, with external positive reinforcement, there is no "spike" or increase in direct pathway dopamine activity, because there is very little dopamine

activity to begin with. Thus, the associations necessary for instrumental and procedural learning are not formed or strengthened. However, negative feedback from the external environment actually results in "dips" in dopaminergic activity. Avoiding external negative reinforcement, based upon dopaminergic decreases, actually sensitizes un-medicated Parkinson's disease patients to be more responsive to the negative reinforcement characteristics of the environment. These patients are already dopamine depleted, so "dips" in activity actually enhance performance to negative reinforcement (Frank, 2005).

These effects can be manipulated with medication. Restoring dopamine through the administration of dopaminergic agonists in Parkinson's disease increases the level of dopamine. As a result, external positive feedback on probabilistic learning tasks now results in dopaminergic "bursts" or "spikes," and this improves the ability to learn positive associations. The tonic level of dopamine now becomes increased with the administration of medication, and greater dopamine availability can help generate phasic "bursts." However, insofar as negative feedback from the environment does not result in dopaminergic "dips" in activity (because of the medication increase in tonic dopamine status), patients now have difficulty benefiting from negative environmental feedback. Medicated patients actually become less sensitive to negative environmental reinforcement (Frank et al., 2004). In fact, some patients on antiparkinsonian therapy develop pathological gambling, excessive spending (shopping), hypersexuality, and binge eating, and it has been hypothesized that this may be the result of disruption in the mesolimbic and mesocortical systems that are involved in reward-related behavior (Isaias et al., 2008; Merims & Giladi, 2007; Torta & Castelli, 2008; Zand, 2008).

Because dopamine depletion is not uniform within the striatum in Parkinson's disease, other learning changes can be seen, depending upon medication status. The ventral striatum and the body and tail of the caudate nucleus demonstrate the least level of dopamine depletion, especially early on in the disease process. The substantia nigra, head of the caudate nucleus and the putamen reveal the greatest dopamine depletion (Frank, 2005).

Medication can restore dopamine in very depleted regions, while actually increasing tonic dopamine levels in relatively preserved regions. These imbalances also affect learning (Seger, 2006). For example, sequence learning can be improved when medicating Parkinson's patients, because this type of task is dependent upon the head of the caudate nucleus and the putamen, as the learning proceeds from "executive" to "motor" loops (see above sections). Increasing dopamine in these regions thus improves the learning of those "dopamine-dependent" tasks.

However, reversal learning (which requires a person to first learn from positive feedback and then to reverse the process by learning from negative feedback) is adversely affected in medicated Parkinson's patients because "dips" in dopaminergic activity no longer occur with negative environmental reinforcement (Cools, Barker, Sahakian, & Robbins, 2001; Cools, Lewis, Clark, Barker, &

Robbins, 2007; Frank, Scheres, et al., 2007; Frank & Claus, 2006). Improvement in learning can be observed on those tasks that are associated with dopaminergic increases, and impairment in learning can be observed on those tasks associated with dopaminergic decreases. In other words, enhancing the level of dopamine alleviates the cognitive deficits that depend upon positive reinforcement, but it impairs those that depend upon relatively unaffected or intact areas of the basal ganglia, as a manifestation of a type of dopamine "overdose" (Frank, 2005). Bellebaum and colleagues have also demonstrated a specialization of subregions of the basal ganglia in different aspects of reinforcement learning. Patients with focal lesions within the dorsal striatum were the most severely affected in performing a task of reversal learning (Bellebaum, Koch, Schwarz, & Daum, 2008).

Similar findings have been reported in healthy normal control subjects. Even low doses of dopamine agonists reduce the range of phasic dopamine activity to the extent that this impairs reinforcement learning on probabilistic learning tasks (Pizzagalli et al., 2008). Compared to a placebo group, healthy subjects receiving a low dose of a dopamine agonist showed significantly reduced overall reward learning, significantly diminished accuracy in choosing the stimulus associated with more frequent reward on a probabilistic learning task, and a reduced likelihood of using a "win-stay" strategy when a current richly rewarded stimulus was followed by another richly rewarding stimulus. These data imply that a disruption in dopamine signaling by altering tonic dopamine levels can impair reinforcement learning. A large dynamic range in dopamine phasic activity appears to be necessary for learning subtle differences between the positive and negative reinforcement values of responses (Frank, 2005). Dopaminergic agonists and antagonists can both presumably compromise this range of activity. Restricting the range of activity to either the higher or lower ends of the dopaminergic spectrum affects positive and negative reinforcement learning accordingly.

Therefore, we hypothesize that when disorders affect the frontostriatal system, a wide range of instrumental learning differences can be observed in response to positive and negative reinforcement. This has direct impact on those learning functions that are dependent upon the basal ganglia. While involvement of motor and cognitive loops would affect sequence and categorization learning, involvement of other segregated circuits would affect behaviors in other domains. Neuroimaging studies of dopamine receptor binding have demonstrated the functional compartmentalization of the striatum (Cervenka, Backman, Cselenyi, Halldin, & Farde, 2008). In this regard, positive and negative reinforcement would have differential effects upon the "instrumental learning" that occurs within different circuitries. Conditioning within the ventral striatum, which generates motivational influence, results in people becoming instrumentally "motivated" to perform various types of activities or to avoid certain types of situations. Similarly, instrumental conditioning within affective circuitry would impact upon the association and generalization of feeling with context. This has implications for both diagnosing and treating a variety of clinical disorders, from developmental disorders such as ADHD to psychiatric conditions including different types of psychosis.

Let's review how the dopaminergic reward circuitry system can be applied to ADHD, just for the purpose of using this condition as a type of model for brain–behavior relationships. To start with, the nigrostriatal, mesolimbic, and mesocortical circuitries can be directly applied to a developmental model of attention deficit hyperactivity disorder (Sagvolden, Johansen, Aase, & Russell, 2005). A hypofunctioning nigrostriatal system would cause difficulties in the modulation of motor functions as well as deficits in "habit formation" procedural learning systems. This would be manifest as motor clumsiness and difficulties in automating "procedural" behaviors. Hypofunctioning mesolimbic circuitry would generate altered reinforcement learning and this would represent the underpinning of a lack of sensitivity to the reward characteristics of the environment. This would result in the above described complaints that reward is often ineffective in managing ADHD behavior. Similarly, lack of anticipatory reward sensitivity could conceivably result in poor sustained attention, disinhibition, and impulsivity. Hypoactivity within the mesocortical system would generate cognitive executive dysfunction.

Consistent with this formulation, hyporesponsiveness within the ventral striatum has been demonstrated in attention deficit disorder under conditions of reward anticipation (Scheres, Milham, Knutson, & Castellanos, 2007). This is associated with a preference for small immediate rewards (Scheres et al., 2006). ADHD is characterized by an abnormal sensitivity to the salience of reward and this sensitivity is mediated by the midbrain dopamine system (Holroyd, Baker, Kerns, & Muller, 2008). Others have manipulated positive and negative reward preferences in ADHD on the basis of psychostimulant medication status (Frank, Santamaria, O'Reilly, & Willcutt, 2007). Unmedicated ADHD patients demonstrated impairment in both positive and negative reinforcement learning conditions on probabilistic tasks. Only the former deficits were ameliorated with psychostimulant medication. Medicated patients also demonstrated improved working memory functions in distracting conditions. Methylphenidate has also been demonstrated to reduce risk-prone betting behavior in ADHD children when performing the Cambridge Gambling Task. The ADHD group made more conservative bets during the medication session than they did during the placebo session (Devito et al., 2008). There is no question that dopaminergic reward systems are affected in ADHD, and that medication intervention affects sensitivity to the reward characteristics of the environment, thereby affecting decision-making.

We believe that abnormalities within the dopamine reward system also speak to a long-standing question regarding why general cognitive working memory deficits can be difficult to treat with medications, even though some studies show improvement in certain aspects of working memory. For example, dopaminergic "bursts" and "dips" drive learning within the striatum in order to facilitate adaptive behavior and to suppress maladaptive behavior. The "behavior" in question can take the form of motor programs, "habits," or even higher-level cognitive processes as described above with respect to reinforcement learning. Chapter 2 described cognitive control through working memory,

using an analogy of the unfolding of a motor program. It has been suggested that dopaminergic "bursts and dips" within the direct and indirect pathways also drive the striatum in the gating or updating of working memory functions, just as dopamine drives the motor system (Frank, Santamaria, et al., 2007). PET data have demonstrated that striatal dopaminergic function is related to prefrontal cortex activation and behavioral performance during working memory tasks (Landau, Lal, O'Neil, Baker, & Jagust, 2008). Dopaminergic "bursts" and "dips" within the basal ganglia play an important role in signaling cortical regions about "when" to become active.

As described in Chapter 2, there is a division of labor within working memory. The prefrontal cortex is critical for the active, "online" maintenance of information within working memory. The basal ganglia "gate" information in working memory, playing the critical gatekeeping role of the "bouncer" for modulating "when" and "when not" to update information into working memory (Moustafa, Sherman & Frank, 2008; Awh & Vogel, 2008; Mcnab & Klingberg, 2008). This updating function is mediated through the direct and indirect pathways of the basal ganglia. The direct pathway "lets in" information and the indirect pathway "bounces" or "throws out" distracting information. Dopamine agonists increase both tonic levels of dopamine within the basal ganglia and restrict the range of phasic changes. This dopaminergic increase facilitates or enhances neural signals within the direct pathway, but it impairs or reduces (inhibits) neuronal signals within the indirect pathway (Frank, 2005). Therefore, enhancing activity within the direct pathway, through the use of dopamine agonists, results in increasing the "updating" of working memory within the prefrontal cortex, in other words, "letting in" more information. However, because of tonic dopamine increases which restrict the range of dopaminergic "dips," neural signals within the indirect pathway are diminished, and this prevents the "bouncing out" of distracting information.

A meta-analytic review of 26 studies demonstrated deficits in both maintenance and manipulation (updating) working memory functions in children with ADHD (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Martinussen & Tannock, 2006). Ponzi (2008) has suggested the importance of dopaminergic reinforcement in the gating of working memory functions. Frank and others have associated tonic and phasic dopaminergic activity to both working memory maintenance in the PFC and updating functions mediated by the basal ganglia (Frank, Santamaria, et al., 2007; Moustafa et al., 2008). It can be proposed that stimulant medication, by altering the range of phasic dopamine activity, has an impact on the "gating" or updating of working memory functions. While medicated patients would be better focused on tasks because more task-appropriate information is "let in" to the prefrontal cortex, internal representations undergoing cognitive maintenance "online" might be difficult to update as the task progresses. Working memory can thus be affected by "unnecessary storage" (Awh & Vogel, 2008; McNab & Klingberg, 2008).

Treating one aspect of a working memory problem does not necessarily address the other. These data actually suggest that improving capacity or maintenance working memory functions could be antagonistic to updating mechanisms, and vice versa. Levy has suggested that optimal levels of dopamine appear to be required for beneficial effects on working memory (Levy, 2008). Stimulation of dopamine receptors (D1) within the optimal range enhances performance, but higher levels erode performance. This might occur because the interplay between information maintenance and updating are dependent upon a wide range of phasic changes in dopaminergic levels. Dopaminergic agononists restrict the sensitive but wide range of phasic changes by increasing tonic levels. Therefore, working memory functions can be difficult to enhance through pharmacologic treatment. For example, Lewis and colleagues evaluated Parkinson's Disease patients both with and without dopamine agonist medication (Lewis, Slabosz, Robbins, Barker, & Owen, 2005). They found that without medication, Parkinson's patients were impaired at manipulation more than maintenance or retrieval of information within working memory. They were also impaired at set-shifting. While L-dopa assisted the working memory deficit in manipulation (improving both accuracy and cognitive response time), it had no effect on the attentional set-shifting impairment (attentional set shifting requires the individual to update working memory by ignoring information that was just previously relevant).

We have outlined a simplified account of a putative dopaminergic mechanism that represents one neurochemical underpinning of working memory. Complex cognitive functions such as working memory that depend upon an interaction between cortical and striatal functions are associated with interactions between dopaminergic and noradrenergic mechanisms. These are important issues because they go beyond insight into working memory functions, and offer better understanding of why certain cases of ADHD can appear to be refractory to longer-term pharmacologic treatment (For reviews, see Levy, 2008; Frank, Santamaria, et al., 2007; Frank, 2005; Moustafa, Sherman & Frank, 2008).

We also believe that the concepts of dopaminergic instrumental learning mechanisms can be applied to orbitofrontal and medial circuits to assist in explaining some aspects of personality functioning. As indicated in the previous chapter, movement has cognitive and affective analogues. Instrumental mechanisms can be identified in motor learning, and these mechanisms have been identified in cognitive categorization learning within positive and negative reinforcement paradigms. Therefore, since these circuitries and "systems" are organized as parallel processes, we believe it is important to extend these learning principles to "emotional/motivational" circuitry as well.

From this perspective, certain personality and behavioral characteristics can be further understood in terms of instrumental learning mechanisms. Many personality preferences are composed of predispositions to act a certain way at a certain time, under the conditions of certain environmental stimulus characteristics. For example, people have certain social extraversive and introversive social preferences. These are likely a manifestation of the reward characteristics

experienced by people developmentally. These reward characteristics experienced developmentally conceivably interact with inherent neurotransmitter/neurochemical levels or capacities in sensitizing people to differing aspects of the reinforcement characteristics of the environment. This is even suggested in comparing prenatal versus postnatal behavior.

Behaviors acquired instrumentally "in utero" can be identical to behaviors exhibited in infancy (see Fig. 4.4). The newborn infant engages in a behavior because "it worked" in utero in providing comfort or "reward." Therefore, these concepts can be applied to instrumental learning within multiple cortical–basal ganglia circuits. Extending this concept to affective circuitry, it is likely that aspects of "emotion" are instrumentally conditioned in the same way, and thus numerous environmental responses in the present have been shaped by previous interactions from the past, for better or worse. This concept is central to psychodynamic and interpersonally driven psychotherapy approaches, and similarities have been systematically observed in pre- and post-natal behavior by psychoanalytically oriented researchers (Piontelli, 1992; Piontelli, Bocconi, Boschetto, Kustermann, & Nicolini, 1999).

For example, many people experience a "favorite" time of year. Many people feel energized in the spring and negativistic in the fall and winter. These "seasonal" changes for some of us can be partly understood as a manifestation of

Fig. 4.4 Illustration of early reinforcement learning. *Left side* of figure: Kaitlyn at 15 weeks in utero, *upper right*: Kaitlyn at three weeks, *lower right*: Kaitlyn at three months

"instrumental emotional responses" we first had in relation to different experiences while growing-up, at different times of year. For example, we might expect an adult who had "school phobia" or "social anxiety," or perhaps who simply disliked school when younger, to experience "instrumentally conditioned" unpleasant feelings at the close of summer, or even vague, anxious feelings "in the pit of the stomach" on Sunday evening, just before returning to "school." Why do some people experience the "Monday blahs" upon returning to work, while others do not have such experience? It may be that certain of these feelings of uneasiness represent the lingering instrumentally conditioned responses associated with developmentally experienced "separation anxiety." These beliefs and experiences, largely occurring outside of conscious awareness, drive significant aspects of our daily lives. They have long been the focus of dynamically oriented therapies, and a number of clinicians and researchers have more recently attempted to directly link current brain research with therapeutic theory and practice, in some cases with specific focus on procedural learning and subcortical contributions to personality dynamics (Pally, 2005, 2007).

Summary

This chapter reviewed the learning functions of the basal ganglia. The basal ganglia are involved in making perceptual discriminations and judgments and the basal ganglia are involved in procedural and instrumental learning. The basal ganglia support the acquisition of both cognitive and motor procedures. Therefore, the functions of the basal ganglia are essential for successful interaction with the environment for adaptation.

Higher-order control involves the frontostriatal system as well as regions of cortical networks that are necessary to complete given tasks. As tasks are practised and become automated, this is accompanied by dynamic changes in the neuroanatomy that governs the task. Automation is not simply a faster version of higher order control. Instead, higher-order control and automaticity are different forms of information processing.

Many of the behaviors that we engage in on a routine basis seem simple and are often taken for granted. However, these daily procedures are really patterns of organized behaviors that achieve highly specific purposes and goals. These "automatic" behaviors are highly efficient, they are represented very economically within the brain, they are reliable, and they require little conscious direction or control. These behaviors are really part of our "executive" system because they allow us to perform practical tasks in an effortless way while benefiting the organism as a whole by ensuring our survival. These behaviors are under subcortical mediation and in this way, the basal ganglia are an essential part of the brain's executive control system.

Can these behaviors be performed by cortex? The answer to this question is an unequivocal yes, absolutely, without question. However, cortex does not

perform these routine behaviors with the same elegance. When cortex is involved in directing these behaviors, performance is deliberate and slow. Behaviors that would ordinarily be performed automatically and accurately require the effort that is characteristic of cortical activity. Difficulty in acquiring behavioral automaticity is often an aspect of a patient's clinical presentation.

The learning systems described in this chapter are typically not assessed within a cortico-centric model of neuropsychology. Traditional neuropsychology seems to make the assumption that all important adaptive behaviors are based upon conscious thinking or higher-order control. However, many behaviors essential to adaptation are not based upon "thinking." Within the broad category of "procedural learning" as discussed in this chapter, executive control or higher-order thinking occurs only during the initial phases of certain types of procedural learning tasks, while it is not involved in certain types of instrumental behaviors. As learning and automaticity are achieved, the neuroanatomy of task performance shifts to the cortico-striatal and cortico-cerebellar systems. The learning capacities of these systems are not typically addressed in current neuropsychological assessment. This leaves significant aspects of cognition, learning, and behavior that remain open to evaluation. Recognizing this clinical shortcoming is the first step towards developing methodologies that would assess these systems for providing a more comprehensive understanding of patient's problems in adaptation, many of which reside within the domain of interpersonal relationships and emotional regulation.

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Chapter 5
The Cerebellum: Quality Control, Creativity, Intuition, and Unconscious Working Memory

In all things of nature there is something of the marvelous.
Aristotle

Intuition will tell the thinking mind where to look next.
Jonas Salk

Cerebellum is a Latin word that means "little brain." While the cerebellum might be little in gross appearance relative to the neocortex, it is certainly not little in terms of its composition and function. The cerebellum actually contains more neurons than the remainder of the human brain, even though it comprises only about ten percent of total brain weight (Houk & Mugnaini, 2003). The cerebellum also lies outside of the cerebral cortex. Perhaps this is one of the reasons why so little attention has historically been paid to understanding its possible contributions to behavior. From the viewpoint of a cortico-centric bias, regions outside the cortex become less important. The cerebellum has traditionally been viewed as a structure coordinating movement, and until recently, this viewpoint has rarely been given a second thought (Bower & Parsons, 2003).

The cerebellum is quite a unique structure. While the cortex is composed of six layers of specialized neurons, and the basal ganglia comprise a single layer of groups of nuclei, the cerebellum is a three-layered structure that is composed entirely of inhibitory and excitatory neurons (Bower, 2002). The fact that it is composed of different types of specialized regulatory neurons might explain why it resides outside the cortex. It performs computations that are completely different from the operations of the cortex. It is a highly specialized computational structure that has widespread reciprocal connections to most regions of the cerebral cortex (Schmahmann & Pandya, 1997). These reciprocal or re-entrant connections, or "loops" of interaction place the cerebellum in an anatomic position to modulate or regulate neural activity in most other parts of the brain (Houk et al., 2007). The cerebellum regulates behavioral output through the influence of its highly specialized inhibitory and excitatory internal connections. These connections determine the appropriate amplification or refinement of behavior through specialized computations. The result of these

L.F. Koziol, D.E. Budding, *Subcortical Structures and Cognition*,
DOI 10.1007/978-0-387-84868-6_5, © Springer Science+Business Media, LLC 2009

computations is sent back to cortex. Said another way, the cerebellum controls the quality of behavioral output. This chapter reviews the anatomy of the cerebellum, it establishes the circuitry that subserves the cerebellum's contributions to motor, cognitive, and affective behavior, and it reviews the functions of the cerebellum as a modulator of behavioral output.

Surface Anatomy of the Cerebellum

The functions of the cerebellum can be understood as organized along the dimensions of an anterior-posterior gradient and a medial-lateral gradient (Schmahmann & Caplan, 2006; Schmahmann & Pandya, 1997). Therefore, it is important to understand the surface anatomy of the cerebellum, which can be subdivided according to these same dimensions.

The cerebellum can be separated into two large divisions, namely, the anterior and posterior lobes. These two lobes are divided by the primary fissure. The term corpus cerebelli is used to refer to these two lobes together. These two lobes comprise the anterior-posterior gradient. A ventral view of the cerebellum actually reveals a third smaller lobe, comprised of the flocculus and nodulus, called the flocculonodular lobe.

The medial-lateral gradient is composed of three regions. The medial or vermal zone straddles the midline. The regions that border the vermis are called the intermediate zones. The remaining regions, or the lateral zones, constitute the cerebellar hemispheres. These areas constitute the medial-lateral gradient. Figure 5.1 depicts the surface anatomy of the cerebellum. Like the cerebral cortex, the cerebellar hemispheres are anatomically asymmetric. The degree of asymmetry is variable between individuals. Certain developmental and psychiatric disorders have been reported as characterized by different patterns of asymmetry (Hu, Shen, & Zhou, 2008).

These regions are of different phylogenetic ages (Guzzetta, Mercuri, & Spano, 2000). The oldest region is the flocculonodular lobe, which is called the archicerebellum. The vermis and intermediate zones are called the paleocerebellum. The cerebellar hemispheres, or the neocerebellum, are the phylogenetically most recent regions. While the cortex expanded greatly over the course of evolution, this neocortical expansion was paralleled by a dramatic expansion of the posterior lobes of the cerebellum (Weaver, 2005). As the cortex grew bigger and became more specialized, the cerebellum also grew in order to enlarge its capacity, since greater demands were being made for regulating neuronal signals in other regions of the brain.

In fact, one specific change relates to the number of cortical–cerebellar connections (Allen et al., 2005). For example, in the macaque monkey, the largest proportions of projections from cortex to cerebellum originate in the cortical motor system with a relatively smaller number of projections from the prefrontal cortex. In humans, the largest proportion of fibers into the

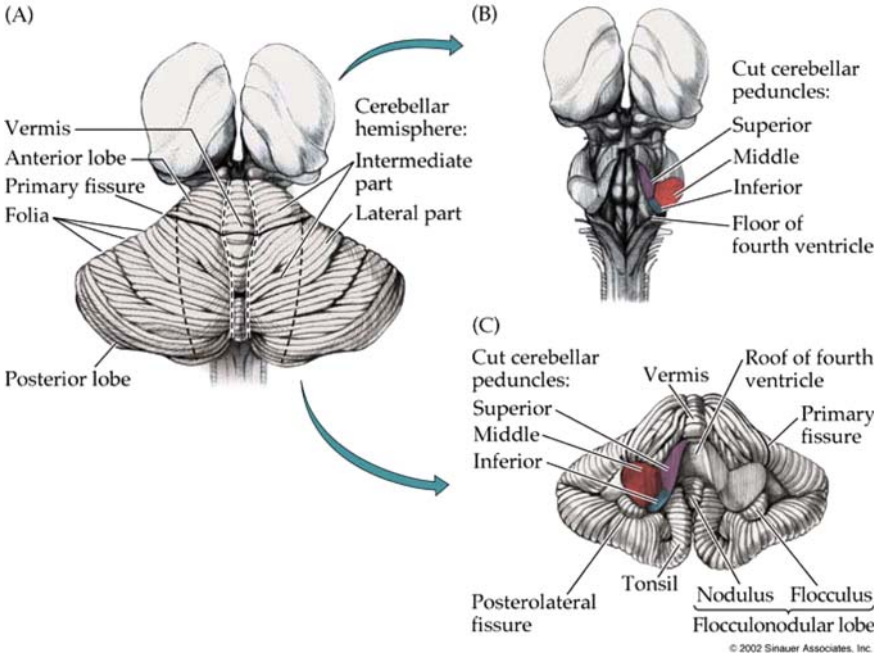

Fig. 5.1 Subregions of the cerebellum, reprinted by permission of Sinauer Associates, Inc., 2002.

pontine nuclei and cerebellum originate from the dorsolateral prefrontal cortex (Ramnani et al., 2006). A similar evolutionary change is observed within the deep cerebellar nuclei. For example, in humans, the ventral dentate nucleus, which receives projections that originate in dorsolateral prefrontal cortex, is much larger than the dorsal region of the dentate which receives its projections from motor areas of the cortex. The Purkinjie cell, which integrates information from both the mossy fiber and climbing fiber inputs, always remains the fundamental information-processing unit of the cerebellum. However, the cerebellum became more complex by evolving different types of inhibitory and excitatory neurons in order to perform its functions of regulating motor, emotional, and cognitive output (Sultan & Glickstein, 2007).

The cerebellar hemispheres are also divided by numerous shallow fissures. These fissures subdivide the cerebellar hemispheres into 10 lobules which are referred to according to a simple Roman numeral classification system (Makris et al., 2003). The anterior lobes are composed of lobules I through V. The posterior lobes are composed of lobules VI through IX. The flocculonodular lobe is designated number X. These lobules are an important feature of cerebellar architecture because different regions of the cerebral cortex project to different cerebellar lobules or zones by way of the pontine nuclei which will be discussed below.

Before discussing the pontine nuclei relay system and how it relates to cerebro-cerebellar circuitry, it is important to review the nuclei within the cerebellum. The cerebellar nuclei are embedded deep within the white matter of the cerebellum. There are four pairs of deep cerebellar nuclei, represented bilaterally on each side of the midline. The medial nuclei are the fastigial nuclei. These nuclei receive input from the vermis. The emboliform and globus nuclei, referred to together as the interpositus nuclei, receive input from the intermediate zones of the cerebellum. The dentate nuclei are the largest and are located laterally, and they receive input from the cerebellar hemispheres. The dentate nuclei expanded over the course of evolution. They became elongated and folded over, developing convolutions. These resulting convolutions further increased the spatial extent of the dentate nuclei, allowing different regions of the dentate to maintain segregated and specialized afferent and efferent projections (Deoni & Catani, 2007; Zhu, Yung, Kwok-Chong, Chan, & Wang, 2006).

Cortex and Cerebellum—Superficial Comparison of Infrastructure

The internal circuitry of the neocortex is characterized by its heterogeneity. The cortex features six layers comprising different patterns of connectivity (Mesulam, 1985). There are four lobes that are composed of different types of sensory, associative, and motor neurons. The cortex can be even further subdivided on the basis of cytoarchitectonic properties. The heterogeneity of Brodman's and von Economo's classification systems speaks to the highly specialized nature of cortex in its performance of specific and diverse functions. The complexity of this infrastructure is the price paid for the capacity to carry out a wide variety of highly specialized sensory and motor functions. In short, the neocortex does very many different things, and these disparate functions are supported by an anatomical structure that is just as complicated as the functions it subserves.

The internal composition of the cerebellum is by no means simple. However, relative to the cerebral hemispheres, the infrastructure of the cerebellum can seem straightforward. The micro-circuitry of the cerebellum is homogeneous. It is a three-layered structure of gray matter that is composed of the same cellular make-up throughout the whole cerebellum. The cerebellar hemispheres tend to "look" the same, regardless of lobule or region (Houk & Mugnaini, 2003). This uniformity of cellular make-up has three implications. First, the computations of the cerebellum result in only one general output operation. According to Houk and Mugnaini, the output of the cerebellum is entirely inhibitory. This is of significance because it is a key to understanding the cerebellum as a modulator of neocortical "amplification" or behavioral output. Determining the proper rate, rhythm, and force of behavior, or the proper restraint and refinement, is a matter of excitatory-inhibitory balance. This is one way of looking at the general function of the cerebellum.

Second, the one operation that the cerebellum performs is performed on whatever afferent information it receives (Schmahmann, 1996). The cerebellum receives information from regions of the brain that process motor, somatosensory, visceral, autonomic, limbic, and cognitive information. This information is projected to specific cerebellar regions or zones. The cerebellum performs the same operation for all modular input. Any seemingly diverse information processing of the cerebellum does not stem from anatomical differences in intrinsic cerebellar circuitry as much as it is derived from the diverse nature and origins of input from the cerebral cortex and other brain regions. Within the cerebellum, all information (motor, autonomic, cognitive, and affective) is processed through the same mechanism (Chavez-Eakle, 2007). The nature of any observed deficit would be dependent upon the specific focal region of the cerebellum that is affected. Because cortical input projects to very specific cerebellar regions, the cerebellum is characterized by functional asymmetry (Hu et al., 2008).

Third, when the cerebellum goes "wrong," it can only "go wrong" in one way. Therefore, regardless of which specific cerebellar lobule or region is affected, the resultant output must have a similar manifestation or analogue dependent upon the specific regions or zones of involvement. This is a key principle in understanding the role of the cerebellum in various "modular" processes. However, because the general function of the cerebellum is to achieve behavioral refinement through the process of regulating neural signals in other parts of the brain, different levels of activation could have a diverse impact upon observable behavior. For the most part, cerebellar dysfunction characterized by under-activation or over-activation is observed in "undershooting" or "overshooting" the target of behavioral output. This phenomenon is clearly observed in dysmetria, in which movements become erratic in size and amplitude. Autonomic, emotional, and cognitive analogues to this type of symptom will be discussed later in the chapter.

Infrastructure of the Cerebellum

The three layers of the cerebellar cortex are named the molecular layer, the Purkinje cell layer, and the granular layer (Blumenfeld, 2002). These layers begin in the outer or pial surface and progress inward. These three layers are composed of three types of neurons: afferent (input) neurons, interneurons, and efferent (output) neurons. The cerebellum receives two types of afferent neurons. These comprise the mossy fiber inputs and the climbing fiber inputs (which are discussed below). Both of these inputs are exclusively excitatory. There are five main classes of interneurons. Three of these interneuron types are inhibitory, specifically, the stellate, basket, and golgi cells. Two of these types of interneurons are excitatory, namely, the granule and unipolar brush cells. There is a single type of efferent neuron, the Purkinje cell. These neurons are

exclusively inhibitory in their output and project to the deep cerebellar nuclei. The deep cerebellar nuclei project back to cortex by way of the thalamus.

Therefore, based upon this neuroanatomical infrastructure, the cerebellum does not appear to function as a primary sensory processor or as a generator of behavior. Instead, it is a modulator, or regulator, of neural signals. The cortex is the primary "processor" of sensory and motor information, and the cerebellum "modulates" the experience and expression of this processed information. Thus, the cerebellum receives information that has already been "processed" by the cortex. It performs a regulatory operation that modulates behavioral experience and expression. However, in this way, it appears to be involved in intensity-dependent analysis, and it has been reported that primary somatosensory processing is altered by cerebellar damage (Hu et al., 2008). Cerebro-cerebellar circuitry is the anatomic underpinning of these modulatory functions.

The molecular layer of the cerebellum is composed of Purkinje cell dendrites and their afferent neurons. These afferent neurons comprise the parallel fibers and the climbing fiber inputs. The climbing fiber inputs originate in the inferior olivary system which is a set of nuclei located in the ventral medulla. The parallel fibers originate from the granule cells in the granular layer. The Purkinje cell layer is only one cell thick. However, its dendritic tree branches extensively within the molecular layer. These dendritic branches synapse with the parallel fibers, which run perpendicular throughout the cerebellar cortex within the molecular layer.

Parallel fibers are extremely numerous. Each parallel fiber contacts many Purkinje cell dendrites, while each Purkinje cell receives input from a high number of parallel fibers (Bower, 2002). For instance, each Purkinje cell can receive inputs from as many as 200,000 parallel fibers (Fox & Barnard, 1957). Purkinje cells are, therefore, in a position to integrate very considerable information from a wide range of sources. Climbing fibers have a unique, preferential relationship with Purkinje cells. One Purkinje cell receives input from just one climbing fiber. However, one climbing fiber can send projections to as many as 10 Purkinje cells (Sugihara, 2006). These climbing fiber-Purkinje cell relationships appear to represent the neuroanatomic underpinning for "fine-tuning" behavioral output (Ekerot & Jorntell, 2003). The significance of this anatomy will be apparent later. Purkinje cell axons terminate by synapsing on one of the deep cerebellar nuclei.

The granular layer is composed of granule cells. These cells are extremely numerous. These are the cells that outnumber the remaining cells in the central nervous system. The granule cells are actually the smallest cells in the brain. The dendrites of the granule cells receive inputs from the mossy fibers. The axons of the granule cells project to the molecular layer. Within the molecular layer, the granule cells bend and branch to form the parallel fibers. The flow of information through the cerebellum is depicted in Fig. 5.2. Mossy fiber inputs project to granule cells. Granule cells ascend to form parallel fibers. Parallel fibers pass through the dendrites of Purkinje cells. Purkinje cells project to either the

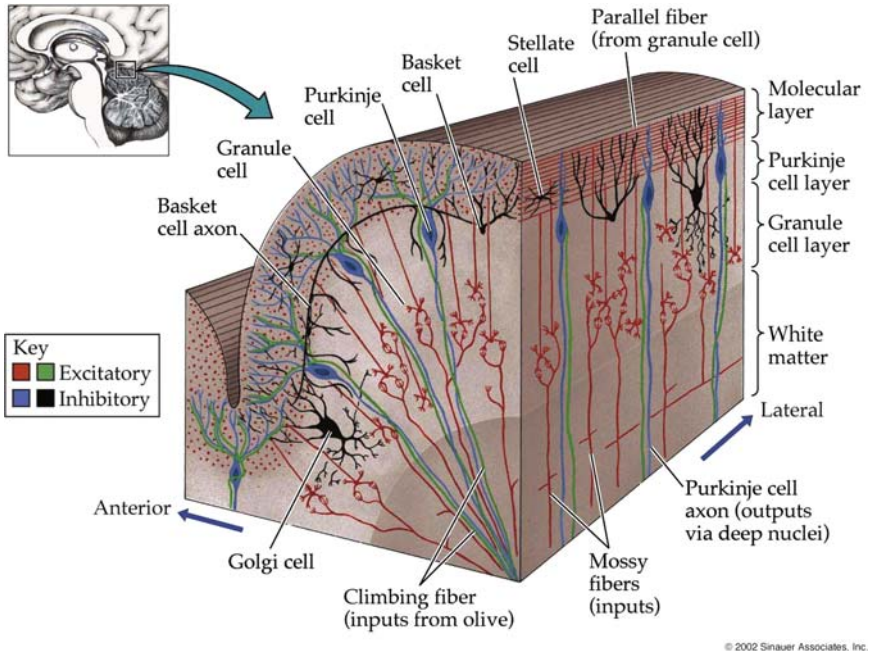

Fig. 5.2 Summary of the infrastructure of the cerebellum. Afferent information arrives through the mossy fiber and climbing fiber input systems. Efferent information exits by way of Purkinje cell axons which project to deep cerebellar nuclei (not shown in this figure), reprinted by permission of Sinauer Associates, Inc., 2002.

dentate, interpositus, or fastigial nuclei. Additional Purkinje cell input stems from the climbing fibers. The cerebellar infrastructure is depicted in Fig. 5.2.

The routes of all nerve fibers to and from the cerebellum pass through the cerebellar peduncles. Grossly speaking, most of the input into the cerebellum, the mossy fiber system, arrives through the middle cerebellar peduncle. Output returning to the cerebral cortex passes through the superior peduncle. Neural information from and to lower level motor systems passes through the inferior peduncle.

The Cerebellum and Non-Motor Functions

The cortico-centric and traditional view of brain function has until recently held that the cerebellum is operant exclusively in motor behavior. The primary role of the cerebellum had been considered to be the coordination of movement. The various cerebellar ataxic syndromes provide volumes of evidence supporting the role of the cerebellum in coordinated motor functioning. The "coordination" of movement really refers to the *quality* of movement. It is not a primary disturbance in motor programming. Patients with cerebellar lesions affecting

motor zones often develop a symptom called dysmetria, in which movements become erratic in size and direction (Houk and Mugnaini, 2003). This symptom is exemplified in intention tremor. The motor program and the motor intention are retained, but the quality of the movement is affected.

One does not have to look too far to find roles for the cerebellum in non-motor functions (Watson, 1978). The cerebellum is critical to classical sensorimotor learning, such as in eye-blink conditioning (Attwell, Ivarsson, Millar, & Yeo, 2002; Jimenez-Diaz, Navarro-Lopez, Gruart, & gado-Garcia, 2004; Lavond, 2002; Weeks et al., 2007). In eye-blink conditioning, a tone is presented followed by a puff of air delivered to the eye. Blinking the eyes at the proper time reduces the adverse effects of the air puff. Damage to the cerebellum impairs the ability to make the anticipatory eye movement during the conditioning phase of the task, and damage to the cerebellum after the task has been learned also interferes with the anticipatory response. The cerebellum is also essential to adjustment to environmental perturbations as in prism adaptation (Bigelow et al., 2006; Morton & Bastian, 2004; Weiner, Hallett, & Funkenstein, 1983). In this task, a subject is required to adjust movement while wearing prism glasses that displace vision, and then readjust movement upon their removal. Damage to the cerebellum results in impaired performance on this task as well. Observations in the performance of both of these tasks support a type of timing and coordination learning function for the cerebellum, particularly with respect to anticipatory behavior (Brunia & van Boxtel, 2001; Simo, Krisky, & Sweeney, 2005). These data imply an anticipatory or predictive learning function of the cerebellum that goes beyond the coordination of movement.

Three types of cerebellar-hypothalamic connections have been identified (Zhu et al., 2006). One connectional pattern originates in the hypothalamus and projects only to the cerebellar cortex; another projects only to deep cerebellar nuclei; and a third type projects to the cerebellar cortex with collateral branches to cerebellar nuclei. Therefore, there is an extensive cerebellar-hypothalamic circuitry. These connections provide the anatomic underpinning for integrating sympathetic and parasympathetic responses with information from other domains that is projected to the cerebellum. These connections appear to be involved in a variety of somatic and nonsomatic regulatory functions. For example, fMRI data have suggested that odor concentration and sniff volume are inversely proportional (Sobel et al., 1998). The stronger the odor concentration, the smaller the amplitude or volume of the sniff. The cerebellum appears to receive olfactory sensory information concerning odor concentration in order to modulate or regulate the force of the sniff, which in turn modulates subsequent olfactory input (Zatorre, Jones-Gotman, & Rouby, 2000). Once again, this reveals the function of the cerebellum with respect to adjusting the amplitude of behavior and modulating functional systems.

Reciprocal and bidirectional connections between the cerebellum and the hypothalamus also provide the circuitry for playing a similar role in the regulation of hunger, thirst, and satiation (Gautier et al., 2001; Griffiths, Derbyshire, Stenger, & Resnick, 2005; Holstege & Georgiadis, 2004; Meston, Levin, Sipski,

Hull, & Heiman, 2004; Savic-Berglund, 2004). These needs and experiences are all associated with a dimension of regulating "force" which appears to be modulated by the cerebellum. The cerebellum is also involved in bodily functions such as micturition and defecation. Roles in all of these functions have been suggested by neuroimaging activation and other physiologic studies while implying that the cerebellum is an integral and essential nodule for linking somatic and visceral systems (Zhu et al., 2006; Zhu & Wang, 2007). In all of these behaviors described above, the cerebellum functions as much more than a "coordinator" of movement.

The Cerebellum in Procedural Learning

While both the cortico-striatal and the cerebro-cerebellar systems are involved in procedural learning, their roles are different. The former system is involved in the learning of new sequences and the latter system is primarily involved in the motor adaptation phases of learning (Doyon, Penhune, & Ungerleider, 2003; Doyon & Ungerleider, 2002). The serial reaction time task (SRT) is an example of a sequence learning task, and prism adaptation is an example of adapting to an environmental perturbation (see Chapter 4 on Procedural Learning). However, procedural learning tasks initially activate those regions of the cortex that are necessary to complete the task, as well as the basal ganglia and the cerebellum. The cerebellum is at least initially involved in the learning of sequences. Patients with focal cerebellar lesions have been described as demonstrating deficits in learning motor sequences (Molinari et al., 1997). This suggests a role for the cerebellum in identifying and coordinating, or timing, event sequences. Patients with damage to the lateral cerebellum have exhibited impairment on the serial reaction time task (Torriero et al., 2007).

Studies with normal controls have shown interhemispheric differences in the role of the cerebellum on procedural learning tasks. It has been suggested that the left lateral cerebellum is more active in procedural learning through the ipsilateral hand, and that the right lateral cerebellum is activated in procedural learning regardless of hand (Torriero, Oliveri, Koch, Caltagirone, & Petrosini, 2004). The role of the right cerebellum has been related to the refinement or timing of signals within the left dorsolateral prefrontal cortex, presumably underlying the role in motor sequence learning. Patients with either focal or atrophic cerebellar damage have also been described as demonstrating impairment in cognitive sequence learning (Leggio et al., 2008).

Taken together, these data suggest that sequence processing is a mode of cerebellar operation. This makes sense, since sequence processing depends in part on the appropriate intensities and durations of neuronal discharges in cortical regions. The cerebro-cerebellar circuit serves as a connective underpinning between cortical and cerebellar regions, while intrinsic cerebellar circuitry is well suited to perform intensity and duration refinement functions. In

any event, there is overwhelming evidence that the cerebellum plays a significant role in non-motor behavior. In our view, the three major regions of the brain, the cortex, basal ganglia, and cerebellum, operate in parallel, with each region making a unique contribution to the differing requirements of behavioral adaptation.

The Cerebro-Cerebellar Circuit

Whether or not the cerebellum contributes to cognitive and emotional functioning has been a controversial topic (Schmahmann & Caplan, 2006). This book is based upon the obvious premise that neuroanatomic connections are neither extraneous nor irrelevant and that structure relates to function. Therefore, if the cerebellum participates in cognitive and affective functioning, then there must be an anatomic basis to support this conclusion. If anatomic connections exist for the cerebellum to participate in autonomic, emotional, and cognitive functions and operations, this circuitry must be functional. The prototypical cerebro-cerebellar circuit establishes the anatomic substrate for the cerebellum's participation in a wide range of non-motor functions.

There is no question that cognitive function is distributed among multiple cortical and subcortical networks (Banich, 2004; Horwitz & Smith, 2008). Each aspect of the network makes a unique contribution to any particular behavior, but the network ultimately operates as a whole in producing any given pattern of behavior. Existing cortico-centric models of cognition have demonstrated that association areas and paralimbic regions of the cortex are necessary to support a range of cognitive operations and emotional experiences. However, previous chapters in this book described cognitive and emotional networks which additionally comprise posterior cortices, anterior cortex, and the basal ganglia. Executive, motivational, and affective circuitries were described as grossly projecting from the frontal lobes to the striatum, from the striatum to the pallidum, from the pallidum to the thalamus, and from there, back to cortex. As we have seen, there is also very substantial anatomic evidence that the cerebellum is linked to these same associative and paralimbic areas of the neocortex. This anatomic linkage consists of cerebro-cerebellar circuitry, which, thus comprises another node or module in the brain's distributed cognitive and affective networks.

The prototypical circuit is a re-entrant system that comprises both feed forward and feedback elements (Schmahmann & Pandya, 1997). The feed forward limb originates in the cortex and projects to the pontine nuclei. The pontine nuclei send mossy fiber inputs to the cerebellar cortex. These inputs pass through the neural infrastructure of the cerebellum and project to the deep cerebellar nuclei, completing the feed forward limb. The feedback limb projects from the cerebellar nuclei to the red nucleus (an "en passant" passing), to the thalamus, and from there, back to the cerebral cortex to the region where the

circuit originated. Therefore, the cerebro-cerebellar circuit forms a loop of interaction that is conceptually similar to the loops of the cortico-basal ganglia system. The "feed forward" limb provides the cerebellum with cortical input. The infrastructure of the cerebellum modifies this information and, therefore, plays an important role in deciding what information is or is not returned to the cerebral cortex (Andreasen and Pierson, 2008). Information is returned to the cerebral hemispheres through the feedback limb.

Nearly all regions of the associative and paralimbic cortices project to the pontine nuclei. These projections are highly specific, segregated, and parallel, so that each circuit projecting to the pons maintains its integrity. For example, the prefrontal cortex, described as essential for higher-order control in functions such as attention, organization, planning, working memory, and language expression, initiates a highly organized projection system that sends input to medial and dorsomedial regions of the pons. Paralimbic regions, such as the cingulate/medial region of the frontal lobes which is essential for motivation and aspects of emotional regulation, project to medial and lateral pontine nuclei. The auditory association areas of the temporal lobes send projection fibers to the lateral pons. The parietal lobes, critical for visuospatial cognition and behavior, have a similarly organized projection system. Superior regions of the parietal association cortices project to the central pons, while inferior parietal regions project to the rostral pons. This circuitry is depicted in Fig. 5.3.

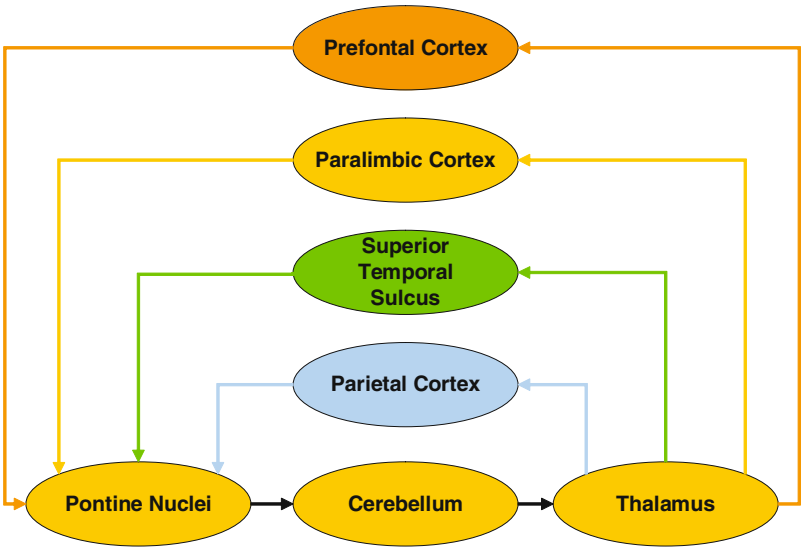

Fig. 5.3 Connections between the cerebellum and the neocortex

The inferior temporal lobes have no identified projections into the pons. This may be because the cerebellum regulates behavioral output and not the sensory visual-perceptual functions such as object identification or recognition. Studies have revealed minimal cerebellar activation when subjects simply view visual stimuli but do not selectively respond (Allen & Courchesne, 2003). Functional differences for these input projection systems have been revealed on certain learning tasks. For example, differences in category learning have been observed in patients with Parkinson's disease versus cerebellar disorders (Maddox, Aparicio, Marchant, & Ivry, 2005). Since the cerebellum does not receive projections from the inferior temporal lobe region which is essential to the category learning mediated by the basal ganglia, this could easily explain why category learning was impaired in Parkinson's patients but not in those patients with cerebellar disorder. In any case, all of these specific circuitries have been identified and described in considerable detail (Schmahmann & Pandya, 1997; Middleton & Strick, 2000, 2001; Ramnani, 2006).

The pontine nuclei project to the cerebellar cortex by way of the mossy fiber inputs. The information currently available concerning the distribution of mossy fiber inputs into the cortex of the cerebellum is less extensive. However, the available information allows classification of inputs within anterior-posterior and medial-lateral gradients. Projections that originate in motor and somatosensory cortices arrive at the anterior lobes of the cerebellum, in lobules I through V. Cortical regions that subserve the various modules of cognitive functioning project to the posterior and inferior cerebellar hemispheres, primarily to lobules VI and VII. There is a secondary sensorimotor representation in lobules VIII and IX. Affective information is primarily projected to the vermal region (Houk and Mugnaini, 2003). Therefore, motor information is primarily represented in the anterior lobes and cognitive information is represented in posterior lobes, resulting in an anterior-posterior gradient. Limbic information is represented medially, and cognitive information is represented more laterally, which results in the medial-lateral gradient.

This projection system appears to remain reasonably specific within the cerebellum itself, at the level of the deep cerebellar nuclei. For example, neurons that originate in primary motor cortex eventually arrive at the dentate in dorsal regions at mid rostral-caudal levels. Neurons that originate in the dorsolateral prefrontal cortex eventually arrive at ventral regions of the middle third of the dentate (Middleton & Strick, 2000, 2001). These ventral regions of the dentate project back to dorsolateral prefrontal cortex via the thalamus, while dorsal regions of the dentate project through thalamus and arrive at motor regions of frontal cortex. Therefore, the input and output channels that influence cognitive and motor functioning are separate throughout the cerebro-cerebellar system (Middleton & Strick, 2000, 2001). The segregation of this projection system implies that other projections from different cortical regions maintain similar integrity. The dentate nucleus is illustrated in Fig. 5.4.

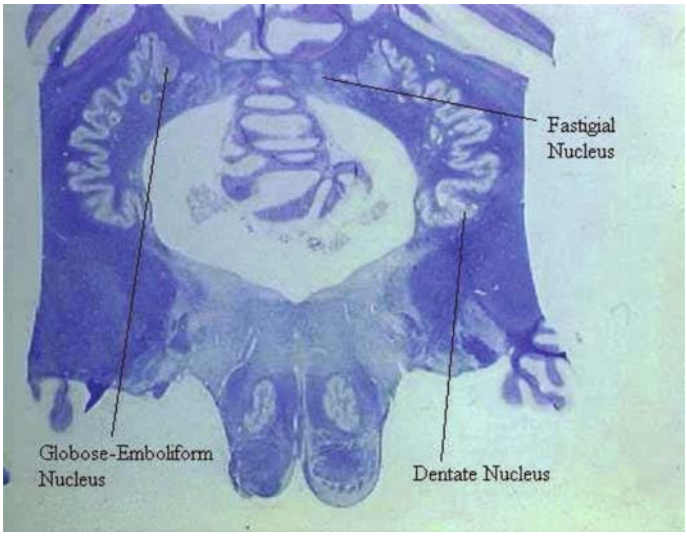

Fig. 5.4 The deep cerebellar nuclei, illustrating the size and convolutions of the dentate nucleus, source unknown.

The Cerebellum and the Principle of Lateral Crossed Control

Many of the cerebellar connections with the lateral motor system are ipsilateral. Therefore, lesions of the anterior cerebellar hemispheres cause motor deficit or ataxia in the extremities that are located on the same side of the body as the lesion (Blumenfeld, 2002). A right cerebellar hemisphere lesion generates a motor deficit in right body-side extremities while a left cerebellar hemisphere lesion results in motor deficits on the left body side. However, cerebellar connections with the cerebral hemispheres are contralateral (Schmahmann & Pandya, 1997). The right deep cerebellar nuclei have reciprocal projections with the left cerebral hemisphere and the left deep cerebellar nuclei have reciprocal projections with the right cerebral hemisphere through the cortico-cerebellar circuitry system. Therefore, this anatomy predicts that lesions of the posterior and inferior right cerebellar hemisphere would affect the regulation of neural signals related to verbal behavior while lesions of the posterior and inferior left cerebellar hemisphere would affect visuospatial functioning (Fink et al., 2003; Jansen et al., 2005).

The Olivo-Cerebellar System

The cerebro-cerebellar circuit establishes “loops” that grossly form reciprocal connections between the cerebral cortex and the cerebellum. Another loop of interaction is formed by the olivary system. However, considerably less

information is known about the olivo-cerebellar system and it is not possible to identify discrete or precise circuitries based upon the current states of knowledge and understanding. Climbing fibers arise from the inferior olive. The inferior olive is a group of nuclei that are located within the ventral medulla oblongata. The olive appears to have three sources of input. One projection system links the cerebral cortex with the red nucleus, to the inferior olivary nuclei, and then through the climbing fiber system to the cerebellar cortex (Blumenfeld, 2002). A second system originates in the zona incerta of the thalamus and projects to the inferior olive. The zona incerta has been described as receiving projections from the frontal cortex (Schmahmann & Pandya, 1997). A third system is the olivocerebellar projection system which projects from the deep cerebellar nuclei to the olivary nuclei, and from there, through the climbing fiber system to the cerebellar cortex. In this way, there are two closely corresponding loops. One of these loops links the cortex with the cerebellar nuclei and the other links the cerebellar nuclei with the inferior olive (Houk and Mugnaini, 2003). While the mossy fiber input system appears to be segregated according to specific cerebellar zones which are dedicated to specific functional modules, the olivo-cerebellar system appears to be organized in an analogous way. Climbing fibers project to segregated zones of the cerebellum that appear to modulate specific motor, autonomic, affective, and cognitive processes (Azizi, 2007). This system appears to function as an error-dector, examples of which will be given below.

Theories of Cerebellar Function

Our understanding of cerebellar functioning is incomplete. Definitive statements cannot yet be made about what the cerebellum does or how it does what it does. However, the knowledge that we have so far accumulated about the cerebellum does allow us to generate hypotheses about its role as a modulator of motor, sensory, autonomic, affective, and cognitive functioning. Currently, there are multiple theories of cerebellar function. These various theories feature more commonalities then they do disparities. None of these theories view the cerebellum as a primary generator of cognition, affect, or behavior. Instead, all current theories view the cerebellum as a modulator of behavioral output. There is general agreement that the cerebellum adjusts behavioral output by regulating neural signals in other brain regions through its interactive loops.

One theory emphasizes the role of the cerebellum in the orientation of attentional resources (Schweizer, Alexander, Cusimano, & Stuss, 2007). The cerebellum is described as rapidly priming brain systems that are relevant to completing various tasks. This facilitates neural responsiveness and, therefore, improves task performance. In this theory, the cerebellum has an anticipatory effect upon sensory, motor, cognitive, emotional, and autonomic systems. This

anticipatory priming functions to ensure that attentional resources are allotted and implemented in a rapid, coordinated manner. The cerebellum is viewed as controlling task performance by detecting patterns of activity within the cortex and then shifting attention towards the modular behavioral systems that are implicated in the ongoing action or performance of the task.

Detection and correction of errors in skill learning and the strengthening of neural traces have also been theorized as basic functions of the cerebellum (Ito, 2002a; Wolpert & Kawato, 1998). Parallels have also been drawn between cerebellar function in error detection in motor learning and in both verbal and nonverbal thought (Ito, 2002a, 2002b).

These functions have more recently been applied to the modulation of cognitive function, specifically, verbal working memory (Ravizza et al., 2006; Schmahmann & Caplan, 2006). The authors of these studies propose that the cerebellum contributes to working memory during initial encoding by amplifying memory traces.

Others have proposed the role of anticipatory behavioral adjustments as a primary cerebellar function, and this has been related to proper timing in performance across a variety of tasks (Akshoomoff, Courchesne, & Townsend, 1997; Bares et al., 2007; Lang & Bastian, 2001). The cerebellum has been posited to function as an internal timing system that provides precise temporal representations across tasks so that they can be performed smoothly (Isope, Dieudonne, & Barbour, 2002; Yarom & Cohen, 2002). The cerebellum regulates neural signals in other parts of the brain through the cerebro-cerebellar circuitry, and it detects errors for making ongoing behavioral adjustments through the olivo-cerebellar system.

The timing adjustment of the cerebellum can on one level be considered as a special case of a more generalized error prediction process. However, neuroimaging data suggest that timing, per se, is a function of the distributed networks that are necessary to perform tasks, and not a unique function of the cerebellum (Jantzen, Steinberg, & Kelso, 2005). For example, cerebellar activation on timing tasks also positively correlates with activation of the dorsolateral prefrontal cortex, the intraparietal sulcus region, and the caudate nucleus (Dreher & Grafman, 2002). Diedrichsen and colleagues recently examined the distinct roles of the cerebellum in motor timing and coordination (or time versus state functions) in relation to arm and thumb movements, and suggested that the anterior cerebellum serves as a critical node in state-dependent motor control. The authors found that the temporal overlap of two movement components resulted in the brain using a state-dependent control process, where the state of one action affected the control of the other action. In the absence of this temporal overlap, the brain used a time-dependent control process, where initiation of each component relied on an internal representation of time. Only the state-dependent control produced robust activation of the cerebellum, which was uniformly on the side ipsilateral to the arm movement. This was interpreted to suggest a role for the cerebellum in state-estimation for coordination (Diedrichsen, Criscimagna-Hemminger, & Shadmehr, 2007).

The cerebellum appears to share timing information with other brain regions, which is consistent with the anatomic circuitries that have been presented above (Xu, Liu, Ashe, & Bushara, 2006). This seems to make sense, since communication within the brain would appear to depend upon the timing, duration, and intensity of signals. The specific role of the cerebellum in timing appears to lie in anticipatory response, as is evident in eye-blink conditioning. The cerebellum appears to play an integral role in estimation of time duration (Dennis et al., 2004; Grossberg & Seidman, 2006). Other theory proposes that the cerebellum is an essential modulator and coordinator for integrating motor, visceral, and behavioral responses (Zhu et al., 2006). This also implies a timing function, permitting homeostatic somatic-visceral integration during ongoing behaviors for adapting to the changes of external and internal environments (Zhu and Wang, 2007; Zhu et al., 2006).

It has also been proposed that the primary and fundamental function of the cerebellum is to learn predictive relationships among sequences of events. This would be important because whenever a similar or analogous sequence starts to develop or unfold in "real time," the cerebellum could generate predictions about what would happen next and prepare the neural systems that are expected to be needed to respond appropriately to such situational contexts. This implies that the cerebellum functions as a "learning machine" (Houk & Mugnaini, 2003). In the absence of this function, other brain systems would continue to operate, but only at a suboptimal level, since cerebellar prediction and priming or preparation might otherwise aid performance (Akshoomoff et al., 1997; Allen & Courchesne, 2003; Courchesne & Allen, 1997).

A Hybrid Model of Cerebellar Function

This brief review reveals general agreement about the cerebellum functioning as a modulator. Some theories stress timing and integration functions, others stress predictive and learning functions, and others stress error detection and correction. Most views combine aspects of these functions. We have developed a hybrid model of cerebellar functioning. The proposal includes features of models described in the above section as well as information derived from computational models. Our goal is to illustrate the role of the cerebellum as a modulator of cognitive and behavioral function while remaining true to the theme of this book, namely, to translate principles of movement to thought.

For the cerebellum, movement and thought are identical control objects (Ito, 1993, 2005). Body parts that need to be moved or coordinated and thoughts that need to be manipulated are treated equivalently (Vandervert, Schimpf, & Liu, 2007; Welling, 2007). Our hybrid approach is derived from this basic viewpoint and thus also departs from the cortico-centric model of cognition. We think this type of proposal provides a more integrated view of

cerebral-basal ganglia-cerebellar operations. The view we present proposes that these three brain regions operate in parallel (Houk et al., 2007).

The cerebellum receives information through the cortico-pontine, mossy fiber input system. This largely consists of information about the states of body parts and about perceptions of objects in the world around us as gathered by our sensory systems. The cerebellum also receives information about internal bodily, autonomic, and affective states. It receives information about the "neural" state of the brain including our purposes, goals and intentions as selected or gated by prefrontal-basal ganglia interactions. In other words, the cerebellum receives information about sensory conditions, about internal and external conditions, and about behavioral selections and plans. The cerebellum uses this information to set up a vector, a unified pattern of what the brain wants to do. This creates a map against which to compare the course and outcome of the behavior.

Ito refers to this type of internal representation as a *forward model* (Ito, 2008, 2005). It is considered a forward model because it *predicts* the outcome of an activity. The model "looks ahead." This type of predictive model is necessary because the cortex cannot respond solely on the basis of sensory-perceptual feedback that works too slowly. The cerebellum sends neural signals to the cortex so that the cortex releases a behavior based upon what the cerebellum has anticipated or predicted the outcome to be. This original map is presumably kept in prefrontal–posterior cortical circuitry, within working memory networks (Higuchi, Imamizu, & Kawato, 2007; Imamizu, Higuchi, Toda, & Kawato, 2007; Ito, 2002a, 2002b). In this regard, *the cerebellum creates a type of "copy" of working memory content*. If the cerebellum is to serve an action learning function, it would need to know what the brain wants to do and it would need to detect, code, and correct errors. This implies that the cerebellum needs a behavioral model or "map" in order to accomplish these functions. This map is the forward model.

In other words, the cerebellum takes information and adapts it to the current context. It is assisted in doing this because some of the information it receives from cortex is contextual, based upon representations stored in cortex from similar contexts, experiences, and behaviors. It also receives information about current circumstances. The cerebellum coordinates neural signals from a wide range of inputs, incorporating these into the "model" or "map." This includes "predictions" about how the behavior should unfold or develop, based upon past experience and current "sensory" conditions. The cerebellum determines the appropriate amplification or refinement of the current behavior in order to "fit" the situation (Petrosini, 2007). We can think of this refinement in terms of rate, rhythm (timing), and force. Based upon the cerebellum's neural composition, this adjustment consists of a homeostatic computation—or integration—of excitatory and inhibitory neural signals (Powell et al., 2008; Yamazaki & Tanaka, 2007). The cerebellum sends this information back to cerebral cortex via the thalamus. The cortex releases and stores the newly modified representation of the behavior.

Dependent upon the type, duration, and complexity of the behavior in question (for example, actions involving swinging a bat at a baseball versus

riding a bicycle versus learning some other new motor skill), the cortex then repeats this cycle by sending a new set of signals about the status of the behavior back to the cerebellum. The cerebellum can now compare the actual behavioral output signals with the original model. The olivo-cerebellar system detects errors in comparison to the model. It codes the error(s) and sends input to particular Purkinje cells to fine-tune the behavior (Ito, 2005, 2008). This process in turn adjusts the behavior by sending a new set of refined signals to cortex. This latter action also updates the model with a new set of adjustments. The cortex stores and implements these refinements.

The information received by the cerebral cortex is retained or represented there. Through practice or repetition, the behavior becomes even more efficient. The behavior becomes increasingly automatic and efficient through this rehearsal process. In this way, the cerebellum actively contributes to procedural acquisition and is, therefore, essential to certain aspects of procedural learning, as indicated above (Fiez, Petersen, Cheney, & Raichle, 1992; Hubert et al., 2007; Torriero et al., 2007; van Mier & Petersen, 2002). The olivary system participates through detecting and correcting "errors." The cerebellum can thus be considered a "supervised" learning system (Doya, 1999). After behavior becomes automatic, it requires no conscious control or input. When engaged automatically, behavior is "controlled" by what Ito refers to as an *inverse* model (Ito, 2008, 2005). An inverse model controls the automatic behavior on the basis of the cerebellum's "learned" experience with that behavior, and is independent of conscious management. It is "intuitive."

Therefore, a *forward* model is based upon anticipation. It *predicts* the outcome of an action, and through rehearsal or repetition (practice), makes appropriate adjustments accordingly through the olivary system. These refinements make the behavior more efficient. This type of learning leads to development of an *inverse* model maintained within the cerebellum. When the behavior is performed automatically it is controlled by this inverse model, which is based upon successful prior learning. This model allows for rapid, skilled, smooth and coordinated movements at an unconscious level, independent of conscious input (Ito, 2008, 2005; Vandervert, 2008b, Working memory, the cognitive functions of the cerebellum, and the child prodigy, unpublished).

Therefore, the cerebellum operates on the basis of two inter-related dynamic models. A forward model is necessary for the acquisition of a behavior. As that behavior is learned, an inverse model is established. As learning occurs, there is a dynamic shift in the behavior's locus of control, from forward to inverse control models.

Three Brain Systems in Parallel

The brain's "language" can be conceptualized as the transmission of neural signals (Yamazaki & Tanaka, 2007). The "grammar" of the brain's language system concerns the proper timing of neuronal impulses. Neuronal impulse

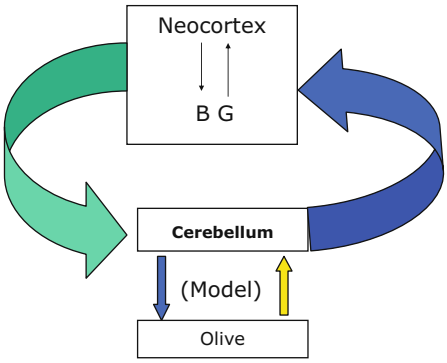

Fig. 5.5 Illustration of cortico-basal ganglia and cortico-cerebellar interactions

timing is based upon proper integration and balance of excitatory and inhibitory processes. Neuronal discharge output signals need to consist of appropriate intensity and duration. The cerebellum regulates these processes, which represents a critical refinement or amplification function. The cortex, basal ganglia, and cerebellum work in concert to achieve the final behavioral product (Hatta et al., 2004). Sensory-perceptual processes, behavioral programs, and ideas are all equivalent excitatory representations residing within the cortex. The basal ganglia select what we will attend to, and what we will do. The basal ganglia accomplish this through a process of selective disinhibition on the thalamus (Frank, Scheres, & Sherman, 2007). These neural representations of perceptions, ideas, and behaviors comprise "in the ballpark" selections that are appropriate to the context, but need to be properly amplified or refined for the specific circumstances (Houk et al., 2007). The cerebellum makes these refinements, again through a process of excitation/inhibition, and projects them to cortex for execution and retention. Therefore, *the cortex is actually driven by basal ganglia and cerebellar input*, and in this manner learns to perform a behavior more quickly, more accurately, and more automatically through practice or repetition in relation to this input. We can thus see clearly that with appropriate practice, the cortex is able to perform the behavior faster, more smoothly and adaptively, not to mention more elegantly, while representing these behaviors in cortex more efficiently (Saling & Phillips, 2007). We can also see how this is made possible through the contributions of subcortical mechanisms. These functions are depicted in Fig. 5.5.

Dysmetria—What Does It Signify?

So, how can this model be concretized; what does dysmetria tell us about the cerebellum, and how can these concepts be applied to thought? Let's start with the simple example of reaching for a glass as you sit in your chair at the table.

You have engaged in this routine behavior countless times. The cortex has stored a representation of this movement sequence. The basal ganglia have released the elements of this sequence every time the behavior has been performed. You have formed the intention of reaching for the glass to drink its contents. All of this information is projected to the cerebellum. This information includes the location of the glass, its distance from you, its position on the table, and so forth. The cerebellum also receives information about your prior sensory experiences of lifting glasses.

However, there is one problem. For the sake of our illustration, let's say your cerebellum is then damaged. The previously established inverse model held within your cerebellum is destroyed and a new forward model cannot be computed. Without a behavioral map or model, your cerebellum cannot send behavioral refinement signals to cortex, nor can it detect errors by comparing your actual movements to a model. As a result, your cortex and basal ganglia attempt to accomplish the goal on their own. The prefrontal cortex instructs the basal ganglia to release the appropriate movements. The basal ganglia appropriately gate the necessary motor sequence. The result is a reaching behavior. However, the execution of this intact motor program is characterized by movements that are erratic in size and amplitude. Your movements are not smooth or coordinated in quality. Instead, your movements are characterized by swaying from side to side, as your arm undershoots/overshoots the "target." Cortical–basal ganglia interactions can select all the proper movements in correctly executing the motor program, but without the cerebellum's model and error detection mechanisms to guide the behavior, the procedure cannot be performed efficiently.

This example reveals a very important point. *The behavior resulting from damage to a particular brain region does not reveal the function of that brain region*. Instead, the resultant behavior reveals how intact brain areas (in this case, intact cortex and basal ganglia) perform the behavior without the affected brain region's input or contribution. Therefore, the above example illustrates how behavioral programs—and their proper selections—need to be refined for efficient performance given environmental characteristics.

So, what does dysmetria tell us about thought and emotion? Thinking and feeling also require refinement to meet the context of the situation. In the absence of the cerebellum's error detection function and accompanying relay of updated, corrected information back to the cortex, thought becomes illogical. Thinking cannot then be properly "coordinated" with the current circumstances because cerebellar output is defective (Andreasen, Paradiso, & O'Leary, 1998; Andreasen et al., 1999). Thinking undershoots, overshoots, or misses its target. Instead of coordinating and refining, the cerebellum "mis-associates" or "misconnects" information and relays this defective output to cortex (Andreasen & Pierson, 2008). This is manifest in overt symptoms through circumstantiality of thought at the very least, or by psychotic thought processes, with associations that make no logical sense, at worst.

For example, a perception might be tied to a variety of extraneous, irrelevant, or erroneous associations. This can lead to oddities, peculiarities, and idiosyncrasies in logic and thinking. If an internal auditory neural impulse is associated with an external feature of the environment instead of its proper inner source, this can lead to experiences such as auditory hallucinations, thought insertion, and thought broadcasting, to name a few psychotic symptoms. Emotional analogues of dysmetria might include a lack of responsiveness, irritability, or exaggerated reactivity (examples of these processes are reviewed in the following sections).

Therefore, the parallel between motor dysmetria and cognitive dysmetria is an important one. The cerebellum enhances the quality of motor acts, making them smoother, more efficient, and ultimately more adaptive. The cerebellum similarly enhances the quality of cognitive acts, making thought, and emotion more coordinated, more efficient, and adaptive. In this regard, the cerebellum treats motor, cognitive, and affective input in the same way.

Working Memory, Expertise, Creativity, and Giftedness

Chapter 2 drew a parallel between a motor plan and a cognitive plan. Motor and cognitive plan execution was demonstrated through examples of working memory maintenance and updating functions. We also noted that working memory tasks activated the cerebellum. We have implied earlier in this chapter that this cerebellar activation might in part represent a manifestation of *"copying" the contents of working memory* in order to establish a forward model. Does the cerebellum play any other role in relation to working memory? The organization of the cerebellum provides a clue, as motor and cognitive input are treated equivalently.

All higher-order control is based upon working memory. The term "working memory" can be understood as convenient shorthand for the process of keeping in mind the cognitions, thoughts, plans, or programs that guide behavior. In Chapter 2, we saw how the basal ganglia treat motor and cognitive programs equivalently. Basal ganglia selections of perceptions, cognitions, and movements were presented as mediated by the same mechanisms. The same principle applies to the cerebellum. Manipulating body parts requires the same mechanisms as manipulating ideas (Ito, 2005, 2008; Vandervert, 2007; Vandervert, 2008a, How cognitive internal models of the cerebellum accelerate working memory to produce giftedness through deliberate practice, unpublished). Let's start to examine this notion further by illustrating how an athlete might become a highly skilled basketball player.

How does an individual acquire the motor expertise to play this sport? Think about the best shooter on the team who can make a basket from almost any position on the floor, while standing still, running, jumping, or while moving sideways or backwards, as if throwing the ball while performing acrobatics in

mid-air. How are these behaviors accomplished? The "expert" player will tell you this occurs by practising, by playing, by doing the same thing, over and over again. But what does this mean for the brain? How does the brain participate in the accomplishment of this expertise?

The cerebellum functions as a learning mechanism. It helps the brain learn through repetition. It manipulates body limbs through two control processes, namely, *forward* and *inverse* models. In initially learning a skill, prefrontal-basal ganglia interactions provide the serial-order processing for learning new motor programs. However, we also know that the neural signals comprising these motor sequencing programs are also projected to the cerebellum. When initially learning a skill, the cerebellum develops a forward control model. This model allows for behavioral predictions that are associated with rapid, skilled movements at a conscious level (Vandervert, 2007; Vandervert, 2008a, b, unpublished; Vandervert et al., 2007; see Chapter 4 for a review of the dynamic anatomy of motor skill learning).

While the skill is first being learned, the rapid motor sequence is controlled by the forward model (through cerebellum signaling cortex). The olivary system detects errors and refines the forward model's predictions. With repeated practice, the behavior becomes automatic. As automaticity is acquired, the cerebellum establishes the inverse control model. This model essentially comprises an internal cerebellar representation learned through the successful execution of forward models. This allows the behavior to be performed without conscious input. So, the more the athlete practices, the more the behavior falls under automatic control, ultimately requiring no conscious thought. Through repetitively shooting baskets from different areas of the court (and while jumping, moving, etc.), initially using forward models, the cerebellum establishes a variety of *multiple inverse control models*. These inverse control models comprise the player's expertise.

However, the player's true "expertise" is seen as the game unfolds—where the action is—as plays develop and circumstances change. While practice results in diverse and efficient inverse models, this practice also allows for extremely rapid, accurate, automatic movements, literally without conscious control. As circumstances unfold and the playing field changes, forward models need to be developed and executed very quickly. The highly skilled player operates with a variety of well-developed inverse control models at his disposal and is thus able to rapidly shift from forward models to one of these inverse models at any given moment. The expert demonstrates higher levels of performance through a process of alternating between and combining forward and inverse models (Vandervert, 2007). The less skilled player likely has both fewer and less well-developed inverse models, and must then rely more upon forward models. In our view, this is one of the essential differences between the expert's "motor creativity" and the more average player's repertoire of skills. (This is presumably in addition to inherent differences in how easily or efficiently the cortex encodes motor neural signals.)

So what does this have to do with cognitive expertise, creativity, and even giftedness? Once again, the process of cognition can be understood as an extension of the motor system. Just as the cerebellum improves the quality and coordination of physical movement, it also improves the efficiency of cognitive "movement." For the cerebellum, *there is no difference between movement and thought once these functions are encoded within the neural circuitry of the cerebral cortex* (Ito, 1993). The cerebellum manages the skillful manipulation of physical movement and it manages the skillful manipulation of ideas in the same way. For example, "learning" the computations that 2 plus 2 equals 4, 4 plus 4 equals 8, and 8 plus 8 equals 16 would initially require relying upon conscious working memory processes and the implementation of forward control models. *Patterns of repetitious working memory processing are learned in the cerebellum* (Vandervert, 2003). Practice results in immediately "knowing" that 2 plus 2 equals 4 and that 4 plus 4 equals 8, and so on. Knowing this is instantaneous or "automatic" and would thus be considered the product of inverse control models that no longer require conscious "working memory," or any conscious thought at all. Knowing and quickly computing that 4 plus 4 equals 8, plus 8 equals 16, divided by 2 equals 8, plus 4 equals 12 requires a combination of forward and inverse control models. In this way, the cerebellum contributes to making cognition more rapid and more efficient. Making this analogous to the development of the basketball player's *motor* expertise, the cerebellum is establishing *cognitive* inverse control models (Ito, 2005, 2008; Vandervert et al., 2007; Vandervert, 2008a, 2008b, unpublished). In other words, a critical role of the cerebellum is to establish models. These models regulate or govern the rapid, efficient manipulation of both motor and cognitive activities. The repetitious processing, or "practice," of the contents of working memory becomes automatic.

Taking this further, it would follow that the expert mathematician (like the expert basketball player) has a variety of diverse, multiple mathematical inverse control models in order to automatically manipulate mathematical cognitions. Mathematical "creation" might similarly result from the manipulation and combination of inverse and forward cognitive control models. Vandervert and colleagues have argued that the cerebellum's ability to generate models and to automate cognitions are at the basis of what generates giftedness and child prodigy (Vandervert et al., 2007; Vandervert, 2007; Chavez-Eakle, 2007; Ito, 2007; Welling, 2007). For example, prodigy is typically associated with overfocused attention or high attentional control. This would theoretically represent the underpinning of what Vandervert refers to as a "deliberate practice architecture" (Vandervert, 2007). Highly focused attention would generate repetitive working memory processes, or "deliberate practice," which would result in the establishment of numerous and highly efficient cerebellar models. The manipulation and combination of forward and inverse models would generate child prodigy for whatever the particular topic or domain, just as the manipulation of cerebellar models results in athletic expertise. This conceptualization raises interesting questions about the relationship between creativity

and "madness," particularly with regard to "genius," psychopathology, and relative contributions of forward and inverse control models. (We would additionally note that even though subcortical brain regions treat motor and cognitive input equivalently, this does not mean that these capacities are "the same," since movement and thought must initially be encoded within the appropriate specialized regions of the cortex. We differentiate here, as in other areas, between content and process.)

Clinical Presentations

The functional neuroanatomy of the cerebellum predicts certain patterns of deficit based upon regional area of involvement. As noted previously, sensorimotor functions are primarily mapped in anterior regions of the cerebellum. Cognitive functions are primarily mapped in posterior and inferior cerebellar regions. Therefore, lesions in the anterior lobes should generate motor deficits, and lesions in posterior lobes should result in cognitive impairment (Hu et al., 2008). In addition, the medial-lateral gradient predicts that lesions within the vermal area should generate changes in affective/emotional functioning, while lesions in lateral regions should result in cognitive deficits.

Anterior lesions primarily result in the cerebellar motor syndrome. This syndrome is characterized by gait ataxia, dysmetria of the extremities, eye movement abnormalities, speech disturbances such as dysarthria and prosodic changes, and dysphagia. Some patients also demonstrate decomposition of movement. In this presentation, multiple joint coordination breaks down. Movements are accomplished by moving one joint at a time, individually, but in the appropriate sequential manner. Not all patients with anterior lobe damage exhibit the full range of these symptoms. However, the classic presentation consists of dysmetria. In this symptom, as described above, movements become erratic in direction and size, with "overshooting" and "undershooting" or a type of "swaying" characterizing the lack of motor coordination. In these ways, it is primarily the quality and efficiency of movement that are affected.

Motor abnormalities also depend upon regional involvement within the cerebellum. For example, lesions near the midline often result in truncal ataxia, a loss of coordination of movements associated with the body's center. Disturbance of the medial motor system often generates a wide-based, unsteady gait. When the intermediate and lateral zones of the cerebellum are involved, patients exhibit ataxia of movement of the extremities, or appendicular ataxia. Making staggered movements when reaching for objects, with a characteristic "undershooting and overshooting," is sometimes referred to as intention tremor because it occurs during the performance of an act.

The concept of dysmetria ties the symptoms of the cerebellar motor syndrome together. With midline involvement, there is a swaying of the trunk, and when walking, there is unsteady, "drunk-like" gait, swaying from side to side.

This is analogous to truncal or gait "tremor." When the upper extremities are involved, the staggering and swaying of the arms and hands is called intention tremor. Within the visual system, there are abnormal saccades, again resembling "tremor," with the characteristic swaying, or under and overshooting of eye movements. A similar lack of coordination is seen in dysarthria, analogous to a "swaying" of speech, and within the vocal system, there are similar volume and prosodic disturbances which again resemble the swaying of "tremor." In all of these instances, the patient's actions demonstrate varying degrees of erratic amplitude. The quality of the symptom is similar whether it concerns the trunk, the lower and upper extremities, the eyes, or the expressive speech system.

When the posterior and inferior lobes of the cerebellum are involved, the primary presentation is that of cognitive deficit. In a study of patients with posterior cerebellar infarct, the typical signs of the cerebellar motor syndrome were minimal or absent (Kalashnikova, Zueva, Pugacheva, & Korsakova, 2005). Instead, the primary presentation consisted of cognitive impairment. Cognitive deficits included impairment in attention, planning, abstract thinking, and memory. There were visuospatial deficits and dysprosodia with left cerebellar hemisphere infarct and language difficulties and executive function deficits with right cerebellar hemisphere infarct. Therefore, deficits resulting from cerebellar infarct were localized. These localization phenomenon have been reported in a variety of studies with adults and children (Gordon, 2007; Hokkanen, Kauranen, Roine, Salonen, & Kotila, 2006; Riva & Giorgi, 2000b; Schmahmann, 2004). When the cerebellar cortex associated with the dominant hemisphere of the cerebral cortex was involved, language disturbances included naming difficulty and agrammatism. A number of investigators have concluded that the cerebellar zones controlling movement and cognitive function are different. The vermal region has often been referred to as the "limbic cerebellum," and focal involvement in this area has been related to changes in emotional responsiveness, alterations in personality functioning, as well as psychotic and behavioral disturbances (Schmahmann, 2004). In these ways, there is a functional asymmetry about the cerebellum (Hu et al., 2008).

The Cerebellar Cognitive Affective Syndrome

The cerebellar cognitive affective syndrome is a descriptive diagnostic term that can be applied to a group of cognitive, emotional, and behavioral symptoms that occur in patients with involvement of the cerebellum (Schmahmann, 2004). Studies have documented this syndrome by evaluating and comparing three independent sources of data. First, the syndrome has been identified through behavioral observation. This observation included report from family members of patients with cerebellar pathology, as well as direct observations made by treatment providers. Second, the syndrome has been identified through direct neuropsychological testing. Third, while some might question the ecological

validity of neuropsychological testing procedures in terms of how they relate to "real life" impairment, the syndrome has also been correlated with symptoms that emerged from bedside evaluation and with levels of impairment in practical, day-to-day functioning. The data gathered have demonstrated a consistent picture of cognitive and affective impairment, particularly in patients with posterior involvement of the cerebellum and in patients demonstrating pathology within the vermis. Further, while the patient populations exhibiting this syndrome did not have cortical pathology, the type and level of impairment that these patients demonstrated was indistinguishable from that observed in individuals demonstrating pathology within the cerebral cortex. It is likely that this occurs because the cerebellum regulates neural signals in these regions of the brain.

The cerebellar cognitive affective syndrome has been identified in both adults and children, with a remarkably similar symptom picture emerging in both populations. For example, disturbances have been identified in executive functioning. These functions include impaired planning, set-shifting, verbal fluency, abstract reasoning, and working memory. Deficits in spatial cognition have also been reported, specifically involving visuospatial organization and memory. Language deficits, in terms of agrammatism, and aprosodia, have been identified in both populations. Personality change, described as blunting of affect or disinhibited and inappropriate behavior, are especially characteristic of patients with midline cerebellar involvement. These symptoms also have been notably evident in patients with chronic alcoholism and related cognitive deficits (Fitzpatrick, Jackson, & Crowe, 2008).

In adult populations, primarily composed of patients with infarct or tumor, the most pronounced deficits were evident in executive and visuospatial functions. The most impaired patients had bilateral cerebellar and posterior lobe lesions. Patients who had very small lesions, or lesions confined to the anterior lobe of the cerebellum, were the least affected in terms of cognitive and affective functioning. Presumably because of the range of cognitive impairment that was evident, general intellectual functioning was also affected. Many cognitive functions were impaired and this had the impact of lowering performance on traditional IQ testing. However, in most domains, the impairment that was initially documented improved over time. For example, less than a year after onset of the condition, most scores on neuropsychological testing were within normal limits, although scores on tests of executive function remained significantly below the mean. In a study of 26 patients with cerebellar infarcts, deficits were observed in visuospatial/motor functioning, episodic memory, attentional shifting, and in working memory during the acute stage of these conditions. Visuospatial deficits were characteristic of patients with left cerebellar lesions, and verbal memory difficulty, with particular problems in working memory, were characteristic of patients with right cerebellar infarcts. By three months, patients improved and over 75% were able to return to work (Hokkanen et al., 2006).

Studies with children are quite similar and allow for some important additional inferences (Steinlin, 2007). However, it is important to differentiate between children with acquired cerebellar pathology and those with early

onset, intrinsic pathology. Older children with tumor and stroke demonstrate impairment in the same functional domains as adult patient populations. Taken together, these studies demonstrate the specialized distribution of cognitive functioning by specific cerebro-cerebellar networks. For instance, impairment in verbal intelligence and higher-level language skills typically follows right cerebellar lesions. In contrast, deficiencies in the performance of non-verbal tasks and deficits in prosody follow left cerebellar lesions. Children with involvement of the vermis, or "limbic cerebellum," develop changes in personality functioning, such as irritability, emotional lability, and even autistic-like cognitive and behavioral features. In young child patient populations, there is a persistence of deficit over time (Guzzetta et al., 2000). In contrast to what is observed in adult populations, there is less improvement.

Therefore, the data demonstrate that throughout the lifespan, the cerebellum plays an essential and fundamental role in the organization and expression of higher-level cognitive functions. The consistency of deficits in adult and child populations confirms that there is a topographical organization of the cerebellum, along anterior-posterior and medial-lateral gradients. The specific cerebro-cerebellar circuits represent the neuroanatomic substrate or underpinnings of this topographical organization. The data further imply that the "feed forward" connections from cortex to cerebellum, and the "feedback" connections from cerebellum to cortex are developed very early in life. Since young children demonstrate persistent deficits, this implies limited capacity for the reorganization of neuronal connections, and limited compensatory strategies, with questionable "plasticity" (Riva & Giorgi, 2000b). The young brain does not appear to be able to fully compensate for the effects of early cerebellar lesions. Cerebro-cerebellar connections appear to be essential to normal development (Diamond, 2000), and the brain does not easily reorganize itself when these connections are affected. Later in life, the cerebellum also appears to be involved in multiple neurodegenerative disease processes, and has repeatedly been implicated in Alzheimer's disease, where atrophy of posterior cerebellar regions has been associated with poorer cognitive function (Thomann et al., 2008). Patients with degenerative cerebellar diseases frequently present for psychiatric evaluation and treatment (Leroi et al., 2002).

The Posterior Fossa Syndrome

Most brain tumors in adult populations are supratentorial. This essentially means that these tumors affect the frontal, temporal, and parietal regions of the brain, while tumors of the posterior fossa occur less frequently. However, in children this relationship is reversed, and the most common tumor site is within the posterior fossa (Stargatt, Rosenfeld, Maixner, & Ashley, 2007). This means that the cerebellum is the brain region primarily affected (Blumenfeld, 2002). Posterior fossa tumors often affect the midline, or the cerebellar vermis.

Approximately 15% of children who undergo resection of midline cerebellar tumors develop what has been termed the posterior fossa syndrome. This syndrome primarily occurs in children between the ages of 2 and 10 years and is characterized by the development of mutism, which occurs a few days postoperatively, usually 1–5 days after the resectioning procedure. In the recovery stages over the following several months, symptoms are characterized by dysarthria and speech/language dyspraxia (Arslantas, Erhan, Emre, & Esref, 2002; Huber, Bradley, Spiegler, & Dennis, 2007).

There are actually two types of language deficits with the Posterior fossa syndrome (Riva, 2000). When the vermis is primarily involved, sparing the cerebellar hemispheres, mutism develops a few days postoperatively and quickly develops into dysarthria. Over time, the dysarthria improves considerably. When the vermis and the right cerebellar hemisphere are affected, the symptom picture is characterized by primary or "real" language disorder. Even when speech recovers, it is slow, monotonous, and often telegraphic. While comprehension remains intact, grammatical disturbances are evident in language expression. Therefore, this language pattern is similar to what is observed in patients with frontal lobe lesions. This again reflects the neuroanatomy of the cerebro-cerebellar circuitry, which is the anatomic substrate for the cerebellum regulating neural signals in frontal and prefrontal brain regions. In any event, these types of language deficits improve slowly and residual symptoms are often evident (Stargatt et al., 2007). In addition, the language deficit observed with right cerebellar involvement does not occur in isolation. It is accompanied by cognitive deficits such as impairment in the shifting of attention and thinking, or perseverative behavior, as well as impairment in problem-solving. In other words, there are executive function deficits as well. In patient populations with involvement in this cerebellar region, residual functional deficits are common (Riva & Giorgi, 2000a; Steinlin et al., 2003).

The two types of language disorder in posterior fossa syndrome appear to have different etiologies. In mutism followed by dysarthria followed by recovery, it is possible that the brain stem manipulation associated with surgery at the midline results in edema and blood flow alterations that normalize in the recovery phase postoperatively. In cases in which the right cerebellar hemisphere is directly involved in the pathology, it is likely that tissue damage within cognitive lobules or zones generates language and executive dysfunction symptoms because the specific cerebro-cerebellar circuits that regulate those cognitive functions are damaged.

There is also a behavioral syndrome accompanying resection of posterior fossa tumors. This behavioral syndrome is primarily characterized by regressive personality changes. These changes in functioning include apathy, withdrawal, and poverty of spontaneous movement. There is little initiation of any activity. Emotional lability is also evident, characterized by irritability, unconsolable emotional reactions such as crying or even laughing, and agitation (Riva, 2000). These aspects of the presentation are actually quite similar to what can be observed in patients with involvement of orbirofrontal or medial frontal

circuitry, and once again, this presumably results from a breakdown in the specific cerebro-cerebellar circuitry that regulates neuronal signals in paralimbic cortices.

Agenesis of the Cerebellum

Agenesis of the cerebellum is a rare condition in which a child is literally born without a cerebellum. However, it is very important to understand that in this condition, agenesis is seldom complete and is almost always partial. Similarly, the agenesis can affect different cerebellar regions (Nowak, Timmann, & Hermsdorfer, 2007; Richter et al., 2005). Therefore, no two cases of cerebellar agenesis are the same, and this can make it very difficult to group together the kinds of symptoms that occur in this condition as well as compare one individual with this condition with another individual. However, that having been said, a variety of cognitive, affective, and behavioral deficits have been reported in children with cerebellar agenesis.

Most conditions of this type are characterized by a generally diminished level of intelligence (Ackerman & Daum, 2003; Richter et al., 2005). IQ values are usually in the defective or borderline psychometric ranges, although some children can function at a somewhat higher level. Impairment in executive functioning is typical. There are deficits in expressive language functions, as well as disturbances in prosody. Visuospatial deficits are reported (Timmann, Dimitrova, Hein-Kropp, Wilhelm, & Dorfler, 2003). Psychiatric and affective disturbances are common, including autistic-like behavior and obsessive rituals (Courchesne et al., 1994). The symptom presentation can depend upon which regions of the cerebellum are most affected by the particular type of structural pathology. Obviously, all affected children do not exhibit each and every symptom, and the degree of agenesis can result in notable variability in presentation between subjects. However, in most cases, there is little improvement in functioning over time (Glickstein, 1994). Differences can be observed between the performance on neuropsychological tests and the level of practical adaptation that is achieved, but this type of discrepancy is certainly not unique to what is observed in pathology of the cerebellum.

Very Pre-Term Infants

Children who are born very pre-term, before 33 weeks, typically demonstrate cerebellar abnormality (Messerschmidt et al., 2008). This is primarily characterized by a smaller cerebellum. In this population, functional deficits have been reported in three areas. First, deficits have been described in executive functions. Second, impaired visuospatial functioning has been reported, and third, impaired language skills have been documented (Limperopoulos, Soul, Haidar,

et al., 2005; Limperopoulos, Soul, Gauvreau, et al., 2005; Limperopoulos & du Plessis, 2006, 2007) Therefore, very pre-term children have been described as exhibiting aspects of the cerebellar cognitive affective syndrome. Ortiz-Mantilla and colleagues found that very-low-birthweight infants are at significantly greater risk for cognitive and language delays, but did not specifically tie these delays to cerebellar dysfunction, per se (Ortiz-Mantilla, Choudhury, Leevers, & Benasich, 2008). Long-term follow up information on this population is limited. Some current research indicates that ongoing adaptive delays are common, although some individuals may experience little, if any, adaptive impairment as adolescents (Nosarti et al., 2008). (See Chapter 11 on the cerebellum and neuropsyhological testing for additional information on a clinical case of premature birth.)

DSM-IV Behaviorally Defined Conditions

The DSM is not a diagnostic manual organized around brain–behavior relationships. The DSM system is organized around behavioral definitions of disorders. This means that a diagnosis is made on the basis of the observational criteria for the condition in question. This makes application of DSM criteria to brain–behavior relationships very difficult. Most DSM categories are understandably driven by the involvement of multiple brain regions. That having been stated, there are a number of diagnostic conditions listed in the DSM in which the cerebellum has been implicated in the behavioral pathology (Rapoport, van, & Mayberg, 2000; Schmahmann, 2000). Some of these conditions will be reviewed in a subsequent section.

Attention Deficit Disorder, Autism spectrum disorder (including Asperger's syndrome), and Schizophrenia are three frequently occurring conditions in which the cerebellum has been consistently implicated (Ahsgren et al., 2005; Allen & Courchesne, 2003; Amaral, Schumann, & Nordahl, 2008; Catani et al., 2008; Krain & Castellanos, 2006; Mackie et al., 2007; Mulder et al., 2008; Okugawa et al., 2006; Stanfield et al., 2007). Focal involvement of the cerebellum in these conditions has been demonstrated through a variety of neuroimaging techniques as well as post-mortem findings (Ashtari et al., 2005; Karlsgodt et al., 2008; Picard, Amado, Mouchet-Mages, Olie, & Krebs, 2008). These conditions are characterized by considerable variability in their presentations, which will be discussed in more detail in another chapter.

However, for now, it will suffice to note that one common feature to these conditions is not only a focal or regional abnormality within the cerebellum, but also, the presence of behavioral chronicity. Sometimes there are global volumetric differences in the cerebellum. Although prognostic outcome in terms of any individual's practical adaptation is variable, the persistence of these disorders is not in doubt. Once again, although many brain regions are involved in

these diagnoses, the role of the cerebellum in relation to the persistence of deficits bears consideration (Gowen & Miall, 2005, 2007; Mackie et al., 2007).

The Cerebellum as a Modulator

Before turning to case studies, it would be useful to review the role of the cerebellum as a modulator of function or behavior. This is important in order to address certain inconsistencies that arise in reviewing the presentations of adults and children with different conditions involving the cerebellum. If the cerebellum does only "one thing," how can we understand its role in conditions with such diverse cognitive, affective, and behavioral presentations? As will be recalled, the cerebellum is not a generator of sensory processing, motor activity, or of cognitive or emotional functioning. Instead, the cerebellum modulates behavioral output by regulating the duration and intensity of neural signals in other regions of the brain. This function has been termed the "Universal Cerebellar Transform" that facilitates automatic modulation of behavior around a homeostatic baseline (Schmahmann, 2004).

Grossly, the cerebellum enacts this role by adjusting behavior on the basis of two sets of input it receives. The first set of input, from the mossy fiber system, provides the cerebellum with a behavioral "vector" including sensory, motor, cognitive, affective, and autonomic information. This informs the cerebellum about changes that are needed in order to efficiently accomplish the behavior, including the appropriate refinement or amplification of behavior. The second set of input from the olivary system allows for a correction or "learning" of new neural associations relating to the "online" adaptation. The behavior undergoing modulation is a manifestation of the specificity of the cerebro-cerebellar circuits, or loops, within the intrinsic connectivity of the cerebro-cerebellar system. Impairment is manifested motorically by the ataxic motor syndrome when the anterior or sensorimotor cerebellum is affected. Impairment is manifested cognitively when the posterior inferior lateral cerebellar hemispheres are involved, and impairment is exhibited affectively and/or behaviorally when the vermal area is involved. In all of these cases, the relevant deficit can be understood as a disturbance in the rate, rhythm, or force of the observed behavioral output (Schmahmann & Sherman, 1998).

A review was presented earlier of adults demonstrating acute onset of cerebellar pathology (excluding the progressively deteriorating cerebellar ataxic disease syndromes, which are not a topic of this book). These patients demonstrated tumor or vascular pathology and showed improvement in functioning over time. Children with similar pathology did not fare as well, and younger children showed the least improvement. Cases featuring cerebellar agenesis were presented as demonstrating chronic deficits, with little functional change over time. Several behaviorally defined DSM diagnoses were also mentioned, and were described as chronic conditions with either focal or more diffuse

impairment of the cerebellum. The apparent disparities in presentation among these various disorders might be better understood by viewing the cerebellum as a modulator of function with learning properties. From this viewpoint, the whole organism benefits from the experience of the cerebellum.

For example, an adult has a history of adaptive functioning and behavior prior to acute onset of a condition such as tumor or stroke. This history establishes an experiential background. While these patients generally do not achieve optimal pre-morbid levels of functioning, they do attain some improvement. It may be that against the background of an acquired adaptive history, the brain can "learn" to live without a cerebellum. Functioning is less efficient without the cerebellum's input, but a brain can learn to adapt well enough from past experience. On the other hand, in cases of agenesis or very early onset posterior fossa tumor, the individual in question never had much of a functional cerebellum to begin with. There is no neural experience or neuronal learning to draw upon, so the individual in question continues to experience problems with motor, cognitive, affective, and/or behavioral modulation. Functioning never achieves the optimal level of a normal control, and the clinical picture, therefore, becomes more chronic.

From this perspective, individuals meeting behavioral criteria for DSM-defined disorders demonstrate a chronic, focal cerebellar abnormality. The focal abnormality might affect a region modulating cognitive, emotional, and/or behavioral functioning. In these conditions, the individual chronically functions with cerebral hemispheres that are essentially being given, or are being fed, "bad data" from a focally abnormal cerebellum or white matter tracts to or from these areas. For example, in a recent study by Ashtari et al. (2005), the authors identified abnormalities within specific cerebellar-prefrontal circuitry which contributed to ongoing symptoms of ADHD. In the context of this circuitry, the individual becomes somewhat functional but continues to demonstrate impairment in adaptation dependent upon region(s) of focal cerebellar involvement.

Jeremy Schmahmann and colleagues have collected voluminous data regarding the clinical presentations of various disorders featuring cerebellar involvement (Schmahmann, Weilburg, & Sherman, 2007). Patients with cerebellar abnormalities presented with a range of behaviors meeting criteria for diagnoses of ADHD, obsessive-compulsive disorder, mood disorder, and autistic spectrum disorder, to name a few. Many of these patients presented with symptoms (such as apathy or irritability) commonly described in relation to disruptions of fronto-striatal circuitry. The authors arranged these patients' symptoms in relation to exaggerated (hypermetric/overshoot) or diminished (hypometric/undershoot) manifestations of emotional or cognitive behavior, and noted five neuropsychiatric domains in which the cerebellum appears to play a significant role, including the areas of attentional control, emotional control, autism spectrum disorders, psychosis spectrum disorders, and social skill set. Schmahmann notes, "In the same way that the cerebellum regulates the rate, force, rhythm, and accuracy of movements, so does it regulate the speed,

capacity, consistency, and appropriateness of cognitive and emotional processes" (p. 263). Hypersensitivities to sensory stimuli might also be understood within this framework. For example, in a descriptive condition called sensory integration disorder, children can experience hypersensitivities to a variety of tactile and auditory stimuli, experiencing sounds and various "touches" as very intense. Schmahmann has also interpreted these hypersensitivities within this modulatory paradigm.

Dysmetria—Undershooting and Overshooting—An Important Paradigm

It is useful to think about the cognitive and emotional symptoms that have been described as analogous to symptoms within the motor system. For example, the disturbances in amplification of motor behavior are often described as affecting the rate, rhythm, and force of the behavior. Ataxia and decomposition of movement can be interpreted along these dimensions. The speech and language disturbances that have been described, such as mutism, slow, monotonous, and telegraphic speech are also conceptually similar to problems with rate, rhythm, and force. Concrete thinking is a cognitive analogue of decomposition of movement. Affective disturbances such as lability and unconsolable crying or persistent laughing can again be classified within these same general dimensions (Parvizi, Anderson, Martin, Damasio, & Damasio, 2001; Parvizi & Schiffer, 2007).

Paralyzing anxiety of panic attack is an example of a disturbance in the "force" of the experience of anxiety (Schmahmann et al., 2007). Anger outbursts and rage can be interpreted along the same gradient. Social withdrawal is also consistent with these dimensions. Becoming aware of these motor, cognitive, and affective analogs allows the formulation of a frame of reference through which to consider the information gathered over the course of an evaluation. Historical information and behavioral observations can be placed within this framework and more easily translated into models of brain–behavior relationships. Examples of applying this frame of reference to behavior will be reviewed in subsequent chapters of this book.

Summary

This model of cerebellar functioning, while heuristic and simplistic, is nonetheless useful as a template for understanding the general functions of the cerebellum in regulating behavioral output. The model helps illustrate the organization of behavior while at the same time reminding us of the fact that behaviors have three brain-related sources of input and variability, namely, the cortex, the basal ganglia, and the cerebellum. We are thus also reminded that

behaviors can be disrupted by disturbances at cortical and/or subcortical levels. The posterior cerebral cortices are highly specialized sensory processors. The prefrontal and frontal cortices are behavioral programming mechanisms. Sensory perceptions and motor programs are stored or represented in these cortical regions. Attention and action selections are gated or released by the basal ganglia. The cerebellum takes these selections and determines the appropriate amplification of behaviors based upon sensory-perceptual context and the goals and purposes of the organism. The cerebellum establishes control models that regulate or govern the rapid, efficient manipulation of both motor and cognitive activities. Therefore, these three brain regions are continuously working in parallel but unique ways.

This chapter reviewed the functional neuroanatomy of the cerebellum. Although there has been controversy as to whether or not the cerebellum plays a role in cognitive and affective functioning, the prototypical cerebrocerebellar circuit was reviewed as the underpinning of the cerebellum's contribution to behavior. This circuitry establishes the neuroanatomic substrate of the cerebellum's participation in sensorimotor, cognitive, and affective behavior. The functions of the cerebellum were described along two distinct gradients. There is an anterior-posterior gradient that mediates motor and cognitive functioning respectively, and a medial-lateral gradient that mediates affective and cognitive functioning. When a lesion occurs within a motor region of the cerebellum, this is manifest as a variation of the motor ataxic syndrome. When a lesion occurs within a non-motor module or zone of the cerebellum, this is manifest by either cognitive or affective pathology, depending on the focal region of involvement. Generally speaking, the cerebellum was described as a modulator of behavior. The cerebellum's role as a modulator can be understood within a diverse array of presentations, from pathology to prodigy.

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Chapter 6
Automaticity and Higher-Order Control in Communication: A Brief Introduction to Language and Social Cognition

You can only see properly with the heart. The essence of things is invisible to the eyes.

Antoine de Saint-Exupery, *Le Petit Prince*

Language is the blood of the soul into which thoughts run and out of which they grow.

Oliver Wendell Holmes

Language is a powerful cognitive tool. It enables us to live in groups and to socialize. These are easy things to take for granted, and we often neglect the fact that language is actually much more than a social enabler. At base, language serves as a categorizer. It allows us to organize our world, to acquire information about it, to think about the world, to manipulate ideas, and to express all of this information to others. It evolved because it was biologically adaptive. It was necessary for language to evolve in order to facilitate interaction with a complex environment.

As the cortex expanded in primates and humans, the capacity for sensory information processing developed greatly. Different specialized sensory processing channels evolved and were neuroanatomically organized in parallel. Sensory processing became distributed within multiple systems in order to manage information from the five senses, along with their specialized attributes. The range of sensory information available to the brain increased dramatically. As a result, it became increasingly difficult to integrate this sensory information into a unified whole. Therefore, it became necessary to develop a system for higher-level information categorization in order to make sense of the environment. The semantic organization of the language system likely evolved at least in part to meet the need for categorization generated by the expansion of sensory information-processing systems (Cangelosi & Parisi, 2004; Hauser, Chomsky, & Fitch, 2002; Lieberman, 2002). In a sense, the semantic categorization system of language allows for making that which is initially unfamiliar, familiar.

Humans have long been occupied with trying to understand and explain what connects us to and separates us from our "lower" animal relations on the

L.F. Koziol, D.E. Budding, *Subcortical Structures and Cognition*,
DOI 10.1007/978-0-387-84868-6_6, © Springer Science+Business Media, LLC 2009

evolutionary scale (or trying to explain how no such scale exists and we all showed up at the same time). One argument has posited that the ability to use language is an important characteristic separating people from animals who occupy a lower position on the phylogenetic scale. The cortico-centric model of cognition has even organized important aspects of brain–behavior relationships in man as based upon a verbal–non-verbal dichotomy.

Despite obvious differences between humans and other animals, there is biological consistency between species. In our view, the brain is not organized along a cortico-centric model in which language versus visual-spatial functioning or verbal versus non-verbal behavior represent the primary dichotomies. Instead, the brain is organized around a fundamental principle of adaptation, namely, to take that which is unfamiliar and make it familiar. This is where the adaptive advantage lies, which is the driving force of the frontostriatal system. We believe that life along the phylogenetic scale follows this principle.

Taking that which is initially unfamiliar and making it familiar also reflects the difference between higher-order control and automatic processing. On the phylogenetic scale, there is no level at which automatic processing stops and higher-order control begins. Instead, both of these processes occur on a continuum. Most occupants along the phylogenetic scale have some limited control in the sense that they make choices. These choices can be extremely limited. Many choices may be stimulus-based, but they remain choices. The basal ganglia serve as the basic gating system and the interface for automatic processing and higher-order control (see Chapter 2). Humans differ from other primates and animals on the basis of being able to adapt to a more complex environment. However, for any species within their appropriate environment, there are routine and novel circumstances. In one sense, all species must face the same dichotomy of routine-novelty challenges in order to adapt and survive within their respective environments.

Podell, Lovell, and Goldberg (2001) proposed the novelty-routinization hypothesis of hemispheric specialization. This view proposes that the right hemisphere is critical for cognitive processing in circumstances in which preexisting codes or strategies of cognition do not readily apply. In other words, this hemisphere manages novelty. The left hemisphere is critical for cognitive processing according to representations and routinized cognitive strategies that already exist. Within this cortico-centric model of information processing and adaptation, the traditional verbal—non-verbal dichotomy serves as a special instance of the more fundamental novelty-routinization principle. Symbolism and language from this perspective can be seen to represent a way of organizing novelty.

We similarly believe that novel information processing is fundamentally based upon discovering stimulus-based characteristics of unfamiliar situations. As sensory-perceptual systems developed during the course of evolution, "codes" had to develop in order to manage the range and characteristics of input that were increasing exponentially. Language, the great categorizer, appears to have evolved for that reason. In humans, the ability to combine and recombine

symbols, the capacity to generalize, the ability to generate new symbolic representations, and the capacity to detach representations and symbols from the concrete are the features of language and cognition that appear to be unique to us (Hauser, personal communication 2008). In our view, this "humaniqueness" hinges on an ability to discover the stimulus-based characteristics of new, complex situations or problems. Thus, language is one of the processes that allow us to take that which is unfamiliar and make it familiar, which is at the heart of adaptation. Because of this, we believe that language must have at least some basis in automatic processing. The process of categorization, through language, involves taking something novel and making it routine, thereby providing a link between higher-order control and automatic processing. That which is familiar or routine no longer requires higher-order control for processing.

Language, which is organized around a system of rules, also has predictable and automatic characteristics. A significant part of its value lies in the ability to manipulate symbols within those rules. The rule-based property of language, namely grammar, makes it a primary candidate for the rule-based processing governed by the frontostriatal system. The vocabulary of the language system, which essentially represents the semantic categories of cortical "sensory-perception," makes it a candidate for mediation through the medial temporal lobe memory system. Therefore, according to this view, language would require an interplay between subcortical and cortical systems. This model, initially proposed by Michael Ullman, is discussed below.

Gesture, Communication, and Speech

Primates and humans evolved to live in groups. Living in groups requires a communicative system. Gesturing was likely the first form of communication in primates. In fact, all primates continue to share some of the same gestures (Subiaul, Vonk, Okamoto-Barth, & Barth, 2008). The concrete meaning of gesture is based upon categorization and automaticity. The gesture, whatever it is, has one meaning all the time. After one learns to generate and read the gesture, the meaning it conveys is automatic. Gesturing as a form of communication likely evolved from motor systems. Just as is the case with locomotion and forms of action, gesturing, and other movements need to be ordered and performed in a particular sequence in order to fulfill their purpose. It is easy to see how gesturing is dependent upon motor systems.

However, gesturing has at least three limitations as a primary communicative system. First, as sensory information capacities expand, it becomes increasingly difficult to represent complex categories and manipulate them through a gesturing system. Second, in gesturing, the receiver of the communication needs to be looking at the communicator in order for the gesture to be effective. Third, it is obviously impossible to communicate through gesturing if one's extremities/

limbs are occupied with doing something else. These limitations of gesturing generated substantial adaptive pressure on the organism to evolve other means of communication. Vocal language was the answer to that adaptive pressure.

However, just as gesturing relies upon movements in proper order, vocal speech sounds need to be organized in proper sequence to convey proper meaning. In this way, oral language is very closely tied to motor sequencing systems. Gesturing and vocalization both rely upon serial-order processing or motor sequencing. This fact already provides some hint that subcortical brain regions would likely play a role in language. For example, as reviewed in Chapter 2, cortical–basal ganglia "loops" provide a specialized neural architecture for ordering the movement sequences necessary for organized behavioral patterns. This suggests that this neural architecture is uniquely suited to provide the underpinning for sequencing the rules of gesturing, vocalization, and grammar. Vocalization combined with the motor system's existing characteristics for adaptation to environmental demands, thus making use of existing systems instead of "reinventing the wheel" in order to generate a totally novel solution to a problem in adaptation. However, in this way, language is dependent upon both the sequential learning processes of the basal ganglia as well as upon the motor programming capacities of the frontal cortex. This again implies that language would consist of an interaction between automatic and higher-order control processes.

The cerebellum would also play an important role in both gesturing and speech from this perspective. Ackermann and colleagues have examined the neural correlates related to the cerebellum and its evolution in relation to speech sound perception and production (Ackermann, Mathiak, & Riecker, 2007; Ackermann, 2008). The authors have delineated at least two main roles of the cerebellum in relation to language. They have found that the cerebellum contributes to the temporal organization of the sound structure of verbal utterances through supporting online sequencing of syllables during overt speech production. Further, they also found evidence for the cerebellum participating in the generation of internal speech, through prearticulatory verbal code. The obvious implications for verbal memory and thought processes were also considered. The authors linked a number of these evolutionary changes to mutations in the FOXP2 gene in particular.

Animals and of course primates can communicate through sound or vocalization. As reviewed by Kolb and Whishaw (2008), chimpanzees have been reported to communicate through at least 32 separate vocalizations. These sounds enable an animal to communicate concrete, categorical information. These include expressions such as fear, puzzlement, annoyance, social fear, distress, food and social excitement, and sociability just to name some of the types of information that can be communicated concretely through vocalization. This suggests that the ability to communicate certain types of information is really an evolutionary old skill which also implies that phylogenetically older brain regions are sufficient to mediate these communications. There is also a stimulus-based quality about these communications that is very comparable to gesture and again, this would likely be supported by subcortical brain regions that contribute to automatic

processing. Previous chapters have already discussed the roles of the basal ganglia in sequence learning and categorization. Both categorization and fundamental types of vocal communication are very likely based in the principles of instrumental and procedural learning. These skills developed because they worked, they were adaptive, and they ensured survival of the species.

Gesturing can readily be recognized as a form of "non-verbal" communication. However, we propose a refinement of the global term "non-verbal" because it often really refers to non-oral communication. There are other forms of non-verbal communication, such as body language and intuition that can be equally important to adaptive socialization. How do we tell who is friend or foe? How do we know who we can trust? In essence, these are categorizations that are made through observation along with the experience of instrumental conditioning.

As reviewed in Chapter 4, not all "categorization" is the same. Categorizations that generate positive or negative reinforcement, or survival "rewards," routinely recruit the basal ganglia. This type of learning need not be conscious. In fact, the data reviewed imply that the basal ganglia are essential in reward-related learning and that this is independent of higher-order control systems. Making automatic judgments about people and the environment can even be considered to originate from basal ganglia dependent learning. This is important because it links the basal ganglia not only with language, but with social functioning as well. Just as not all communication requires higher-order control, so too, not all socialization requires higher-order conscious control. While aspects of language and communication require higher-order processing for adapting to novelty, certain aspects of socialization also require the capacity to interact with others under novel conditions. In our view, both language and social cognition require both stimulus-based and higher-order control systems.

It provides biological consistency when we consider all primates on a continuum, and if we consider socialization and language as distributed along a continuum, then we are almost compelled to conclude that subcortical regions played and continue to play a role in these complex behaviors. Social cognition and language are complex systems that actually require two subsystems, namely, both automatic and higher-order control, in order to generate adaptive behaviors across differing contexts. The following sections review how both cortical and subcortical systems contribute to social and language processing. Specific theoretical differences and controversies within associated disciplines such as linguistics and anthropology fall outside the scope of this book and will thus not be directly addressed here.

The Declarative-Procedural Model of Language

Speech, language, and the various disorders involving their development have long comprised a main area of neuropsychological inquiry and clinical assessment. The central roles of temporal, frontal, and prefrontal cortical brain regions in language and speech function have been well documented through

lesion and imaging-based studies (Dronkers, Wilkins, Van, Redfern, & Jaeger, 2004; Katzir, Misra, & Poldrack, 2005; Pexman, Hargreaves, Edwards, Henry, & Goodyear, 2007; Ruschemeyer, Brass, & Friederici, 2007). The concept of subcortical contribution to language function is not new, and these regions have also received some amount of attention historically (Botez & Barbeau, 1971; Cohen & Kegl, 1999; Crosson, 1999, 1992). However, relatively speaking, subcortical aspects of language have received limited attention, and it is only recently that cortical–subcortical interactions in the context of distributed networks have been systematically considered with regard to language function (Duffau et al., 2005; Duffau, 2008; Ketteler, Kastrau, Vohn, & Huber, 2008). In this regard, Duffau suggests moving from localizationalist or associationist views of language function to a "hodological" view of white matter connection patterns linking distributed groups of neurons (ffytche & Catani, 2005; Salmelin & Kujala, 2006). Combined use of multiple imaging methods, for example, tractography and electrostimulation, is increasingly possible as a means of elucidating these networks. These more current views of distributed language processes are consistent with contemporary research specific to the areas of attention and behavioral selections in frontostriatal circuits reviewed in previous chapters (see Chapter 2 for descriptions and literature related to this).

The declarative or explicit learning and memory system mediates the acquisition and retention of factual information and conscious episodes of experience. The procedural memory system mediates the acquisition of new, and the control of previously learned, motor and cognitive skills, procedures, and habits (Squire, 1987). These two divisions of memory have long been established and they are dependent upon the operation of distinct brain circuits. Declarative memory is mediated by the medial temporal lobe structures for the encoding, consolidation, and retrieval of memories. These structures include the hippocampal formation and the entorhinal, perirhinal, and parahippocampal cortices (Squire, Clark, & Bayley, 2004). Frontal systems appear to play a critical role in the conscious memory retrieval of declarative information (Yener & Zaffos, 1999). The procedural memory system is dependent upon the basal ganglia, frontal cortices, cerebellum, and those cortical regions necessary for completion of the task in question (see Chapter 4). Therefore, from a neuroanatomic point of view, these two types of memory are actually linked together through aspects of frontal systems. Ullman (2004) has taken these two dichotomous memory systems and related them to language processes.

Ullman and his colleagues have proposed a theory of language function and impairment from the well-documented cognitive perspective of what has been termed the Declarative-Procedural model (Newman, Ullman, Pancheva, Waligura, & Neville, 2007; Ullman, 2001, 2006; Ullman & Pierpont, 2005). From this perspective, Ullman has asserted that language function can be separated roughly into two domains, namely, the mental "lexicon," and a computational "mental grammar." The lexicon is subserved by the declarative memory system anatomically emphasizing deep temporal lobe structures.

This aspect of the language system encompasses all arbitrary words, facts, and other concrete and abstract aspects of language. The rule-based mental "grammar" is subserved by the procedural memory system and is associated with cortical– subcortical structures and circuits. The latter system underlies the rules related to the ordering or sequencing of both linguistic and nonlinguistic aspects of language, particularly grammar.

The "mental lexicon" is the brain's dictionary of words. This not only includes the words we know, but also all idiosyncratic word-specific information that is not "rule-based." This is the type of information that has to be memorized. For example, the words "dog" or "neuropsychology" are really arbitrary pairings of sound with meaning. These words are part of our vocabulary, or the mental lexicon. There is also certain word specific information managed by the mental lexicon. For instance, certain words take unpredictable form in conveying the appropriate meaning. The past tense of "think" is "thought," and not the rule-based "thinked." There are also idioms in any language that, on the face of it, have an abstract meaning, as in "he has a chip on his shoulder," which is obviously not a concrete, literal interpretation. All of these non-rule-based examples are theoretically derived from arbitrary word meanings and are mediated by the declarative memory system. Simply put, this is memorized, declarative information.

The rule-based grammar system is predictable and manages those properties of language that consist of regularities or predictability in language. All of these regularities are subsumed or captured under the rules of grammar. These rules allow us to combine words to make complex representations. These rules are absolutely critical because they allow us to interpret the meanings of very complicated forms of language, even if we have not seen them or heard them previously. This system underlies the rules related to the sequencing of both linguistic and nonlinguistic aspects of language, particularly grammar. For example, the sentence, "The spong plicked the golb," is recognized as something performing an action on something or someone else regardless of what nouns and verbs are inserted. We can comprehend this complex form, even though the words are not in our vocabulary or are theoretically "meaningless."

Correct word form also has its own "rules." In fact, evidence suggests that the ability to use and detect correct word forms develops in children by the age of 6, approximating adult performance (Ambridge, 2008). This has been termed "intuitive grammar," since even young children know when a made-up word just does not sound right, although they are unable to explain why this is the case. This implies that rule-based grammar develops very early in life and that it is dependent upon the procedural learning system. The declarative-procedural language model also proposes that both systems interact, and that word forms can also be represented in more than one language system. For example, if a word form has not been encountered before, as in learning to apply the word form "taught" for "teached," initially acquiring this word and its proper application would be mediated by the declarative system. However, after the new word form was encountered and automated, it would be represented within the

procedural system (Ullman, 2004). In this way, these language systems have the capacity to accommodate regular and irregular morphology in an economical way. Therefore, this dual system model is flexible and adaptive (as well as consistent with the operations of the frontostriatal system and procedural learning systems as presented in previous chapters).

There are several lines of evidence to support this model of language functioning. For example, patients with anterior aphasia have been described as performing worse on all language tasks requiring the use of regular versus irregular past tense forms. Patients with posterior aphasia show the opposite pattern, having more difficulty with irregular past tense expressions (Ullman, 2001). Patients with dementia affecting semantic networks (Semantic dementia and Alzheimer's disease) have more difficulty in recognizing and generating irregular than regular past tense forms, consistent with pathology that primarily affects declarative memory systems. Patients with Parkinson's disease, without dementia, show the opposite pattern from patients with dementia that affects semantic networks. Parkinson's patients reportedly make more errors in producing regular versus irregular past tenses. This is very consistent with the basal ganglia involvement that affects the procedural learning system in that condition. In fact, the data also reveal a lateralization pattern within the basal ganglia, since degeneration of the left-sided basal ganglia is associated with these tense usage problems while right-sided basal ganglia PD patients show little evidence of language production deficits (Ullman, 2004, 2001).

In the developmental condition known as Specific Language Impairment (SLI), subjects have been described as having difficulty in acquiring grammatical rules and are, therefore, forced to consciously memorize both regular and irregular forms. These same subjects also demonstrate impairment in motor sequence learning. These subjects have been reported to demonstrate abnormalities within frontal cortices such as the left hemisphere supplementary motor area and within the basal ganglia (Ullman, 2004, 2001; Walenski & Ullman, 2005). Neuroimaging from fMRI and PET scanning has also revealed that tasks designed to probe the semantic and lexical processing systems generate different patterns of activation. Semantic processing recruits cortical regions, while lexical tasks activate frontal-basal ganglia circuitry (Ullman, 2004). Therefore, different independent sources of data support the distinction of declarative and procedural language systems. This has implications for neuropsychological evaluation, which will be discussed below.

Social Cognition—Automatic and Higher-Order Control Systems

The field of social cognitive neuroscience has expanded exponentially over the past several years (Adolphs, 2003; Beer & Ochsner, 2006; Blakemore, Winston, & Frith, 2004; Cunningham & Zelazo, 2007; Frith & Frith, 2007). This is a very broad area and deserves (and has received) multiple books in its own right.

A body of research has particularly focused on right hemisphere brain development, attachment style, interpersonal attunement, and self-regulation (Schore, 2002, 2005; Siegel, 2007). Much of the research within this large domain focuses on the important contributions of various cortical regions—particularly areas of the frontal lobes—and their interconnections with limbic system structures to interpersonal perception, perspective taking, and social valuation (Amodio & Frith, 2006; Beer, John, Scabini, & Knight, 2006; Ciaramidaro et al., 2007; Koenigs et al., 2007). For example, a recent lesion study by Shamay-Tsoory and Aharon-Peretz found a dissociation between prefrontal networks related to cognitive and affective theory of mind (ToM) function (Shamay-Tsoory & Aharon-Peretz, 2007). The authors found that while both cognitive and affective ToM depend on intact PFC cortex, cognitive ToM is affected by widespread prefrontal (Ventromedial + Dorsolateral cortex) damage, but affective ToM impairment results from circumscribed ventromedial prefrontal damage. They interpreted this to support the suggestion that the medial and orbital parts of the prefrontal cortex are important for integration of affective and non-affective information.

The role of mirror neurons in the ventral premotor and rostral posterior parietal cortices has received extensive study with regard to empathy and theory of mind (Rizzolatti, Fogassi, & Gallese, 2006; Rizzolatti & Craighero, 2004; Uddin, Kaplan, Molnar-Szakacs, Zaidel, & Iacoboni, 2005). Much of the research related to social cogntion emphasizes the role of these and other cortical structures while de-emphasizing the subcortical regions connecting to these important cortical areas. In other words, many of these studies appear to be biased by a cortico-centric model of behavior to varying degree. However, there is good reason to believe that not all aspects of social cognition are cortically based. For example, Schulte-Ruther and colleagues studied the common and different neural mechanisms for "self-" and "other-" related attribution of emotional states through gaze behavior using fMRI (Schulte-Ruther, Markowitsch, Fink, & Piefke, 2007). While the study demonstrated differential activation in a variety of cortical regions dependent upon the task, a common network activated by both tasks included orbital and medial prefrontal regions, temporal regions, as well as the right cerebellum.

Basal ganglia structures play well-documented roles in categorization and implicit learning linked to multiple social functions, including stereotyping and prejudice (Knutson, Mah, Manly, & Grafman, 2007). Dopamine-mediated reward systems involving the ventromedial prefrontal lobe and ventral striatum play a significant role in social valuation in addition to general decision making (Fliessbach et al., 2007; Heekeren et al., 2007). For example, Fliessbach and colleagues found evidence that social comparisons influence well-being and decisions using functional magnetic resonance imaging (fMRI). While being scanned in two adjacent fMRI scanners, pairs of subjects had to simultaneously perform a simple estimation task that entailed varying monetary rewards for correct answers. Variations in one subject's payment affected responses in both subjects' ventral striatum. The authors interpreted these findings as demonstrating

that social comparison activates ventral striatum even if subjects are not actively engaged in decision making, and linked this with competition and economically related behavior.

The cerebellum is intimately involved in social function, as current research regarding autism and schizophrenia has richly documented (Amaral, Schumann, & Nordahl, 2008; Baron-Cohen, 2004; Catani et al., 2008; Lamm, Batson, & Decety, 2007; Picard, Amado, Mouchet-Mages, Olie, & Krebs, 2008; Schutter & van, 2005). (see Chapter 8 for a review of the role of the cerebellum in clinical disorders.) These studies have discussed the role of the cerebellum in social withdrawal and social competence. Schmahmann and colleagues reported a number of clinical cases presenting with lack of empathy and an inability to appreciate social boundaries in which cerebellar pathology was considered the primary neuropathic event (Schmahmann et al., 2007).

In our view, an evolutionary model of development implies biological and functional consistency among all species. Animals live in groups, they have rudimentary forms of communication, they adapt to environmental changes at least to a certain extent, and they all survive. All of this occurs with comparatively little cortex as compared to humans. In fact, it has even been suggested that insight is not dependent upon cortex, and that certain animals have a rudimentary form of insight in the absence of laminated brain structures (Kirsch, Gunturkun, & Rose, 2008). How can this be? Does this suggest that aspects of "social ability" might be stimulus-driven? Does this imply the involvement of phylogenetically older brain regions in aspects of social behavior? In order to understand this it is useful to review a few principles of adaptation.

All living things like predictability. As reviewed in Chapter 1, interacting with a predictable environment provides an adaptive edge. Automatic approach and avoidance behaviors are essential to surviving under conditions of both security/nurturance and threat. It is true that the stimulus-bound nature of these stimulus-based behaviors makes them inflexible. However, under the proper circumstances, these behaviors not only work, but are also essential. They are elegant in that they require little conscious processing while they get the job done efficiently. On the other hand, environmental novelty requires the generation and synthesis of a new response. These circumstances require higher-order control in order to develop and implement a related goal directed behavior. In addition, this control system has the capacity to make these "new" solutions familiar, thus freeing-up higher-order control processes for the next novel situation.

We believe that social cognition can also be framed within this context. Many aspects of social situations are routine and familiar. The possession of automatic social skills allows a person to exploit the routine or repetitive features of a social environment. What are automatic social skills? Being able to notice or "read" emotions, intuitively "knowing" who is friend or foe, and the ability to read and generate appropriate gestures are all features of what we believe to be automatic aspects of social cognition. "Knowing" how to initiate a conversation, knowing how to take turns in order to maintain conversation, and knowing when and how to terminate certain conversations can all frequently

be aspects of social functioning that are automatic and do not require a second thought. In a sense, these are "social procedures" that often do not require conscious, higher-order mediation. There are, of course, numerous aspects of social situations that are novel. For example, going on a job interview, making friends at the start of a new school year, or meeting new people at a social event are circumstances that for many of us require conscious direction and deliberation. Adapting in these situations is perhaps best accomplished by gathering new information about these situations "online" and flexibly considering what to say or do. This adaptation requires higher-order social cognition.

However, even aspects of these novel situations are stimulus-based in which an "automatic" or practiced response will suffice. In this regard, social situations are at base like any other circumstances in that the social context requires alternating episodes of stimulus-based social processing and higher-order control.

In short, we believe that social cognition can also be broadly organized around two systems. There is a system of automatic social skills that develops through instrumental conditioning and procedural learning (see Chapter 4). This system governs the stimulus-based social skills that are necessary for successful routine interactions. There is also a system of higher-order social processing that allows us to think about what to say or do, to consider the thoughts, ideas, and feelings of others, to manipulate or comply with situations, and to reflect upon ourselves. These two systems can operate independently, but they mostly interact since most social circumstances require alternating implementation of these two systems. We believe that the interaction of these two systems is just as critical for social functioning as is the interaction of declarative and procedural systems for language function. Failures in social behavior can result from impairment of the "automatic" stimulus-based processing system or because of failure in higher-order social processing. Dependent upon the level of impairment, the observed social deficit would take on its own characteristic presentation.

Reflexive and Reflective Systems

Our view is similar to what has been proposed by Lieberman who also describes two broad organizing principles of social cognition within the brain (Lieberman, 2007). He proposes the X-system, named for the "x" in reflexive, and the C-system, named for the "c" in reflective. He sees the former system as responsible for social processes that can be termed automatic and the C-system as directing those social processes that are controlled. Both systems process socioemotional information and work together to achieve socioemotional goals (Lieberman, 2007). However, each system is composed of processes and functions that are relatively absent from the other system. This is implied from reviewing the neuroanatomy that supports these systems.

The X-system is composed of brain structures that are activated under conditions that generate non-conscious, implicit, or automatic processing of

social information. These structures include the amygdale, basal ganglia, lateral temporal cortex, ventromedial prefrontal cortex, and dorsal anterior-cingulated cortex (Lieberman, 2007). These regions are closely associated with the paleocortical evolutionary progression that has been termed the orbitofrontal paralimbic division of the limbic system (Mega, Cummings, Salloway, & Malloy, 1997). The C-system is composed of the anterior cingulated, the dorsolateral prefrontal cortex, the posterior parietal cortex, and the hippocampus and medial temporal lobe system (Lieberman, 2007a). This system is closely associated with the phylogenetically newer archicortical evolutionary progression referred to as the hippocampal paralimbic division (Mega et al., 1997). The paleocortical limbic division mediates the implicit integration of affect, drives, and object associations, and as such, it is an anatomic underpinning of the implicit processing of social information.

Attentional control, explicit sensory data processing, and contextually appropriate encoding of this information are functions of the archicortical division and this represents the anatomic underpinning of controlled, reflective and deliberate social interaction. Implicit learning activates the paleocortical division, including the basal ganglia. Explicit learning activates the archicortical division. Implicit learning of social valuation, decision-making, and non-conscious behavior require the basal ganglia. The explicit learning system acquires and stores episodes of social experience of which we are consciously aware.

Social Intuition, Social Skill, and Non-Verbal Communication

Subcortical structures are critical components of implicit instrumental and procedural learning's neuroanatomic substrate (see Chapter 4). We propose that unconscious social valuations are subserved by the mechanisms of category learning, and that social interactive skills are mediated by procedural learning systems (Eitam, Hassin, & Schul, 2008; Frank, O'Reilly, & Curran, 2006). We acquire unconscious attitudes, prejudices, and intuition in much the same way that we acquire information about category membership. We make quick, intuitive social judgments in much the same way that we make instantaneous, automatic categorization judgments. Instrumental learning principles underlie these associations. We acquire the behavioral "sequences" and procedures that are necessary for social interactions in much the same way that we acquire motor skills. For example, there are rule-based "procedures" for initiating, maintaining, and terminating social interactions just as there are procedures for dressing, hygiene, dining, etc. All of these aspects of social functioning need to be framed within the context of non-verbal communication.

For example, think about a routine social interaction with one other person in which you are discussing a recent dinner at your favorite restaurant. For our purposes, the topic of the conversation is not necessarily important because this is likely a manifestation of controlled processing. However, considerable

non-verbal communication is present, although this often goes unnoticed by the participants. At least the participants are not consciously aware of these non-verbal cues. So what is this non-verbal communication? Facial, vocal, and gestural cues are aspects of behavior that are based upon temporal and spatial sequences. These cues are instrumentally coupled with our inner states of attitude and emotion. These are non-verbal social cues.

As reviewed by Lieberman (2000), a number of studies reveal a role for the basal ganglia in the perception, comprehension, and production of non-verbal cues. These studies concern patients with basal ganglia disease without dementia or cortical involvement. Almost all studies find impairment in the generation or production of non-verbal cues such as emotional prosody or the "melody" of speech. Deficits are also evident in the production of facial expression. Neuroimaging studies implicate the basal ganglia in recognizing emotional expression, both when subjects are presented with facial stimuli and when subjects did not even consciously detect the presence of facial stimuli.

When the caudate is affected, as in Huntington's disease, studies consistently demonstrate impairment in the comprehension of non-verbal cues. In addition, non-verbal social cue comprehension is differentially impaired by region of basal ganglia involvement. For example, non-verbal comprehension deficits are observed in patients with Huntington's disease but not in Parkinson's disease, implying caudate involvement (see Chapter 2 for a review of the basal ganglia and sensitivity to context. Differences are also observed in region of subcortical activation dependent upon the positive and negative valence of non-verbal stimuli. See Lieberman, 2000, for a review). In addition, as we have seen, processing of both monetary and social rewards are mediated by the same brain region. For example, Izuma and colleagues recently found that acquisition of a person's good reputation activates the ventral striatum, overlapping with the region activated by monetary reward (Izuma, Saito, & Sadato, 2008).

A neural circuitry of trust can also be identified. This circuitry features subcortical components. An fMRI study investigated how the hormone oxytocin influences trust behavior. When trust was breached, subjects receiving placebo decreased their expressed trust. However, no changes in trust behavior were observed in the group receiving oxytocin. This difference in trust adaptation was associated with decreased activity within the amygdale, midbrain regions, and within the dorsal striatum in participants who were administered oxytocin. These results were interpreted as indicating that systems mediating fear processing (the amygdale) and adaptation to informational feedback (the striatum's sensitivity to context) modulate the effect of oxytocin on trust (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Delgado, 2008).

Social isolation and loneliness have also been related to the neural networks of reward processing, specifically involving activation of the ventral striatum. Lonely young adults are less rewarded by social stimuli. This was demonstrated by relatively diminished ventral striatal activation when these subjects were shown pleasant pictures of people in comparison to pictures of objects. Non-lonely people demonstrated an opposite pattern, characterized by stronger activation of

the ventral striatum to pictures of people as compared to objects (Cacioppo, Norris, Decety, Monteleone, & Nusbaum, 2008). Lower levels of ventral striatal activation correlated with high loneliness ratings but were not associated with differences in fusiform gyrus activation between lonely people and normal controls. Therefore, this difference was related not to facial perception, but instead to reward characteristics. In addition, the right caudate was the only regional inactivation predicted by loneliness in response to pleasant and unpleasant social stimuli, which is consistent with accumulating evidence for the caudate's role in reward-based learning. The authors raised the possibility that loneliness may result from a reduction in neural activity in the ventral striatum in response to social rewards. They hypothesized that pleasant social stimuli do not have particularly powerful positive reinforcement value for lonely people, and this might make it difficult for them to deemphasize self-interests in relation to the interests of others, leading to further social isolation. In any event, there is considerable evidence to associate subcortical social processing skills with the basal ganglia. This has obvious implications for traditional approaches to psychotherapy as well as for neuropsychological assessment.

In our view, this dual-system model redefines "non-verbal" social behavior and has dramatic implications for re-framing what has traditionally been called "non-verbal learning disability." This dual-system approach also holds significance for developing our understanding of mental disorders including symptoms such as social avoidance, social awkwardness, phobic social anxiety, and diagnostic conditions such as schizophrenia and autism in which social and interpersonal skills are markedly affected.

Implications of Dual-System Models for Social Cognition and Language

Dual-system models cannot be easily applied within the traditional cortico-centric perspective of neuropsychology. Clinical neuropsychology has never developed assessment methodologies for evaluating subcortical functions, primarily because most neuropsychological problems have been assumed to be cortically driven. The focus is upon what is presumed to be cortically mediated cognition, motor systems are compartmentalized and viewed as unessential to thinking processes, and this general view does not welcome the interpretation of co-morbidities. Clinical assessment methodologies have not been developed for directly evaluating dual-system models. Interpreting most currently available neuropsychological tests founded upon a cortico-centric school of cognition does not lead to an understanding of the differential contributions of cortical and subcortical regions and functions. We believe that test interpretation that focuses only upon presumed cortical functions is incomplete, and that an evaluation that includes the roles of subcortical brain processes and functions can substantially change our understanding of people and the clinical conditions with which they present.

For example, while the syndrome of Non-Verbal Learning Disorder (NVLD) has been proposed as a manifestation of disturbance in white matter tracts, predominantly located in the right cerebral hemisphere (see Rourke, 1989 for a full description and discussion), the prototypical syndrome has never been considered a possible manifestation of subcortical pathology (Klin, Volkmar, Sparrow, Cicchetti, & Rourke, 1995; Rourke, 1989; Rourke & Tsatsanis, 1996). Similarly, this syndrome has not been framed within the context of differences between stimulus-based and higher-order control systems. The current model of non-verbal learning disorder includes a cortico-centric bias that assumes a verbal versus non-verbal dichotomy as a primary organizing principle of brain–behavior relationships.

However, a fundamental aspect of the presentation of individuals with this condition concerns a notable deficit in functioning under conditions of novelty, which in this model is considered primarily from the vantage point of left versus right hemisphere function. However, the way in which NVLD is currently defined can also be conceptualized as a disorder of the frontostriatal system. For example, the role of the frontostriatal system is to adapt to novel circumstances and to take that which is initially unfamiliar or novel and make it familiar or routine. This interpretation raises a question regarding how procedural learning systems might be involved in the mediation of the NVLD syndrome. While the disorder is called "nonverbal," subtle language-related difficulties are observed within this syndrome, which appear to be "procedural" in nature. Further, it is also clear that the NVLD syndrome is not purely cognitive. For example, individuals with this condition are described as exhibiting vaguely identified, non-specific "psychomotor" problems. Similarly, deficits in social skills present as a fundamental aspect of the condition.

Could these be "procedural" deficits? Without directly evaluating procedural learning systems, questions concerning the contribution of subcortical regions to the various manifestations of this syndrome cannot be answered. This is not merely a question of theoretical relevance, since assessing subcortical contributions could lead to enhanced differential diagnosis, subtyping of the condition based upon different areas and levels of brain involvement, as well as the development of practical treatment approaches depending upon type of systemic involvement. Cortico-centric cognitive "tests" simply do not approach the motor and social aspects of the condition.

The cortico-centric approach has similar problems with respect to the assessment of language functions. As argued by Ullman, the developmental condition called specific language impairment results from abnormality within the cortico-striatal procedural learning and memory system. Declarative and lexical knowledge are at least relatively unaffected in this condition. The primary deficits are observed in grammar and morphology. In addition, this condition is typically co-morbid with motor skill problems. Ullman has related this "syndrome" to pathology within the basal ganglia and cortico-striatal learning mechanisms. Current cognitive tests do not allow for differentiation between functional

differences with respect to the efficiency of declarative versus procedural neural networks.

Finally, the traditional model of cortical control restricts our understanding of learning disabilities such as reading disorder. For example, reading problems should really be viewed as an extension of language problems (Mann, 2003). As reviewed in Chapter 5, the cerebellum plays a role not only in procedural learning, but also in language processing. Cerebellar damage, particularly in posterior inferior regions, can result in agrammatism, dysnomia, and diminished levels of verbal fluency. In addition, the cerebellum has been tied to reading disorders, especially phonologically based dyslexia (Finch, Nicolson, & Fawcett, 2002; Nicolson & Fawcett, 2006; Vlachos, Papathanasiou, & Andreou, 2007). Nicholson and Fawcett have proposed that if a child has cerebellar impairment, this would be evident developmentally as mild motor difficulty. The achievement of motor milestones would be slightly delayed, manifest by the infant being slower to sit up and to crawl and to walk. There would be greater problems with fine muscular control. Complex motor skill "procedures" that need very fine and precise control over muscular sequencing, such as articulation, could easily be affected. This would delay language development, manifest in slower speech onset such as late babbling and talking, and difficulties with the precise timing required in phonological processing.

Cerebellar deficits could also contribute to specific procedural learning deficits, depending upon the site of regional abnormality, particularly since the cerebellum at least plays a role in the early phases of sequence learning. This could impact upon the development of the language system and could very conceivably have an impact upon the development of automation in reading and spelling. Therefore, there may be many "routes" to reading disorder and to developing phonological and orthographic processing deficits, but the critical point here is that all causes need not be cortical. By assessing both cortical and subcortical processes, specific "syndromes" could be better identified. Dual-system models of assessment would allow for a more integrated understanding of these conditions, especially since these models can account for co-morbidity in different domains of functioning while maintaining a holistic framework (Fawcett & Nicolson, 2007; Nicolson & Fawcett, 2007).

Summary

This chapter reviewed language functioning and social cognition. Although these functions have traditionally been understood as solely under cortical mediation, we proposed and reviewed dual-system models. These models are characterized by both rule-based stimulus processing and higher-order control. The former system allows for automatic processing and the latter system allows for adaptation to novelty. These systems interact to allow for appropriate flexibility in adaptation.

These two systems have distinct neuroanatomic underpinnings. The system of stimulus-based control is mediated by the procedural learning system and phylogenetically older brain regions. The higher-order control system that functions to place both language and social behavior in situational context is subserved by the medial temporal lobe system and associated extended structures. The interaction of these systems features the greatest flexibility in adapting to novelty by allowing for complex problem solving and eventually making that which was initially novel, familiar. We view the traditional verbal versus non-verbal dichotomy as a special instance of this novelty-familiarity organizing principle.

The cortico-centric viewpoint of cognition does not easily accommodate the clinical assessment of dual system models. We propose a more holistic assessment paradigm that includes evaluating multiple neural systems at different levels. This type of approach would allow for a greater understanding of those difficulties that bring people to clinical attention.

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Chapter 7
The Vertically Organized Brain in Clinical Psychiatric Disorders

As I grow older I pay less attention to what men say. I just watch what they do.

Andrew Carnegie

Every problem has in it the seeds of its own solution. If you don't have any problems, you don't get any seeds.

Norman Vincent Peale

The supposition that the future resembles the past is not founded on any kind, but is derived entirely from habit.

David Hume

Neuropsychology has long struggled with issues of diagnosis. As neuropsychologists, we are trained in the language of brain–behavior relationships. However, most patient populations carry diagnoses made through application of behavioral criteria determined by the Diagnostic and Statistical Manual (DSM) (American Psychiatric Association, 2000). The DSM is decidedly and purposely not brain-related or in any way neuroanatomically based. Although many of the conditions listed in the DSM have cognitive and emotional components, in most instances, these components are not directly measured with cognitive or psychological tests to make the diagnosis. This chapter reviews several disorders that are listed in the DSM-IV. These are behaviorally defined diagnoses. Instead of listing specific cognitive testing criteria, the DSM infers the cognitive and emotional components comprising these conditions through behavioral observations or report. These facts have important implications for neuropsychological testing in that the relationships between DSM behaviorally defined disorders and cognitive, neuropsychological, or psychological tests are not clearly known or documented.

We certainly acknowledge the view that DSM diagnostic categories can be correlated with performances on neuropsychological tests. Many clinicians have attempted to establish neuropsychological test result "profiles" for different DSM categories. However, this methodology can be problematic. A statistical correlation between test results and any particular DSM diagnosis essentially reveals the percentage of time the test results and the specific diagnosis co-occur.

L.F. Koziol, D.E. Budding, *Subcortical Structures and Cognition*,
DOI 10.1007/978-0-387-84868-6_7, © Springer Science+Business Media, LLC 2009

It does not establish a specific relationship. For example, from the point of view of "blind diagnosis," even a pattern of neuropsychological test results does not generate a specific DSM diagnosis. Conditions such as attention deficit disorder, schizophrenia, and even certain kinds or levels of traumatic brain injury (TBI) just to name three can be characterized by such overlap in test findings that differential diagnosis is impossible. Neuropsychological tests measure brain–behavior relationships. DSM diagnoses are based upon the identification of specific behaviors. Therefore, we propose an alternative system of keeping "apples" and "oranges" separate by making the DSM diagnosis on the basis of observable behavioral data, while also illuminating the nature of the identified brain–behavior relationships with a descriptive narrative. This method leads to an understanding of the patient's cognition irrespective of diagnostic labeling, while fulfilling the purpose of generating a specific "label." In the final analysis, patients are typically treated on the basis of symptom presentations, and not "labels," so that identifying brain– behavior relationships is the most clinically useful course to follow.

Neuropsychological testing and/or a specific pattern of neuropsychological test results are not listed as a part of the diagnostic criteria for most of the conditions in the DSM. In fact, the only condition in which neuropsychological testing is listed as a possible aspect of the diagnostic criteria is cognitive disorder, not otherwise specified. This essentially means that there are no neuropsychologically defined criteria to be used as reference points in making these diagnoses. From a neuropsychological point of view, this makes it impossible to use only neuropsychological test results to diagnose the conditions and it makes it difficult to use neuropsychological test results to make inferences about the brain–behavior relationships that underlie these behaviorally defined conditions. Simply put, there are no points of reference. The DSM provides no guidelines for considering neuropsychological test correlates of disorders, and there is no systematic neuropsychological nomenclature to guide decision-making for generating a DSM diagnosis. These are two different evaluation systems. In practice, clinicians might "mix and match" in trying to compare aspects of test results to specific DSM behavioral criteria, but there is no established standard or agreed-upon protocol for applying this type of approach.

Nevertheless, certain conditions in the DSM can readily be diagnosed with the help of neuropsychological tests because the primary presentation of the condition includes cognitive symptoms. For example, the learning and memory difficulties and instrumental cognitive deficits such as the aphasic and apraxic symptoms of dementia can easily be identified through the application of conventional neuropsychological tests. A diagnosis of dementia is often made through pathognomonic signs of cognitive impairment, and whether these behaviors are identified upon quantifiable testing or through behavioral observation makes little difference. However, the problem becomes starker when looking at disorders not traditionally defined as "cognitive." The DSM has minimized the brain–behavior relationships of traditional "psychological"

disorders even though most of these conditions have a strong cognitive component. This includes diagnoses such as attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), schizophrenia, and a host of other conditions.

To illustrate, let's take ADHD as an example. A good behavioral assessment may provide findings that identify the cognitive complaints of ADHD. These are not in and of themselves pathognomonic signs specific to the condition, in that disturbances in attention are not unique to attention deficit disorder. For instance, behavioral symptoms such as "does not seem to listen when spoken to directly," "often does not follow through," "has difficulty organizing tasks and activities," and "is easily distracted by extraneous stimuli" are not unique to what is observed in attention deficit disorder. People with depression can be inattentive, they can have difficulty mustering the motivation to get things done, they can have problems with organization, and they can be easily distracted by their internal preoccupations. These kinds of attention problems can also be observed in all phases of schizophrenia as well. The point here is that symptoms in various DSM categories can overlap, and people can present with such a range of symptoms making an accurate diagnosis problematic. In one investigation, children presenting clinically met full DSM-IV criteria for 1–5 diagnoses (Yaryura-Tobias, Rabinowitz, & Neziroglu, 2003).

Adding to the confusion is the fact that neuropsychological test data can be difficult to apply to the behaviorally defined diagnostic criteria associated with various diagnoses. A problem arises from trying to use tests designed to elucidate specific cognitive functions—such as encoding a string of numbers—and then apply this to a multiply determined set of circumstances, such as classroom behavior. Frame of reference becomes an important variable in understanding this potential error. A parent or teacher rating an item such as, "does not listen when spoken to directly," is not using a digit span or sentence repetition test performance as a frame of reference to identify the behavior (Fletcher, Shaywitz, & Shaywitz, 1994). An omission error score earned performing a continuous performance test is similarly not the frame of reference used for an observation such as, "fails to follow through and finish tasks." Commission errors implying disinhibition from continuous performance tasks or from competing programs go–no-go tasks are not reference criteria for observations such as, "often blurts out answers," or, "often interrupts or intrudes on others." Reference-based criteria for applying neuropsychological testing are absent.

To illustrate this dilemma, let's take the example of disorganization. The observation, "difficulty organizing tasks and activities," clearly implies an executive function deficit. However, from a cognitive perspective, executive difficulty is not a homogeneous or monolithic entity. Organizational difficulty can result from impairment in different aspects of executive function that can be identified by different types of neuropsychological tests. If executive deficits are defined cognitively in terms of working memory, inhibition, attentional shifting, and planning functions (Pennington, 1997), the main deficit area that

routinely occurs in attention deficit disorder is disinhibition, but this does not necessarily or easily translate behaviorally to "difficulty organizing tasks and activities." Therefore, there are obvious problems in applying neuropsychological test performances to many of the behaviorally valid diagnoses that are listed in the DSM.

Neuropsychology is based upon a characterization of brain–behavior relationships without using a well-defined nomenclature consisting of diagnostic labels. The nomenclature of neuropsychology is descriptive. Consequently, within this nomenclature, brain–behavior relationships are identified and described. Combining the behavioral, categorical nomenclature of the DSM with the descriptive, dimensional system of neuropsychology is like mixing apples with oranges. Therefore, relying on a behavioral system for neurocognitive findings predictably leads to diagnostic inconsistencies.

A related consideration concerns the fact that the diagnostic categories described in the DSM are not anatomically organized. Sometimes the same or similar symptom listed in the DSM can result from different anatomical conditions. A simple example of this is the symptom of memory difficulty. This can be caused by a variety of problems, some of which include vascular dementia, Alzheimer's disease, and post-concussion disorder. For the sake of argument, assume that the medial–temporal lobe memory system is affected in all three cases. Knowing about a DSM diagnosis or symptom does not speak to the anatomy that drives the condition. Making the diagnoses of ADHD, OCD or schizophrenia can be based upon very heterogeneous groups of behavioral observations. The heterogeneity of the behaviors defies any straightforward unifying anatomy. The fact that anatomic heterogeneity occurs within the same specific diagnostic category has been demonstrated in many behaviorally defined DSM conditions. In some conditions that have over-arching labels like OCD, different symptom dimensions are associated with different neuroanatomic abnormalities, as will be described below.

Similarly, there are no disorders that have been studied anatomically that implicate only one brain region. It used to be stated that frontal lobe abnormality was the "central event" that drove the symptoms of ADHD, but subsequently gathered neuroimaging data have demonstrated that this condition is characterized by a number of anatomical abnormalities within the brain. This is a truism for most of the pathologies that are described in the DSM; most disorders are characterized by abnormalities in multiple brain regions. Therefore, it is impossible to "pin" the wide range of symptoms of any disorder listed in the DSM upon one single brain area or structure. The contribution of subcortical structures to these conditions adds to the complexity. As has been consistently shown throughout the book, the contributions of vertically organized, cortical–subcortical systems have only recently begun to be accounted for in understanding the complex interconnections of brain regions that impact cognition and emotion. Thus, the chasm between traditional diagnostic assumptions and recent neurocognitive research into brain function becomes

greater, since there are few documented or established methodologies for measuring subcortical–behavioral relationships. In fact, the cortico-centric model of cognition seems to defy discussion of such relationships, as it focuses on the idea that cortex is the primary driver of behavior.

It is within the context of this theortetical challenge to traditional assessment methods where this chapter begins. We wish to suggest that what is known about specific brain–behavior relationships can be applied to the myriad symptoms that might be characteristic of any disorder as listed in the DSM. We begin by reviewing the neuroanatomic abnormalities characteristic of a few select disorders described in the DSM, including OCD, ADHD, and schizophrenia. The specific behaviors of various conditions will be linked to brain-related networks, based upon prediction from functional neuroanatomic principles. We hope this type of approach will foster a more integrated view of brain–behavior relationships in both "normal" and "pathological" conditions. The goal of this review is not to present an exhaustive analysis or comprehensive discussion of any particular diagnostic condition featuring subcortical involvement. Instead, we will use these different disorders as models of brain–behavior relationships in order to promote a more integrated understanding of cortical–subcortical functioning.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is a classic condition involving the frontostriatal system. Some studies reveal volumetric reductions in the orbitofrontal cortex and the basal ganglia, but functional neuroimaging studies routinely demonstrate abnormal neuronal activity within prefrontal-striatal-pallidal-thalamic circuitry. Abnormal activity has been identified within the orbitofrontal cortex, the dorsolateral prefrontal cortex, the anterior cingulate, the caudate nucleus, and within the thalamus (Remijnse, Heuvel, & Veltman, 2005; Westenberg, Fineberg, & Denys, 2007). Hyperactive neural activity is often observed in orbital and medial circuitry, usually more in the right than in the left cerebral hemisphere, and hypoactivity is seen in dorsolateral circuitry, particularly in the symptomatic state or in cases with comorbid depression (Baxter, Clark, Iqbal, & Ackermann, 2001; Zald & Kim, 2001). There is no clearly established pathology of OCD (Cummings & Mega, 2003). However, several different models have been developed to infer and explain the pathophysiology and symptoms of OCD within the framework of this neuroanatomy of abnormal circuitry functions (Fontaine, Mattei, & Robert, 2007). Most of these models apply the symptoms of OCD to the circuitry of the direct and indirect pathways of the basal ganglia (described in Chapter 2).

One of the functions of the striatum is to process information automatically, without conscious representation. This is accomplished through the processes of attention and action selection. The striatum integrates sensory, ideational,

and motor input from the posterior and frontal cortices respectively. It uses this information to select established cognitive and motor programs by selectively releasing inhibition on the Globus Pallidus (Gpi). This, in turn, allows thalamic activity to excite the cortex and therefore release behavior. Hyperactivity within this circuitry would lead to the repetition of an idea or the repetition of a behavior, depending upon the circuitry affected.

The neuroimaging data implicate three separate prefrontal–striatal circuits in the mediation of OCD, namely, the dorsolateral, orbitofrontal, and medial/anterior cingulate circuits. The dorsolateral circuit is involved in executive cognitive functions, including planning and organizing responses to novel problems, generating behaviors that are independent from immediate environmental contingencies or circumstances, and shifting from one behavior to another. The orbitofrontal circuit mediates socially appropriate behavior including aspects of affective expression, and the medial/anterior cingulate circuit mediates motivation. Some recent imaging has also implicated the cerebellum in expression of this disorder (Kim et al., 2001; Pujol et al., 2004; Tolin, Kiehl, Worhunsky, Book, & Maltby, 2008).

The topographical organization of the striatum (putamen, dorsal and ventral caudate nucleus, nucleus accumbens, olfactory tubercle) and its pattern of cortical projection inputs has led to the conceptualization of different symptom manifestations within the spectrum of OCD, Tourette's syndrome, and simple tic symptoms (Baxter et al., 2001). The neuroimaging of Tourette's syndrome reveals a similar pattern of involvement of the frontostriatal system as seen in OCD, but in Tourette's, the motor circuits are primarily involved. Differences in blood oxygenation levels in Tourette's syndrome have been observed within the basal ganglia, thalamus, and cingulate, prefrontal, temporal, and parietal cortices (Frey & Albin, 2006). Increased activation has also been reported within primary and supplementary motor frontostriatal circuits (Frey & Albin, 2006). The temporal and parietal cortical activation was interpreted as demonstrating the cortical regions necessary to recruit for tic suppression. Activation in motor and language circuits (Broca's area) correspond to the modality specific pathways of behavioral expression in motor and vocal tics, respectively (Stern et al., 2000; Stern, Blair, & Peterson, 2008). The frontostriatal system is generally important for the mediation of simple and complex stereotypic behavioral routines. Simple and complex tics are mediated by the motor "loops."

The behaviors of OCD center around themes of hygiene/cleanliness, the environment/symmetry and order, sexuality, social/territorial concerns, and survival/security issues. The behaviors associated with these "themes" are routine and require the orchestration of repetitive sequential acts. Different circuitries are involved in the mediation of different obsessions and compulsions, related to the topographical organization of the striatum. For example, sexual obsessions and compulsions suggest involvement of the circuitry projecting through the septum/olfactory tubercle. Obsessions and compulsions associated with survival and security issues likely relate to circuitry involving the nucleus

accumbens. Social concerns imply involvement of specific orbitofrontal circuits. Auditory obsessions (such as "stuck tunes") imply disturbance in the circuitry linking auditory cortex to the body of the caudate. In these ways, symptom presentations can suggest regional areas of anatomic involvement within specific circuitries (Baxter et al., 2001). These symptoms can be understood in part as inhibitory failures. Reduced frontal activity has been reported during the no-go condition of competing programs tasks in OCD patients, and this inhibitory deficit has also been cited as a major contributing factor to the pathogenesis of OCD, since this might underlie a deficient mechanism in inhibiting compulsive behaviors (Herrmann, Jacob, Unterecker, & Fallgatter, 2003).

The striatum functions as a filter, or switch, particularly with respect to the release of stereotyped, repetitive, "rule-governed" behavior. In OCD, the orbitofrontal and medial circuits are hyperactive. This has been explained as occurring by way of feedback loops through the direct and indirect pathways (Baxter et al., 2001). OCD might be the result of increased activation of the direct basal ganglia pathway, which could be responsible for an inability to inhibit intrusive thoughts or repetitive ideation. The "urge" to act might be generated by the medial circuit, while the specific idea might be generated by the lateral division of the orbitofrontal circuit (Mega, Cummings, Salloway, & Malloy, 1997). Insufficient tone within the indirect pathways of these circuits prevents indirect pathway input from countering this drive, disrupting a gating function and perpetuating ideas and behaviors. The finding that dorsolateral activity decreases in symptomatic OCD also helps to understand how OCD often becomes worse with depression, since depression is associated with hypoactivity of dorsolateral circuitry. This also helps to explain cognitive treatment through invoked resistance, since this would theoretically activate dorsolateral circuitry and serve to "balance" activity between the circuits, restraining OCD behavior. This represents a specific example of how accurately assessing the correct frontal–striatal circuitry directly influences treatment and potential outcome.

Different symptom dimensions are associated with different neuroanatomic abnormalities. For example, in washing compulsions, there is increased activity within the right caudate nucleus, in checking compulsions there is increased activity within the putamen, globus pallidus, and dorsal PFC regions, and in hoarding compulsions there is increased activity within the left precentral gyrus and right orbitofrontal cortex (An et al., 2008; Husted, Shapira, & Goodman, 2006; Lawrence et al., 2007; Phillips et al., 2000; Thielscher & Pessoa, 2007). The main common anatomy of these conditions concerns increased activity within ventromedial prefrontal regions. However, activity in this region is not specific to OCD. Therefore, the symptom dimensions of OCD are mediated by relatively distinct components of frontostriatal circuits that are involved in cognitive and emotional processing. Obsessive-compulsive disorder is simply not a unitary nosologic entity, even though it is described as if it was "one thing" according to the DSM.

Neuroimaging data reveal dissociable neuronal mechanisms involved in the mediation of different OCD symptom dimensions. OCD is a clinically and anatomically heterogeneous condition. Certain neuropsychological tests also demonstrate distinct symptom dimensions in this disorder. Recent studies support the connection between certain assessment techniques and typical symtomatology. For example, in a recent study of patients with prominent hoarding symptoms, Lawrence found these individuals exhibited poor decision-making on the Iowa Gambling Task relative to patients with symmetry and ordering symptoms as well as in relation to normal controls (Lawrence et al., 2006). While set shifting deficits on the Wisconsin Card Sorting Test has been an inconsistent finding in OCD (Fontenelle, Mendlowicz, Mattos, & Versiani, 2006) specific symmetry/ordering symptoms have been correlated with poor set shifting (Lawrence et al., 2006).

Therefore, dissociable symptom dimensions and cognitive functions have been demonstrated on tasks that assess decision-making related to ventromedial functions as inferred from the Iowa Gambling Task and dorsolateral functions as inferred from performance on the Wisconsin Card Sorting Test. Taken together, current anatomical and neuroimaging data for OCD suggest important distinct anatomical pathways that vary depending upon symptomology. Further, specific assessment techniques may be useful in helping to identify these symptoms and therefore highlight the impaired circuitry. By specifically locating abnormal anatomical circuits, professionals in the field can contribute to more effective and specific diagnostic and treatment options.

Attention Deficit Hyperactivity Disorder

According to static neuroimaging studies, there are a variety of structural differences in the brains of people with ADHD as compared to normal control populations. Differences have been observed in several brain regions and have been identified with reasonable consistency (Voeller, 2004). ADHD appears to be associated with an atypical pattern of brain development. Evidence has related this pattern of abnormal development to maturational factors or issues of rate of maturity (Rubia, 2007; Shaw et al., 2006, 2007). However, there is no single pathophysiological profile underlying this disorder (Di Michele, Prichep, John, & Chabot, 2005).

People with ADHD are described as demonstrating less total cerebral volume than normal control subjects. This reduction of total brain volume approximates 5 percent (Castellanos et al., 2002). Volume reduction appears concentrated in certain specific brain regions. The volume of the frontal lobes is most notably reported as smaller in people with ADHD (Castellanos, Giedd, Hamburger, Marsh, & Rapoport, 1996; Castellanos et al., 2002; Kates et al., 2002; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002). However, at the subcortical level, abnormalities have also been reported in various regions

of the basal ganglia, particularly within the caudate nucleus (Castellanos, Giedd, Marsh, et al., 1996; Filipek et al., 1997; Hynd et al., 1993). A decrease in cerebellar volume has also been reported (Berquin et al., 1998; Carmona et al., 2005; Hill et al., 2003; Valera, Faraone, Murray, & Seidman, 2007).

A diffusion tensor imaging study reported abnormalities in the white matter tracts connecting the frontal lobes to the cerebellum, implicating the cerebrocerebellar circuit in the pathophysiology of the disorder (Ashtari et al., 2005). This conclusion has also been implicated by the performance of ADHD children on motor timing tasks (van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005). Some investigators report the most prominent regional differences as subcortical, occurring in the basal ganglia and cerebellum (Castellanos & Acosta, 2004). One recent study featuring MRI data highlights an increased left versus right asymmetry of the basal ganglia (Uhlikova et al., 2007). Therefore, a very heterogeneous picture emerges with respect to regional areas of brain involvement, with a particular emphasis on frontal–subcortical systems. A strong understanding of the role of subcortical features is thus necessary for a complete understanding of the physiology and symptomatic dysfunction of this disorder.

Functional imaging has also demonstrated significant basal ganglia contributions to ADHD (Cheon et al., 2003; Di Martino et al., 2008; Easton, Marshall, Fone, & Marsden, 2007). Functional neuroimaging studies with PET and fMRI are very consistent with the volumetric findings. The most common finding concerns dysfunction of the frontostriatal system, and this abnormality has been reported to be greater in prefrontal–subcortical regions of the right hemisphere (Lou, Henriksen, Bruhn, Borner, & Nielsen, 1989; Overmeyer et al., 2001; Overmeyer & Taylor, 2000; Zametkin et al., 1990). Studies employing go–no-go tasks (see Chapter 10 for a description of these procedures) have demonstrated that children with ADHD do not activate frontostriatal systems to the same extent as do normal control children (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Durston et al., 2003). Another study utilized a go–no-go paradigm in comparing normal control subjects with ADHD children while on and off psychostimulant medication. Methylphenidate increased frontal activation in both groups of children. However, the drug increased striatal activation in children with ADHD while decreasing activity in the striatum within the control group (Vaidya et al., 1998). This suggests specific advantage to medications in children with ADHD that target abnormalities in basal ganglianic structures.

The anatomic heterogeneity described above is paralleled by the cognitive and behavioral variability observed in the condition. Altered brain mechanisms in ADHD are associated with a variety of attentional and behavioral deficits (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006). Since ADHD is characterized by distributed cerebral abnormalities, any simple or straight forward localizing interpretation of the range of cognitive and behavioral difficulties that characterize the expression of the condition is impossible. The term "attention" is a semantic issue since attention must be related to more

than one anatomical network involving several brain regions (Gunay Kilic, 2005). In other words, the manifestations of the disorder cannot be blamed on one single brain region or network. However, it remains possible to try to explain specific behaviors as a manifestation of abnormality within particular brain systems through knowledge of brain–behavior relationships.

Therefore, neuroimaging data reveal differences between the brains of children and adults with ADHD in a variety of areas. Abnormalities are consistently found in differences within the cerebral cortex, within the frontal lobes, within the basal ganglia, and within the cerebellum—particularly within the vermal region (Durston, 2003; Mackie et al., 2007). Differences are also noted within white matter tracts connecting cortical with subcortical regions (Casey et al., 2007).

How can these anatomical differences be understood? It has been stated that dysfunctions in arousal, attention, and inhibition result from structural abnormalities in frontostriatal regions, resulting in diminished activity otherwise essential for normal functioning (Hale, Hariri, & McCracken, 2000). However, the behavioral and cognitive dysfunctions observed in ADHD are most likely a manifestation of disruptions within distributed functional systems (Willis & Weiler, 2005). Particular behavioral manifestations do not necessarily align with specific neuroanatomical "zones." Instead, the cortex, basal ganglia, and cerebellum have been increasingly demonstrated to operate in parallel, as individual systems contributing to an adaptive behavior. Each region makes its own unique contribution to the neuropathology of the various behaviors, and ultimately to the entire condition. In this regard, a few general "rules of thumb" are useful in providing a framework for understanding these contributions.

First: Sensory inattention and certain cognitive processing deficits can be traced to the posterior cortices, specifically temporal and parietal lobes. It is these posterior regions that are likely involved in symptoms of sensory inattention, such as failing to attend to information or details. This makes sense since attention, especially passive attention, seems to have a notable sensory–perceptual component (Dockstader et al., 2008). This also helps explain the frequent co-morbidity of "sensory integration" problems among individuals diagnosed with ADHD, since basic sensory processing can be affected in both conditions. One recent study found sex differences in tactile defensiveness among boys and girls diagnosed with ADHD, with girls featuring greater defensiveness (Broring, Rommelse, Sergeant, & Scherder, 2008). Another study from the same research group found that both children with ADHD and unaffected siblings demonstrated relative problems with tactile perception in the absence of kinesthetic problems in addition to less pain sensitivity (Scherder, Rommelse, Broring, Faraone, & Sergeant, 2008).

The posterior cortices are also involved in cognitive processing. One study compared boys with ADHD with normal control subjects when completing items from the Raven's Progressive Matrices test. The children with ADHD demonstrated significantly less activation in posterior parietal regions and in the temporal lobes, as well as in lateral prefrontal cortices and within the

striatum. The authors interpreted these findings as implicating deficits in a widespread functional network in ADHD. This network includes deficits in cortical brain regions fundamental for processing visuo-spatial information (Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2008).

Second: Impulsivity and cognitive disinhibition involve problems with gating information. Primarily, problems with acting too quickly or without executive control imply deficits in frontostriatal systems (Denckla & Reiss, 1997; Fuentes, 2004; Menon, Adleman, White, Glover, & Reiss, 2001; Ray Li, Yan, Sinha, & Lee, 2008; Vaidya et al., 2005). These types of problems imply deficits in intention programs; that is, having control over how and when to act. The idea of setting out to perform an activity, getting distracted by something else, and straying "off-task" clearly features a quality of loss of control over voluntary intention. In connection to frontal systems, it is the frontostriatal gating system that is responsible for proper gating: letting what needs to come in, and keeping everything else out (Awh & Vogel, 2008). For example, DSM symptoms such as, "is often easily distracted by extraneous stimuli," suggest involvement at the level of the striatum. The striatum is important in attention and action selection through its selective regulation of the Gpi, which in turn releases cognition and behavior through selective thalamic disinhibition–inhibition. Therefore, dysfunction within this region could conceivably result in distractibility and problems in staying on task and following through with things to completion.

Problems such as "interrupts or intrudes upon others," and, "blurts out statements and questions," or "difficulty in awaiting turns" are also symptoms of disinhibition. These symptoms represent problems refraining from responding. Failure to inhibit behaviors or thoughts implies mediation by the brain's intention programs governed by the basal ganglia. These symptoms could conceivably result from irregular activity within the frontal–subthalamic nucleus (STN) pathway that serves as a type of thermostat in regulating the Gpi. This, in turn, influences behavioral output. Evidence of the importance of some of these older structures comes from findings from treatment paradigms. For example, it has been demonstrated that deep brain stimulation of the STN generates cognitive side effects such as impulsivity (Frank, Scheres, & Sherman, 2007). Thus, to find sources of problems with impulsivity and disinhibition, understanding the role of basal ganglianic projections is vital.

Third: Problems with behavioral regulation can be traced to the cerebellum. An important finding from recent functional imaging studies extends cerebellar pathology beyond motor ataxia to more broadly encompass disturbances in rate, rhythm, and force. One characteristic of attention deficit disorder relates to variability in the manner and timing in which one responds to situations. This notable inconsistency in attention and behavior may be related to the "rhythm" functions of the cerebellum. The pragmatics of social interactions necessitate proper timing of verbal exchanges. A significant source of this problem may be disinibition (saying the wrong thing) and as such is more squarely frontal–striatal. However, the problem likely also has to do with bad timing; specifically,

talking when it is not time to do so. It is with this timing problem that cerebellar pathology may play a key role.

As earlier chapters have shown, the cerebellum has been demonstrated to be involved in executive functions such as planning and working memory, presumably due to regulating the strength of neural signals or excitation in prefrontal and frontal brain regions (Ravizza et al., 2006). Therefore, executive deficits can be generated from improper cerebellar excitation. This interpretation would be consistent with abnormalities in cerebro-cerebellar circuitry (Ashtari et al., 2005). Others have also described the cerebellum as playing an important role in the inhibition of prepared motor responses (Hirata, Tanaka, Zeng, Hozumi, & Arai, 2006). This has considerable implications for social interactions. Children and adults with ADHD are often described as having difficulties with emotional control and in the management of anger. Children are often reported as experiencing exaggerated "temper tantrums," and as generally overreactive to the valance of situations. This suggests involvement of the circuitry that connects paralimbic cortices with the cerebellar vermis. These problems with emotional regulation can be understood as disturbances in the "force" of emotional expression (Schmahmann, Weilburg, & Sherman, 2007).

Cerebellar development in ADHD has been related to clinical outcome, and both fixed and progressive neuroanatomic deficits within the cerebellum of children with ADHD have been identified (Mackie et al., 2007). Mackie and her colleagues studied a group of children who had been diagnosed with Attention Deficit Disorder and compared them to a non-clinical population. They found that the ADHD group had significantly smaller volumes of the superior cerebellar vermis and whole vermis at the start of the study. They then continued to follow this sample over time. When studied longitudinally, cerebellar hemispheric differences were observed between those with better and worse clinical outcomes. Those subjects in the worse clinical outcome group demonstrated a progressively smaller cerebellar volume over time, with most decreases observed in the posterior–inferior cerebellar hemispheres.

This regional finding correlates with the executive function deficits such as planning and working-memory problems, and linguistic and visuospatial problem-solving deficits observed in patients with cerebellar lesions in this region (Kalashnikova, Zueva, Pugacheva, & Korsakova, 2005; Schmahmann, 2004). Better clinical outcome was associated with volumetric normalization that occurred over the course of the study, with subjects in this group exhibiting a developmental trajectory that ran parallel to that of the control group (Mackie et al., 2007). These anatomical studies strongly suggest that cerebellar pathology is linked with the categorical diagnosis as well as the clinical outcome of ADHD.

As can clearly be seen from these various anatomical findings, attention deficit disorder is a pathology derived from multiple brain systems. Rather than localizing this pathology in any simple way, the available data imply disturbance in the joint, parallel operations of frontostriatal and frontocerebellar circuitry or "loops" in selecting appropriate behaviors and in refining these

selections to meet contextual requirements (Frank et al., 2007; Houk et al., 2007; Nigg & Casey, 2005). Future cooperation between various disciplines within the neurosciences such as neuroimaging, neurophysiology, neuropsychiatry, neuropharamcology, and neuropsychology will increasingly inform our understanding of the neuronal substrates of ADHD (Kelly, Margulies, & Castellanos, 2007; Rapoport & Shaw, 2008).

Schizophrenia

Schizophrenia is another disorder in which pathology has been consistently reported in both cortical and subcortical regions. Various neuroimaging modalities, namely, CT, MRI, PET, fMRI, SPECT, and DTI demonstrate the most prominent findings to be enlargement of the lateral ventricles, an undersized temporal lobe, and frontal system abnormalities (Kile, 2007). While three-quarters of all studies carried out on the temporal lobes reveal a statistically significant difference in volume, this appears to be the brain region demonstrating the most consistent structural changes as compared to normal controls (Henn & Braus, 1999). Volumetric alterations are not uniformly distributed and are primarily observed within the superior and medial temporal lobes. Although hypofrontality is a very frequently observed finding in activation studies, about half of the structural studies reveal volumetric reductions within the frontal lobes (Bradshaw, 2001; Henn & Braus, 1999). These findings very often co-occur with enlargement of the lateral ventricles. In addition, these findings have been directly linked with various cognitive deficits such as lower premorbid intelligence, verbal and non-verbal memory deficits, and problems with executive abilities including deficits in attention and working memory (Antonova et al., 2005; Crespo-Facorro, Barbadillo, Pelayo-Teran, & Rodriguez-Sanchez, 2007; Laywer et al., 2006).

Schizophrenia is clearly a multiple systems disorder. The symptoms of this condition can be understood in terms of the connectivity problems within white matter tracts connecting different regions of the cortex (Skelly et al., 2008), in terms of abnormalities within the frontostriatal system (Bradshaw, 2001; Fusar-Poli et al., 2007; Rusch et al., 2007), and in terms of cerebellar abnormalities (Picard, Amado, Mouchet-Mages, Olie, & Krebs, 2008). Therefore, this is again a disorder where cortical abnormalities work in tandem with deficits in subcortical structures.

Just as not every patient exhibits the same symptomatic presentation, not every patient demonstrates every neuroanatomic abnormality. The negative symptoms of schizophrenia such as apathy, lack of motivation, poverty of speech, and inattention have most often been associated with deficits in executive functioning while implicating frontostriatal circuitry (Ropacki & Perry, 2007). Positive symptoms such as hallucinations and delusions have been associated with cortical connectivity (Price et al., 2008; Volpe et al., 2008).

However, these two symptom clusters can overlap, and in all likelihood, there are several etiological subtypes of the disorder.

Even a single symptom such as auditory hallucinations has proven to be etiologically elusive. For example, a variety of functional domains have been implicated in the genesis of verbal auditory hallucinations (Woodruff, 2004). In PET and SPECT imaging studies that require patients to signal the presence of hallucinations, activation of the temporal cortex, the anterior cingulate gyrus, and subcortical regions including the striatum, thalamus, and cerebellum have all been demonstrated (Tracy & Shergill, 2006). Studies with fMRI have also been conducted that require patients to "imagine" speech. Imagining speech is believed to consist of retrieving the voice to be imagined from memory and internally reproducing and monitoring the auditory image. When patient groups were asked to perform an "imagined speech" task, auditory verbal imagery was associated with decreased activation in the lateral temporal cortex and the cerebellum. Within patient groups, hallucination-prone patients showed less activation in the right posterior cerebellar cortex as compared to non-hallucinating patients. This finding was interpreted as reflecting the role of the cerebellum in modulating activity within the temporal cortex, implicating the cerebellum in auditory hallucinations (Tracy & Shergill, 2006).

As reviewed in Chapter 4, the right posterior cerebellar hemisphere has reciprocal connections with the left superior temporal lobe. Given the anatomy, it is likely that auditory hallucinations may in part be a manifestation of abnormal cerebellar regulation of the temporal lobe. White matter abnormalities have also been associated with auditory hallucinations in schizophrenia. White matter changes were primarily observed in the frontal and temporal areas, including alterations in the white matter tracts of the arcuate fasciculus (Higgens & George, 2007; Seok et al., 2007). Taken together, these data imply that auditory hallucinations are derived from abnormalities in the regions that register and/or regulate external sounds. The experience of auditory hallucinations may result from a misidentification of "inner speech" as originating from an external source due to a lack of integrity of the system (Andreasen & Pierson, 2008).

The Basal Ganglia in Schizophrenia

Several lines of evidence suggest that the basal ganglia are important in the pathophysiology of schizophrenia and that structural abnormalities of the basal ganglia are implicated with the disease (Busatto & Kerwin, 1997). These differences include increases in the total volume of basal ganglia structures. Notable differences in shape have been reported to accompany these volumetric changes in the caudate, putamen, and globus pallidus (Mamah et al., 2007). Abnormalities in the caudate and within the dorsal medial and anterior nuclei of the thalamus have also been reported (Rose et al., 2006). While schizophrenic

patient populations have been described as exhibiting impairments in episodic memory and executive control processes (Reichenberg & Harvey, 2007), 2007), there are also disruptions in non-declarative learning tasks that require regionally specific striatal circuits as in motor skill and probabilistic category learning tasks (Weickert et al., 2002).

Other data described schizophrenic patients as impaired at acquiring cognitive skills dependent upon specific striatal circuits but not in sequence learning as measured by a serial reaction time task, giving evidence of selective impairment in cognitive "loops" connecting the basal ganglia and thalamus (Foerde et al., 2008; Keri, 2008). Other lines of evidence include subgroups of schizophrenic patients exhibiting dyskinesias consistent with basal ganglia pathology that occur independently of medication status (Boks, Liddle, Russo, Knegtering, & van den Bosch, 2003; Malla, Norman, Aguilar, Carnahan, & Cortese, 1995). In addition, symptoms of psychosis have been reported in disorders of the basal ganglia such as Parkinson's disease (Aarsland & Larsen, 2003), and Huntington's disease (Guttman et al., 2003). Anti-psychotic medications effective in treating Schizophrenia primarily target dopaminergic transmission within the basal ganglia (Miller, 2008).

While frontal–striatal glutamate neurotransmission has also been implicated in the pathophysiology of this condition (Higgins & George, 2007), glutamatergic synaptic pathology within the caudate nucleus has also been reported in schizophrenia (Nudmamud-Thanoi, Piyabhan, Harte, Cahir, & Reynolds, 2007). In this regard, there are many different lines of evidence that converge upon the basal ganglia as a region of pathology within schizophrenia. There is also a very strong demonstration that inactivity within the globus pallidus is involved in the mediation of schizophrenic symptoms, particularly with respect to the cognitive dimensions of psychosis (Galeno, Molina, Guirao, & Isoardi,, 2004; Menon, Anagnoson, Glover, & Pfefferbaum, 2001). In one study with 10 schizophrenic patients who were never medicated for the condition, there was a consistent abnormality in blood flow found in the left globus pallidus. This decrease in perfusion was not observed in any of the 20 subjects comprising the control group (Early, Reiman, Raichle, & Spitznagel, 1987).

It is absolutely fundamental and essential for adaptation to select appropriate movements and to arrange or sequence them in the proper order, dependent upon situational context. These are functions of the basal ganglia, as described in Chapters 2 and 3. The anatomic architecture of the frontal-striatal-pallidal-thalamic loops places the basal ganglia in a unique position to select the appropriate action by way of timing patterns of neural firing. However, in order to accomplish this arrangement of movements, the basal ganglia must "learn," and this is accomplished through reward-driven dopaminergic instrumental learning. This allows the basal ganglia to "learn" or "bind" appropriate patterns or "chunks" of movement. Disruption within these loops of interaction in motor circuits results in disturbances in patterns of movements as evident in movement disorders.

However, what the basal ganglia do for movement, they also do for cognition. When dysfunction occurs within channels that select and sequence perceptions and cognitions, the result is likely to be a disturbance in cognitive patterns (Graybiel, 1997). In Huntington's disease, reduced activity within the Gpe results in the adventitious release of patterns or fragments of purposeful movements. When dorsal regions of the pallidum are affected, it is hypothesized that the result would be the adventitious release of patterns or fragments of cognitions, resulting in psychotic symptoms. Just as the Globus Pallidus is part of the mechanism that selects purposeful movement, it must also help direct purposeful thought. Therefore, the symptoms of schizophrenia can be understood as reflecting a disturbance in perceptual and action selections (Houk et al., 2007).

The Cerebellum in Schizophrenia

The cerebellum has been implicated in a variety of neuropsychiatric disorders, especially in autism and schizophrenia. A restricted set of motor symptoms observed in these conditions suggests regional instead of global cerebellar dysfunction (Gowen & Miall, 2007). There are also other lines of evidence implicating the cerebellum in the pathogenesis of schizophrenia (Andreasen & Pierson, 2008). As we discussed in Chapter 5, the cerebellum is critical for eye blink conditioning. Smaller anterior cerebellar volumes and eye blink conditioning impairments have been associated with schizophrenia (Edwards et al., 2008). Individuals with Schizophenia have been shown to demonstrate impairment in relation to prism adaptation tasks, which feature significant cerebellar contribution for correct performance (Bigelow et al., 2006). Cerebellar "soft signs" in schizophrenic patients have been associated with negative symptoms of the disease, cognitive deficits, and decreased cerebellar volume (Varambally, Venkatasubramanian, Thirthalli, Janakiramaiah, & Gangadhar, 2006).

Male schizophrenic subjects have been described as exhibiting significantly smaller volumes of the whole vermis, but not abnormal volume of the lateral cerebellar hemispheres (Joyal et al., 2004). Increased cerebellar vermis white matter volume has also been reported in male schizophrenics, and this was correlated with verbal executive dysfunction (Lee et al., 2007). Cerebellar white matter abnormalities have been reported in early-onset schizophrenia (Kyriakopoulos, Vyas, Barker, Chitnis, & Frangou, 2008), and abnormalities of this type have also been correlated with positive psychotic symptoms such as delusions and hallucinations (Whalley et al., 2007). Imaging studies with DTI have demonstrated connectivity abnormalities in the middle and superior cerebellar peduncles, which are the afferent and efferent fiber tracts that carry information to and from the cerebellum (Okugawa et al., 2004; Okugawa, Nobuhara, Sugimoto, & Kinoshita, 2005; Okugawa et al., 2006).

It has been proposed that the psychotic thinking and cognitive deficits of schizophrenia should be considered in terms of "cognitive dysmetria" (Andreasen et al., 1996; Andreasen et al., 1999; Schmahmann, 2004). Doing so implicates prefrontal–cerebellar–thalamic circuitry in the pathogenesis of the disorder. Disturbances in this circuitry generate poor "mental coordination" that is characterized by difficulties in prioritization, processing, coordinating, and responding to information. However, not all patients present with cerebellar abnormalities or dysfunction. The data reviewed suggest that when cerebellar dysfunction occurs in schizophrenia, it may be focal, that is, restricted to specific regions or zones (Picard et al., 2008). Relative inactivity of the vermis would theoretically be associated with the negative symptoms of schizophrenia, such as apathy, lack of motivation, flat affect, and social withdrawal. Involvement of the posterior inferior cerebellar hemispheres would theoretically be associated with psychotic symptoms and disturbances in cognitive functioning (see Chapter 5 for further discussion).

It has been posited that serial ordering (mediated by striatum/basal ganglia gating), and on-line error correction (mediated by cerebro-cerebellar circuitry), are prime examples of natural action selection (Houk et al., 2007). These two systems operate in parallel and are essential for accomplishing coordinated adaptive behavior. Under this model, dysfunction in either or both circuitries could conceivably result in the debilitating symptomatology of schizophrenia. For example, inappropriate selective "disinhibition" from the Gpi to thalamic circuitry projecting to temporal lobe cortex could result in the adventitious release of verbal auditory perceptions, experienced as hallucinations. Similarly, faulty cerebellar "modeling" or error detection necessary for action coordination could impair the inner speech processes that ordinarily guide behavior, resulting in one's own inner speech being experienced as an external voice. As schizophrenia is clearly a complex, heterogeneous disorder, future findings will likely demonstrate multiple subtypes with differing etiologies.

Mapping Anatomy and Symptomology

Thought disorder is sometimes considered a unitary entity. However, this general symptomology is often divided into two types of thought disorder; namely, disorders of thought content and disorder in the process and form of thought. Disorders of thought content are delusions. Formal thought disorder refers to illogical thinking or oddities and peculiarities in the pattern of thought. Based upon what has been proposed about the functions of the cortex, basal ganglia, and cerebellum, three different types of thought disorder, subserved by three different neuroanatomies, can be suggested and characterized. These types of thought disorder are delusions, the intrusion of irrelevant ideation, and circumstantiality/tangentiality.

Delusions are defined by the DSM as false beliefs based upon incorrect inferences about external reality. These beliefs are firmly sustained in spite of contrary evidence or the opinions of others (DSM-IV, 1994.) Most delusions are content-specific, which means they have a specific theme or content. Delusions occur not only in schizophrenia, but also in individuals who have sustained neurological insult or disease. Nevertheless, the content of delusions can be very similar in neurological patients and in psychiatric populations. (For a review of content-specific delusions, see Richardson and Malloy, 2001).

Delusions have been related to cortical pathology. The pathology usually involves right hemispheric processes. The type of delusion may depend upon the specific region of pathology. Right hemisphere posterior temporoparietal involvement can generate a lack of familiarity concerning place, and inferior temporal lesions can result in disorders of recognition of person. Damage in these regions can disconnect these cortices from the prefrontal lobes, which could generate reduplicative delusional phenomenon. Anterior parietal lesions would theoretically be important in the generation of dysmorphic distortions resulting in body dysmorphic delusions (All of the above as reviewed by Richardson and Malloy, 2001). It has been proposed that frontal lobe pathology needs to be superimposed upon regional "sensory-lobe" pathology to generate these types of delusions. For the purposes of this discussion, it is proposed that delusions can theoretically result as manifestations of pathology at the frontal–cortical level generally.

The second type of thought disorder can be defined as the intrusion of irrelevant ideation. In this subtype, the patient has difficulty staying "on track" during the course of conversation. The patient gets distracted and says something that is totally irrelevant to the topic at hand. It is betrayed by the fact that the subject states something or asks something that represents a logically complete idea, but it is simply unrelated to the current topic of conversation. Therefore, it is an idea expressed at the wrong time, rather than an idea that is inherently illogical. An example of this might be seen when, after giving a patient a test instruction, he or she asks, "are you going on any trips this year," or states, " I had a great time at the ballpark yesterday." It is proposed that this type of "thought disorder" may be a manifestation of impairment in frontostriatal connections, since this resembles a disturbance in intention, specifically, not "knowing" when to start/not start a verbal behavior.

The basal ganglia play a critical role in action selection. Abnormal pallidal disinhibition of the thalamus could conceivably result in the adventitious intrusion of irrelevant ideation, which would be manifest as saying the wrong thing and introducing an irrelevant idea or asking an irrelevant question during the process of discourse. This can also be associated with tangentiality in which the individual literally goes off on tangents, from one topic to another, never quite making the point. This type of losing track of one's thought process has been attributed to working memory deficits (Goldman-Rakic, 2001). This can also be interpreted in terms of abnormal pallidal disinhibition of the thalamus, akin to what might be described as a failure of the "bouncer in the brain" to

inhibit distracting or irrelevant ideation (McNab & Klingberg, 2008) (see Chapter 2). These examples can be understood as specific instances of verbal disinhibition.

The third subtype of thought disorder is manifested by circumstantiality. In this type of thought disorder, the patient goes on and on, giving all sorts of examples, some of them only remotely related to the topic, to the extent that the overall verbalization becomes illogical while the patient takes forever to "make the point" or perhaps does not realize the point was made. At its worst, statements can be totally illogical and idiosyncratic. This has been referred to as "cognitive dysmetria" (Andreasen, Paradiso, & O'Leary, 1998; Andreasen et al., 1999). An example of this might be observed in the course of administering a patient a Wechsler cognitive battery. Consider the following simulated Similarities (Wechsler, 2003) item asking, "how are a lion and a tiger alike?" When the patient states," they are alike because they are both animals, but a lion was in the Wizard of Oz but tigers were not, and both are wild animals, in contrast to rats and mice, which are larger and smaller versions of rodents, which are another type of animal," this can be conceptualized as a type of cognitive dysmetria. In this type of verbalization, it can be hypothesized that a perception is connected with unessential or even erroneous associations (Andreason & Pierson, 2008). The response quality here seems illogical, and it demonstrates the cognitive equivalent of dysmetria. There is a lack of cognitive coordination of the response, characterized by the quality of overshooting and undershooting the answer, while the patient has difficulty in terminating the reply.

Thought disorder has not been systematically studied according to the above descriptions. However, the examples given represent testable and verifiable hypotheses, based upon what might be predicted from neuropsychological principles. All clinicians reading this book can likely relate to the examples of thought disorder that were given, and have seen "thought disorder" occurring differently in different patients either in combination or independently of each other. The value in thinking about thought disorder in this way is that it can lead to systematic investigation of these differing presentations, which would enhance our understanding of brain–behavior relationships and the roles various brain regions play in the pathogenesis of psychiatric conditions and behavioral disorders.

Other Clinical Disorders

Autism Spectrum Disorder (ASD—Including Asperger Syndrome)

As noted previously, most disorders described in the DSM can be viewed as pathologies involving multiple systems or brain networks. None of these disorders are completely understood. However, in most conditions,

abnormalities can be demonstrated at the levels of cortex, basal ganglia, and cerebellum. While the cerebellum has traditionally been understood as a co-processor of movement, this view has been changing dramatically over the past 25 years. As we have seen, evidence has accumulated demonstrating cerebellar abnormalities in disorders such as autism, mood disorders, and even dementia (Rapoport et al., 2001). In autism, disturbances have been hypothesized within multiple networks. Neuroimaging studies have documented metabolic deficits within the frontal cortex, temporal cortex, basal ganglia, and cerebellum (Rumsey, 1996; Rumsey & Ernst, 2000). Investigations have correlated abnormalities in social functioning with face processing deficits in Autism (Pelphrey, Adolphs, & Morris, 2004). Individuals with autism reportedly spend less time scanning the core features of faces such as the eyes. This impairment in facial scanning might represent reduced activation throughout the visual sensorimotor system. The facial scanning deficit may represent pathology within prefrontal–striatal–thalamocortical circuitry during visually guided saccades and not necessarily pathology within the fusiform gyrus of the temporal lobes (Takarae, Minshew, Luna, & Sweeney, 2007).

Within the cerebellum, abnormalities have been reported in Purkinjie cells, within the deep cerebellar nuclei, and within olivary nuclei (Rumsey & Ernst, 2000). Other studies have demonstrated limbic system abnormalities, as well as hippocampus, basal forebrain (the frontostriatal system), and cingulate and orbitofrontal cortex involvement (Weidenheim et al., 2001). An impairment in attention is a consistent symptom in autism and this has been directly related to cerebellar abnormality (Allen & Courchesne, 2001). Studies have suggested that developmental cerebellar abnormalities have differential functional implications for cognitive and motor systems. For example, it has been proposed that an early loss of Purkinje neurons might cause more basic functions typically mediated by paleocerebellar regions to be displaced into the neocerebellum (the posterior superior and inferior regions of the cerebellar hemispheres) at the cost of tissue that subserves cognitive functions such as attention and language (Allen & Courchesne, 2003). This might result in an overall lack of functional efficiency of the cerebellum as a manifestation of "crowding effect" since many modular functions would be displaced into a smaller, limited region of the cerebellum.

While the feed forward limb of the cerebro-cerebellar circuit provides cortical input to the cerebellum, Andreasen and Pierson have argued that Purkinje cells play a critical role in deciding what information is or is not returned to cortex by way of inhibitory mechanisms (Andreasen & Pierson, 2008). However, abnormalities in the feedback limb of the circuit can also prevent the cerebral cortex from receiving the proper input from the cerebellum. A DTI study has demonstrated abnormalities in cerebellar output tracts in individuals with Asperger syndrome as compared to normal control subjects, but no differences between groups in input tracts (Catani et al., 2008). The findings were described as suggesting a vulnerability of cerebellar feedback pathways in

individuals with Asperger syndrome. These abnormalities may prevent the cerebral hemispheres from receiving the cerebellar feedback input necessary for successful social adaptation. Based upon the seemingly divergent findings observed in ASD, it can be hypothesized that any pathological process that affects the infrastructure of the cerebellum or its output circuitry is likely to cause significant behavioral dysfunction.

Mood Disorders

Multifactorial involvement is also the rule of thumb in affective or mood disorders. Patients with depression have demonstrated abnormalities in activity within the frontal lobes, within the head of the caudate, in inferior and medial prefrontal cortices, and within the temporal lobes (Mayberg, 2002). Therefore, prefrontal, basal ganglia, and paralimbic regions have all been implicated. There is no clear consensus concerning left versus right hemispheric areas of involvement, although some reviews have emphasized the anterior left hemisphere (Cummings, 1993). Perhaps of particular interest is the finding that in major depressive disorder, patients exhibit chronic abnormality in cerebellar activation, regardless of mood state or medication history (Konarski, McIntyre, Grupp, & Kennedy, 2005).

In early onset Bipolar disorder, structural abnormalities have been reported in total cerebral, white matter, and temporal lobe volumes, as well as within the putamen, thalamus, amygdala, and hippocampus (Frazier et al., 2005). Functional neuroimaging studies generate a model of bipolar disorder that includes dysfunction within subcortical, frontostriatal networks, the temporal lobes, the associated modulating limbic regions, as well as involving midline cerebellar regions (Bearden, Hoffman, & Cannon, 2001; Bruno, 2005; Konarski et al., 2005; Monkul et al., 2008; Peter, Brent, Phillip, Emily, & Michele, 2005; Phillips, Ladoucer, & Drevets, 2008; Sax et al., 1999; Strakowski, Delbello, & Adler, 2005). Significant regional differences have not been observed when comparing the neurobiological findings of Bipolar I disorder versus Bipolar II disorder, though the evidence for progressive changes in bipolar disorder is considered tentative (Monkul, Malhi, & Soares, 2005).

Alzheimer's Disease

Alzheimer's disease, one of the most common causes of dementia, is characterized by a variety of cognitive deficits, chief of which is memory disturbance. Disturbances in executive functions, language, and visuospatial skills are typically evident during the course of the disease process. Degeneration of the temporal lobes, neurofibrillary tangles, and amyloid plaques are characteristic

pathological findings. However, of interest is the fact that the posterior cerebellar lobes are also significantly smaller in Alzheimer's patients as compared to normal controls. This atrophy of the posterior cerebellar regions corresponds with poorer performances on cognitive tasks, even in cases with mild cognitive impairment (Thomann et al., 2008). This suggests a role for subcortical, cerebellar involvement in Alzheimer's disease.

Summary

These data suggest that there is really no current ideal model within which to conceptualize the disorders that are behaviorally defined within the DSM. All disorders are characterized by disturbances within multiple brain networks. In many disorders, these networks appear to overlap, accounting for certain symptom similarities between conditions. For example, cognitive abnormalities consisting of various executive function deficits would appear to be characteristic of conditions in which the prefrontal lobes, corticostriatal, or cerebro-cerebellar systems are involved. Abnormalities can be structural, morphological, connectional, cellular, metabolic, or neurochemical to name a few possible etiologies. Interrupting or disturbing a neural network, regardless of etiology, will likely generate the cognitive deficit mediated by that particular network.

This has important implications for clinicians in that current neuropsychological tests are sensitive to the integrity of brain–behavior relationships but are not specific to any one given etiology. Similarly, neuropsychological test results are not sensitive to most DSM-defined conditions. It is not at all likely that even a comprehensive neuropsychological evaluation that assesses language, visual–perceptual–spatial, learning and memory, attention and executive, and sensory and motor domains will ever be able to generate specific neuropsychological "profiles" that would be uniquely specific to the different behaviorally defined conditions of the DSM.

Neuropsychological methodologies and behavioral observations are two different systems that do not merge or compliment each other within the diagnostic categories of the DSM. It is suggested that neuropsychology can assist in understanding these conditions because of its descriptive and functional nomenclature. In order to contribute to an understanding of disorders, patients might be grouped on the basis of a discrete symptom or deficit, instead of behaviorally grouping patients according to diagnosis. Patients can be evaluated with neuropsychological testing methodologies according to these discrete deficit and symptom groupings. This will assist in understanding the brain–behavior relationships that generate or "drive" symptoms. In this way, neuropsychology can contribute to an enhanced understanding of brain–behavior relationships in both health and disease.

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Chapter 8
Familiarity and Novelty—Evaluating the Frontostriatal System

To arrive at the simplest truth requires years of contemplation.
Isaac Newton

Out of intense complexities intense simplicities emerge.
Winston Churchill

Previous chapters of this book have demonstrated that behavioral output is a function of cooperation between three brain regions, namely, the cortex, the basal ganglia, and the cerebellum. It was proposed that posterior cortices primarily function to process sensory–perceptual information. The frontal lobes and prefrontal cortices generate action or motor programs. The basal ganglia participate in attention and action selections and in binding action sequences as instrumental and procedural learning mechanisms. The cerebellum refines these selections of potential behavioral output to meet the amplification requirements of the given behavioral context. This "division of labor" has implications for neuropsychological testing because test results are affected by these same three brain-related sources of variability.

Levels of performance on neuropsychological tests can be influenced by lesions within the cerebral cortex, by pathology within the basal ganglia, and by disturbance within the cerebellum, not to mention pathology within the thalamus, hypothalamus, or white matter tracts connecting various brain regions. There is no specific level of performance, no specific cognitive profile currently understood to signal disturbance at any particular level. Looking at and interpreting test data from the perspective of *blind diagnosis*, especially when using a simple normative level of performance criteria, thus will not assist with differentiating pathology within the cortex, basal ganglia, or cerebellum (see Chapters 10 and 11). Instead, a set of test results can be consistent with impairment of either cortical or subcortical functions. Depending upon the clinical setting, this lack of localization specificity is more or less problematic. For example, in certain clinical populations with tumor, CVA, or other documented localized pathology, there is often no reason to suspect subcortical pathology, as the locus of the lesion is frequently cortical. Using traditional approaches to neuropsychological test data to

L.F. Koziol, D.E. Budding, *Subcortical Structures and Cognition*,
DOI 10.1007/978-0-387-84868-6_8, © Springer Science+Business Media, LLC 2009

localize pathology often works fine under those conditions. However, in outpatient settings where a wide variety of pathologies can be seen-including cases of psychopathology and developmental disorders of the frontostriatal system-this lack of specificity in relation to neuropsychological test data can become a very problematic issue.

Different approaches are called for when evaluating a person with known localized pathology versus the point of view of blind diagnosis when the range of possible pathology can be very wide. However, because each brain region makes a unique contribution to behavior, it could be argued that impairment at the level of the cortex, basal ganglia, or cerebellum should have its own characteristic impact upon behavior and test results. These three brain-related factors influencing test results might require different interpretive approaches apart from (or in addition to) basic normative level of performance criteria. However, every neuropsychological test used or administered might not be amenable to multiple approaches in test interpretation. Most tests are not sensitive enough if one is relying upon basic statistical comparisons in which a test score is simply compared to a population norm. Clinical evaluation incorporating behavioral observations with the interpretation of test data is an approach capable of greater differential diagnostic power. However, even so, if cognition is organized according to brain networks, we cannot expect any single test to be able to localize all regions of the network.

For example, working memory, a critically important executive function, is strongly affected by each of these three sources of variability. Working memory impairment can result from disturbances within prefrontal cortex, or through disturbances within prefrontal–parietal lobe or prefrontal–temporal lobe connections, as these regions subserve the maintenance of working memory content (Baddeley, 2003; D'Esposito, 2008). A working memory disturbance can also be caused by dysfunction within the striatum or the globus pallidus, because these structures interact with cortex in manipulating the contents of working memory (Frank, Loughry, & O'Reilly, 2001; Hazy, Frank, & O'Reilly, 2006; McNab & Klingberg, 2008). Further, dysfunction within the cerebellum can also result in an impairment in working memory (Ben-Yehudah, Guediche, & Fiez, 2007; Ravizza et al., 2006). A disturbance at the prefrontal–cortical level can result in difficulties keeping information in mind or in mentally manipulating information. Involvement at the level of the basal ganglia can result in distractibility related to problems preventing intrusion of irrelevant information. Impairment within the cerebellum can alter the strength of the neural signals that are necessary for keeping memory traces active.

Working memory tests such as repeating digits forward, digits backward, Letter-Number sequencing, or the Brown-Peterson Technique, also known as Auditory Consonant Trigrams (ACT) (Strauss, Sherman, & Spreen, 2006), can all identify working memory deficits. However, results from these measures are not differentiating in terms of site of pathology. These measures provide a level of performance compared to a normative standard. The result says nothing

about the reason for the poor performance, nor does it speak to the localized area of the brain contributing to that performance. A similar conclusion can be drawn for other executive function-related tests, such as the various Trail Making Tests, Wisconsin Card Sorting Test, or the Tower of London Test. Deficit range performance on these tests may reflect impairment in executive function, but these tests do not allow for specific localization within the frontal lobes, basal ganglia, or the cerebellum (Alvarez & Emory, 2006; Hirata, Tanaka, Zeng, Hozumi, & Arai, 2006). Again, pathology in any of these three brain regions can influence test performance. Therefore, when interpreting neuropsychological test results as an independent source of examination data, the test results need to be presented in cognitive and behavioral terms instead of in anatomical terms.

This chapter has several purposes. Neuropsychological test interpretation will be considered as it specifically relates to the frontostriatal system. We will review relevant brain functions of this region. We will evaluate properties of various commonly used cognitive tests in order to determine what these tests actually measure in relation to the functions of the cortex and basal ganglia. We will then suggest some possible methodologies for evaluating subcortical brain regions. We believe that functional neuroanatomy should be the driving force behind test construction and test interpretation. This chapter develops a framework for this approach.

The Frontostriatal System

What does the frontostriatal system do? Previous chapters described the functions and properties of the frontostriatal system in detail. For the purpose of neuropsychological testing, the frontostriatal system can be described as controlling cognitive processing according to goals (Richer & Chouinard, 2003). This system sets the context for stimulus-based responding (Toates, 2005b). Therefore, the frontostriatal system directs problem-solving behavior. For novel situations, the frontostriatal system develops problem-solving behaviors by determining the stimulus-based characteristics of the problem and by applying behaviors to fit that context. In familiar or routine situations, the frontostriatal system selects the most appropriate stimulus-based, routine, or automatic behavior that fits the current familiar context (see Chapters 2 and 4). Since a fundamental purpose of the frontostriatal system is to adapt to the environment, this would naturally include making that which is initially novel familiar. If the same or similar set of circumstances occurs in the future, the brain will have a pre-programmed or stimulus-based response available. Therefore, the frontostriatal system can be described as controlling cognitive processing according to goals in three ways:

1. Assessing a novel problem and discovering its stimulus-based characteristics for effective problem-solving, which can be referred to as *higher-order control*.
2. Selecting appropriate stimulus-based behavior to fit a routine or familiar situation, which can be referred to as *automatic processing*.
3. Automating solutions to problems that were initially novel, which is an aspect of *instrumental and procedural learning*.

From our point of view, a neuropsychological evaluation needs to examine all three of these areas, as all three areas are essential to adaptation. In other words, these are the things that the brain does to interact with and to adapt to an environment. A neuropsychological evaluation is in this way a "sample" of the environment, if only for that particular assessment session. The purpose of the evaluation is to assess the adequacy and efficiency of available adaptive resources. Therefore, test data need to be obtained that provide information about these processes. We must ask whether the typical neuropsychological assessment evaluates all of these areas, and if not, what adjustments and additions might be made to the evaluation to ensure that these essential areas of functioning are measured. Perhaps more fundamental questions concern whether or not neuropsychological tests can be developed or adapted in order to adequately identify and measure the contributions of the cortex, basal ganglia, and cerebellum so that specific regions of localization can be identified.

Neuropsychological tests have generally been constructed on the foundation of a cortico-centric model of cognition. In this model, emphasis is primarily focused upon the functions of the frontal, temporal, parietal, and occipital lobes. Frontostriatal system function is not generally considered. There are no commercially available neuropsychological tests that have been specifically designed to assess all the functions of the frontostriatal system when this system is considered as a group of related processes serving the three purposes described above. In fact, given what the frontostriatal system does, it is impossible to conceive of one specific, individual test that would simultaneously assess novel problem-solving, automatic responding, and processes of procedural learning. These functions all require different tasks.

There are also no commercially available neuropsychological batteries of tests that systematically evaluate the functions of every aspect of the frontostriatal system. Nevertheless, certain neuropsychological tests do assess aspects of frontostriatal functions. Notably, none of these tests rely upon simple level of performance criteria in order to make an interpretation. There is no "score" that identifies frontostriatal network pathology when the score is compared to a population norm. Instead, a group of test performances can establish a pattern that might provide interpretive information about the integrity of the frontostriatal system. Different tests, or aspects of tests, can be used in combination to provide synergistic interpretations. Comparing performances on these tests provides unique information that could not be obtained through interpreting each test in isolation.

The Frontostriatal System in Operation

Before returning to the topic of neuropsychological testing, we will review a few examples of behavior in order to demonstrate the roles of the frontostriatal system. For example, consider these numerical and alphabetic sequences:

1-2-3-4-5-6, etc.
A-B-C-D-E, etc.

For the normal control subject, reciting these sequences is automatic. Higher-order control is not required. "Knowing" these sequences includes the underlying analysis that the response "1" serves as a stimulus for the response "2," while the response "2" serves as a stimulus for the response "3." Similarly, the response "A" provides the stimulus for the response "B," and the response "B" serves as a stimulus for the response "C," and so on and so forth (Graybiel, 1998; Toates, 2005a) (This is an example of the serial-order processing described in Chapter 2.).

Now, consider these following sequences:

1-3-5-7-9, etc.
A-C-E-G-I, etc.

For the normal control subject who has mastered counting, the numerical sequence of counting by twos with odd numbers is also automated (at least for the first several numbers in the series). The number "1" serves as a stimulus for number "3" which serves as a stimulus for number "5," etc. Higher-order control is not relied upon to recite the sequence if counting by twos is mastered or "known," and it takes very little time to perform the counting recitation. The task of counting by twos would thus be performed quickly. This is consistent with the premise that automatic behavior is performed with little effort and that this is usually evident in speed of performance (Saling & Phillips, 2007).

However, this is generally not the case for reciting every other letter of the alphabet in sequence. For most of us, reciting the sequence, A-C-E-G-I, etc., is not automatic and requires considerable cognitive control, or "thinking." The amount of cognitive effort required is very evident in the time needed to complete performance of the task. This task would not be performed quickly in comparison to the prior 1-3-5, etc. task. Reciting this alphabetic sequence elicits a "cognitive control" or "frontostriatal" episode (Richer & Chouinard, 2003). This *cognitive control episode* consists of activating several functions.

For instance, working memory is required in several ways. The stimulus-based characteristics of the new task must be kept in mind and must be updated during task performance. The sequence of the standard alphabet needs to be activated from declarative memory. While the new sequence is recited, the potential recitation of every other letter in the sequence must be inhibited. At the same time, the current position of the letters must be updated while reciting the new sequence. In other words, the sequence needs to be constantly updated as the task progresses. Perhaps the easiest way to initially perform the task would

be to silently say to oneself the "every other letter" aspect of the sequence that is being inhibited from recitation. This "formula" requires developing a strategy. All of this would appear to seriously tax working memory functions. Said another way, the task of reciting the A-C-E-G-I, etc., sequence comprises an executive control task that requires working memory characterized by information maintenance, continual updating, and inhibiting responding to aspects of a previously automated sequence and other distracting influences. Aspects of these processes are mediated through the looped architecture of prefrontal–basal ganglia circuitry that manages serial-order processing. The time it takes to complete this task would comprise a by-product of cognitive or executive control (see Chapter 9 for a more detailed discussion of processing speed).

The cognitive demand of this task is considerable. However, if this new sequence was practiced, over and over again, this sequence would also become automated, just like the automation of counting by twos starting with odd numbers, or like the sequences of counting or reciting the alphabet. With repetition, the response "A" would eventually become a stimulus for the response "C", which would become a stimulus for "E," and so on and so forth. With practice, cognitive demand would be reduced because responses would presumably be "chunked" together (Graybiel, 1998). As competency in performing the task is acquired, brain activation decreases would likely be seen. This typically occurs in relation to complex working memory tasks that do not involve a change in the underlying cognitive operations, and this would be interpreted as increased neuronal efficiency in task processing (Kubler, Dixon, & Garavan, 2006). As this sequence became automated, it would be demonstrated by taking significantly less time to recite the sequence of "every other letter of the alphabet." It would eventually be performed quickly. The changes in "processing speed" would be considered by-products of changes in cognitive control.

These examples illustrate the concepts of stimulus-based responding, higher-order control, and aspects of the process of automation. This later example also illustrates the concept of "processing speed," when defined as the time needed to perform various cognitive operations (Reichenberg & Harvey, 2007). (see Chapter 9, this volume, for a specific discussion of processing speed). This example also implies that when higher-order control is involved, the function is likely to be performed slowly in contrast to the quick, accurate performance of automation, which relies upon previously acquired associations. Executive control works slowly. The length of time required to perform a task often betrays a "cognitive control" episode. These episodes imply involvement of the frontostriatal system.

Interpretation Paradigms

Embedded within these examples is a test interpretation paradigm consisting of two parts. The first aspect compares how a subject performs on an automated stimulus-based processing task versus how he or she performs

on a novel variant of the task that requires higher-order control. In other words, comparing an automated task performance with an appropriate novel task performance would provide information about the operation of the frontostriatal system. The second feature concerns the time required, or the number of trials necessary for the subject to automate the new task. Currently available tests do not provide this normative standard concerning number of trials it takes to "learn" (this will be discussed in Chapter 9). However, it is possible to use existing tasks to compare stimulus-based responding with higher-order control.

The test interpretation derived from comparing such performances would be synergistic. Comparing patterns of performance in relation to these tasks would be considerably more revealing and diagnostic than simply knowing how the subject performed on each component of the task. Certain currently available neuropsychological tests are amenable to aspects of this type of interpretive methodology, and will be discussed in the next section. We believe that using pattern analysis in approaching test interpretation is an absolutely critical strategy for understanding these cognitive operations.

Dynamically Changing Locus of Control

Another common example is useful to review. If asked to spell the word, "receive," it is very likely that many people would engage a "cognitive control episode," even though on the face of it, this seems like a very simple task. For instance, it would be very common to write or say without thinking, "r-e-c," and then say to oneself, "i before e except after c," and then continue with the automatic sequence, "e-i-v-e." This cognitive control episode was very brief, but was nevertheless composed of several steps. Inhibition was required to stop after the initial stimulus-based spelling of "r-e-c." Working memory was necessary to retrieve the rule "i before e except after c," from declarative recall, while holding in mind the stopping point of "c" in the initial partial spelling, and then re-engaging in automatic responding to complete the spelling of the word. The point here is that even seemingly brief and simple tasks can, and often do, contain *alternating episodes* of automatic responding with cognitive control. Most tasks in life, and most tasks in neuropsychological test batteries, require these alternating episodes of stimulus-based responding and higher-order control.

Therefore, as these examples reveal, the frontostriatal system affects the control of cognitive processing according to goals. Automatic or stimulus-based responding achieves goals by operating on the basis of acquired associations. Cognitive control episodes are necessary at those times when automatic processing does not immediately work. Such episodes require an individual to discover and apply new stimulus-based characteristics to tasks being performed. These cognitive control episodes are composed of:

1. Inhibition.
2. Working memory.
3. Identification, recollection, and retrieval of relevant declarative information.
4. Application of this information to the task.
5. Task execution.

This, in essence, is "thinking." This type of cognitive processing requires the contribution of cortex. Higher-order "processing" takes time and is not performed quickly. Cortex is a specialized problem-solver, but it works slowly in solving problems.

These examples demonstrate ongoing shifts between automatic responding and higher-order control during the completion of tasks. As tasks are learned, they become automated and also run on the principle of acquired associations. Since neuropsychological "tests" are behavioral samples just like any other tasks, these principles of the frontostriatal system must emerge in relation to neuropsychological tests, and would naturally include alternating episodes of higher-order control and automatic responding. Automatic responding would theoretically be evident in quick, effortless responding and higher-order cognitive control episodes would be demonstrated by increased time for task completion. Applying these basic principles to neuropsychological testing provides important information about the integrity of the frontostriatal system. In this regard, both automatic and higher-order goal controlled processing need to be measured, as well as the actual process of automation or "action learning."

Neuropsychological Testing and the Frontostriatal System

Cognitive control episodes, or times when "thinking" is required to solve problems, are mostly evident in novel or ambiguous circumstances. As the above examples imply, these higher-order control episodes are also evident in task situations that involve interference from competing stimuli or responses. Interference always requires inhibition of obvious, automatic, or prepotent responses in order to act upon ideas generated in working memory. Episodes of conscious cognitive control are not evident in practised, over-learned situations or in those circumstances that are automatic. However, many situations are composed of both familiar and unfamiliar elements, and these circumstances require "switching" between automatic and consciously controlled responding during different phases of the task. Therefore, most situations can be thought of as intermediate, or as lying on a continuum of stimulus-based versus consciously controlled responding.

Neuropsychological tests are no different. For example, test items experienced as "easy" do not require much effort or thought and are usually mediated by previously learned associations as in "automatic" responding. Test items experienced as "difficult" require thinking, or cognitive control. All tasks comprising neuropsychological test batteries lie on this continuum of familiar

versus novel, or automatic versus cognitively controlled. The commonly used Trailmaking test (TMT) and its newer varieties illustrate this fact. The numerical sequence for TMT A is automated (although the search strategy is not), while TMT B is a novel task for those people who have not previously practiced it. This implies that the greatest diagnostic value in using the Trailmaking test concerns comparing performance on TMT part A with performance on TMT part B. The individual "scores" in isolation are of some diagnostic value, but comparing these two phases of the task generates synergistic information. For example, a quick and accurate performance on TMT A in contrast to a slow performance on TMT B identifies a cognitive control episode in completion of TMT B, and reveals the level of efficiency of the frontostriatal system in the application of that cognitive control episode.

Similarly, certain single tasks within a neuropsychological test battery can be subject to alternating episodes of automatic responding and cognitive control. For instance, consider the Wisconsin Card Sorting Test (Heaton et al., 1993). A subject who quickly masters the first three categories of color, form, and number requires controlled responding mostly at points of "switching," but requires little thought regarding a card-by-card analysis of right versus wrong when completing the 10 trials to category completion. After discovering response categories, a subject often responds very quickly, even in a seemingly "impulsive" way, when matching to the correct category. When negative feedback is given after 10 trials of correct responding, performance often becomes considerably slower, betraying a "cognitive control" episode, once again illustrating that control is most often required at the points of "switching" that require thinking on this particular task. To be sure, this is a qualitative observation for which norms do not exist, but it reveals considerable information about sensitivity to reinforcement or "feedback." (see Chapter 4).

Contrast this example with the patient who responds quickly throughout, while making numerous mistakes, as if insensitive to the reinforcement characteristics of the task. In this regard, a neuropsychological test battery, and sometimes even a particular neuropsychological test, is not much different from any other situation that requires "online" problem-solving adjustment. However, viewing the neuropsychological evaluation in this way requires a paradigm shift from simple level of performance comparisons to a model of pattern analysis in which the subject also acts as his or her own "control." It also requires incorporating certain qualitative observations into the process of test interpretation. This is hardly a new level of analysis even when applied to cortico-cortical brain–behavior relationships (Lezak, Howieson, & Loring, 2004). However, the pattern analysis approach takes on a different interpretative meaning when shifting from a cortico-centric approach to an approach that considers the vertical organization of the brain, in this case, the frontostriatal system.

When frontostriatal system dysfunction is involved in the presenting pathology, the patient usually demonstrates deficits in cognitive control as part of the symptom picture. Problems are usually evident in performance of those

neuropsychological tests that assess what is traditionally known as "higher-order control" or "executive functioning." This is especially the case when the dorsolateral– prefrontal circuit is involved. However, because of the spatially restricted nature of the basal forebrain region, lesions within the basal ganglia that primarily affect different prefrontal–basal ganglia circuits can also generate deficits in cognitive control (Middleton, 2003). Therefore, frontostriatal systems can generate the impression of being involved in general purpose processes that influence a range of functions (Owen, 2004) (see Chapter 10 for case examples.).

The cognitive control deficits seen in frontostriatal system impairment can be observed in problems with attention and concentration, deficits in learning and retrieval, and in difficulties determining the stimulus-based characteristics of problem-solving situations. Some of the deficits within frontostriatal systems are observed in terms of time. When the frontostriatal system is involved, attention and concentration are affected. This is often apparent in relation to timed tests that are traditionally known for being dependent upon speed of novel information processing. It takes patients longer to learn new information, so that learning slopes on semantic/medial temporal lobe learning tests tend to be shallow or even flat. Retrieval of newly learned information is often slow and incomplete. Improved performance is often observed in recognition paradigms (Yener & Zaffos, 1999). Performance deficits are generally observed on tests of executive functioning, which are essentially problem-solving tests. All of these types of tasks require the type of thinking governed by the frontostriatal system. When the frontostriatal system is engaged, this can be termed a frontostriatal or a cognitive control episode.

Test Methodologies for Identifying the Integrity of the Frontostriatal System

Let's start with a novel application of learning and memory tests. Because the frontostriatal system participates in learning and recall, learning and memory tests can be interpreted within a score comparison paradigm to obtain clues about the functioning of this system. Even when learning tests are dependent upon the declarative and semantic memory systems under the mediation of the medial temporal lobe, the frontostriatal system is involved in task performance. This book assumes the reader is familiar with the anatomy and functions of the medial temporal lobe memory system which is not a topic of this book. For a review, see Squire, Stark, and Clark (2004). The medial temporal lobe hippocampal learning and memory system functions as an extension of perception. This system acquires information or experience quickly, it stores this information within posterior, semantically organized systems, but it relies upon anterior brain systems for voluntary access to this information. This is essentially a recognition memory system.

Anterior brain regions assist in information acquisition through the development and application of learning strategies. The subject has to "figure out" how to learn the material. Voluntary recall is achieved through the activation of prefrontal–subcortical circuitry. Therefore, anterior brain regions organize the complex mental activity necessary for efficient learning, memorization, and recall. The medial–temporal lobe hippocampal system is the mechanism that allows for storage or retention. Because the medial temporal lobe and frontostriatal systems provide different functions contributing to learning and memory in their own characteristic ways, this establishes a test interpretation paradigm for identifying the levels of functioning of these two systems.

This can best be observed through the interpretation of word list learning tasks. The natural structure of language inherent in narrative learning and memory tasks provides too much organization to allow evaluation of this area, but word list learning tasks lack this obvious inherent organization. The methodology of word list learning tasks allows a synergistic interpretation through test score comparisons that identify the level of integrity of both posterior and anterior brain systems. Two examples illustrate these points. Consider the following scores:

Word List Learning Test 1—CVLT—Geriatric version (Spreen & Strauss, 1998).

Trial 1	1
Trial 2	3
Trial 3	5
Trial 4	6
Trial 5	4
Total 19 words	
List B	1
SDFR	3
LDFR	3
Rec 9	
No intrusions/no perseverations	

These scores were obtained from a 65 year-old woman. Several features of this raw score profile are striking. However, for the purposes of this discussion of the frontostriatal system, three particular aspects of the data warrant consideration. First, recognition recall is completely intact. The patient correctly recognized all nine words of the original word list, and there were no false positive identifications. This implies that the hippocampal system is intact because new information was acquired and retained. Second, there is an obvious disparity between limited response production on voluntary recall trials and completely intact recognition. The results of this comparison imply a lack of integrity of the frontostriatal system. There is very good retention but very poor self-activation that results in limited voluntary access. Third, frontostriatal involvement is implied by the shallow learning slope. Therefore, this pattern analysis methodology is synergistic, since the comparisons generate

meaningful conclusions that would not be generated by evaluating only the individual performances in isolation. We also believe that scaled score comparisons to group data would not necessarily allow this level of interpretation. The second case that follows provides a similar set of raw data.

Word List Learning Test 2—CVLT-C (Delis, Kramer, Kaplan, & Ober, 1994)

Trial 1	4
Trial 2	5
Trial 3	7
Trial 4	8
Trial 5	8
Total 32 words	
List B	6
SDFR	6
LDFR	6
Rec 12	

This pattern is of course very similar to the previous data. The medial temporal lobe storage system appears to be intact. Again, three points are in order. First, the patient, who is a 15 year-old girl, recognized 12 items out of 15 (the normative standard indicates this is less than expected for her peer group, but one of the purposes of this exercise it to clinically evaluate raw data in order to integrate this approach into test interpretation). The 12 items that were correctly recognized represent a notable six-word increase as compared to any free recall trial, so obviously, there is no anterograde amnesia or information retention problem judging from these data. This individual did not "forget" anything. Second, there is a notable disparity between free recall and recognition memory, a difficulty with retrieval, with the pattern of performances indicating she knew much more information than she could voluntarily access. Again, a synergistic comparison of performances implicates the frontostriatal system. Third, there is a shallow but incremental learning slope that implicates frontal systems.

Why might learning slopes on word list learning tasks implicate the integrity of the frontostriatal system? These types of learning tasks either lack an inherent organization, as in the Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996), or they provide minimal organization through underlying semantic categories, as in the different versions of the California Verbal Learning Tests (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987, 2000). In the RAVLT, the stimulus words are not related to one another in any obvious way. In the CVLT, the stimulus words can be organized categorically. One aspect of the list learning process involves "figuring out" how to learn the words. This actually requires recruiting the working memory system to provide the mental "space" or capacity to devise a strategy. The most efficient way to accomplish this task is to form associations to the words. In the RAVLT, all of the work of imposing an associative organization on the task falls upon the subject. In the CVLT,

where a category structure is inherent in the task, the subject must "discover" these provided category structures. Discovery of these category structures facilitates learning and recall, and the subject's ability to do so is compared to a normative group in this regard.

From our perspective, the process of forming associations to the stimulus words in order to facilitate memorization and recall demonstrates a person's ability to establish the context for stimulus-based responding. Trying to learn to recall words by categories or by forming one's own associations to stimulus words reveals a process of imposing stimulus-based characteristics upon the task, which is a critical function of the frontostriatal system. Flat or shallow learning slopes can thus imply difficulty with this process, therefore implicating anterior brain regions, including the basal ganglia.

These two provided case examples feature very different pathologies. The first set of data was obtained from a woman diagnosed with Parkinson's disease. On MRI evaluation, there was no evidence of any cortical pathology. Therefore, the profile of learning and memory scores that was generated can be attributed to the functioning of anterior brain regions with primary pathology within the basal ganglia. The second set of data was obtained from an adolescent with a diagnosis of Attention Deficit Disorder, Inattentive Type. It might be tempting to localize the pathology as focal within the frontal lobes, but this is not possible if it is known that this same type of profile can be generated by subcortical pathology only. If a test performance can be attributed to two (or more) different sources of anatomic localization, the interpretation obviously does not have anatomic specificity. However, the "bullet point" is that test score comparisons on word list learning tests can generate a synergistic interpretation that implicates the integrity of the frontostriatal system.

The putative anatomy of this retrieval–recognition pattern also needs to be considered. Voluntary recall is under the mediation of dorsolateral PFC-striatal-pallidal-thalamic-prefrontal circuitry. Imaging data have demonstrated that the right hemisphere prefrontal cortex becomes active on delayed free recall condition trials (McDermott & Buckner, 2002; Rugg, Otten, & Henson, 2002; Wagner, 2002). Consistent with the anatomy presented in previous chapters, the dorsolateral–prefrontal cortex would need to activate the striatum for information to be retrieved. The striatum would select the information to be retrieved by inhibiting the appropriate region of the Gpi, thereby releasing tonic inhibition on the thalamus which would in turn "release" the representation of the words stored in cortex. This anatomy can help explain why patients with prefrontal lobe and basal ganglia pathology generate similar-looking profiles on word list learning tests. If damage to the prefrontal cortex prevents striatal activation, the information cannot be retrieved. If there is pathology within striatal–pallidal–thalamic circuitry, the information cannot be retrieved. Therefore, the same type of retrieval problem can result from either cortical or subcortical pathology because prefrontal–basal ganglia interactions are affected. However, the recognition condition theoretically bypasses frontostriatal systems. Recognition, at least in part, relies on activating posterior cortical

perceptual systems (Rugg, et al., 2002; McDermott & Buckner, 2002). This can generate the improved recognition performance in patients with intact hippocampical and posterior cortical systems, but with anterior brain region pathology. Perhaps one immediate solution to the lack of specificity of neuropsychological tests in this area of assessment is to avoid making reference to "frontal lobe pathology" in neuropsychological reports. More accurate report writing statements would refer to the frontostriatal system, frontal systems, or even "anterior brain regions."

Verbal Fluency Tasks

Verbal fluency tasks require a similar paradigm of performance comparisons. Performance on tasks of categorical fluency (as in naming animals) needs to be compared to performances on tasks of letter or phonemic fluency (as in retrieving words according to starting letter). Words are stored in semantic networks, or according to meaning (Salmon & Chan, 1994). Therefore, this task requires word retrieval from the medial temporal lobe declarative memory system. The storage space for this system is primarily located within temporal and parietal lobes. In one sense, the instruction for the brain is to "say as many words as possible by retrieving them according to the manner in which they are stored" or remembered. This task requires the anterior–frontostriatal system to retrieve words from the posterior (temporal and parietal) cortices.

The requirements of the semantic word retrieval task are different from the cognitive demands made by the letter fluency task methodology. Words are not "stored" in the brain according to starting letter. This latter task requires the subject to determine the stimulus-based characteristics of the task by devising a way to quickly retrieve words. To perform well on this task, the subject needs to develop a strategy or method for retrieving words in a different way than that in which they are semantically stored (Lezak, 1995). While this task still requires the subject to "tap" the declarative storage system, the burden of this task falls clearly on anterior brain regions, and specifically the prefrontal cortex, in order to develop a new cognitive method to be appropriately productive. These two tasks, when considered in combination, provide a comparison standard for making inferences about the integrity of anterior brain systems.

Knowing that a person did not compare favorably to the general population on any single fluency task provides limited information. However, when using an individual comparison standard in relation to fluency tasks, three patterns commonly emerge. First, when a person does well on category fluency and poorly on letter fluency, this does not represent a specific retrieval problem. Instead, this pattern implies frontostriatal involvement, presumably affecting the prefrontal cortex, since the specific pattern suggests difficulty devising an appropriate strategy in order to be productive. The subject was unable to break the task down into stimulus-based characteristics. He or she was thus poorly

productive, in contrast to good performance on category fluency, which does not require that type of strategy generation. This contrast implies that retrieval mechanisms per se are intact. Second, when the subject performs well on letter fluency but poorly on category fluency, this is not a specific retrieval problem either. The pattern suggests good strategy generation, or intact anterior systems, as manifest by appropriate word productivity, coupled with an impairment in semantic networks or in declarative memory systems (this can also result from lack of cultural or educational experience so that an appropriate level of categorical knowledge was never developed). However, when a subject performs poorly on both category fluency and letter fluency tasks, this combined pattern of poor performances implicates the frontostriatal system. This is a general spontaneous word generation or retrieval problem. With this pattern, it is frequently not possible to differentiate if the deficit is within the prefrontal lobes or within the striatum. However, once again, if we compare the two tasks, we learn something new about the individual, inferred from the three patterns described above, that could not be determined by interpreting each task individually, in isolation.

The Stroop Color Word Test

This popular neuropsychological test, in its various forms, is one of the few tests that by itself is sensitive to frontostriatal system function (Golden, 1978). This is because of the way the test is structured. The different phases of the task require both stimulus-based responding and higher-order control. The test relies upon an individual comparison standard in which the subject acts as his or her own control, while interpreting test performance according to a pattern analysis methodology. The first part of the task involves asking the subject to read simple words which represent colors, such as yellow, orange, and purple. The second part of the test requires naming samples of colors themselves. The third part of the task presents words printed in ink of a different color (for example, the word "purple" printed in green ink). The subject is instructed to ignore the word and instead name the color of the ink. This engages the frontostriatal system because it changes the stimulus-based characteristics of the task. If the subject does not have a history of reading or naming problems, parts one and two of the test are based upon automatic processing. The reading of simple words and the naming of basic colors are based upon previously acquired associations. The naming of colors written in different colors of ink significantly changes the stimulus-based characteristics of the task. Stimulus-based responding that runs on acquired associations no longer works to solve the problem this task presents. Additionally, the subject must inhibit the previously acquired associations in order to perform the task. This is thus considered a task of inhibition that taxes the frontostriatal system.

The concepts underlying the Stroop Color Word Test actually demonstrate several principles of the frontostriatal system. For example, initially learning to read is a laborious process. In watching a young child struggle with the pronunciation of new words, one can easily ask how the task will ever be accomplished. Yet, with sufficient practice over time, the task usually becomes automatic. In fact, the fluent reader cannot help but read a word, even when it is an irrelevant distractor within the Color Word segment of the Stroop test. The task requires the individual to inhibit the impulse to attend and respond in the habitual way through reading. This task actually reveals the power of acquired associations and demonstrates that acquired associations can be just as powerful as inherently based biological predispositions (Kinsbourne, 1993).

The act of naming the color while inhibiting word reading requires considerable cognitive effort. This is a task of higher-order control that typically activates both the orbitofrontal and anterior–cingulate frontal regions in healthy control subjects (Malloy & Richardson, 2001). In this task, conscious cognitive effort is measured in terms of time. The subject who performs the task relatively quickly requires less concentration and effort than the individual who performs the task slowly. The individual who performs the task quickly is likely to experience it as "easy." The person who performs the task very slowly would be inclined to experience it as "difficult." The subject who worked quickly likely has an intact frontostriatal system. The subject who worked slowly only for the Color Word segment of the task engaged in a more taxing cognitive control episode. The anatomy of the frontostriatal system predicts that if the color word segment was practiced repetitively, over and over again, it would become automatic. Subjects would become very familiar with the previously novel stimulus-based characteristics of the task (perhaps examiners who administer the test and silently take the test themselves in the process of this administration observe improvement in their own performance!).

In cases with a history of difficulty learning to read, word reading on the Stroop is often a lower or even much lower than expected performance relative to the general population. This most likely reflects that reading even simple words is less automatic for that individual or that naming has been a developmental problem. When this type of performance occurs in people without history of reading disorder and who otherwise are considered good readers, a slow performance on the word reading segment might actually implicate the involvement of subcortical systems. This type of performance can be interpreted as reflecting a lack of automaticity, or a lack of appropriate acquisition of the required associations, a function in which the basal ganglia have been demonstrated to play an important role.

However, the key point in interpretation of the test concerns the comparison standard. Word reading is compared to color naming which is compared to color word reading which is compared to word reading. If word reading is relatively slow but color word reading is average, implying a lack of automaticity, the interpretation is generated through test score comparisons, and not from a simple level of performance on only one single dimension of the test. If

word reading and color naming are intact, but color word reading is very slow, the integrity of the frontostriatal system is inferred from the pattern comparison of scores. If all scores are low, the same interpretation cannot be made for the individual as when only one performance is differentially lower. The point is that test interpretation becomes synergistic when the appropriate comparisons are made, revealing something that is not known by looking at each score in isolation. It is not so much the specific "test" that leads to diagnostic hypothesis, but instead, it is the understanding of the methodology that is essential. Understanding methodology should be what drives test development just as understanding pattern analysis should be what drives test interpretation.

The Stroop paradigm is clearly dependent upon inhibitory processes. As indicated, orbitofrontal and medial frontal cortices are often activated. However, it also has been reported that the Stroop test recruits a much broader network of integrated cortical regions (Bondi et al., 2002). Therefore, while the Stroop might be considered sensitive to cognitive impairment, it is not necessarily specific to frontal system functions.

Traditional "Frontal Lobe" Problem-Solving Tests

The Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtis, 1993) and the Tower of London Test (Culbertson & Zillmer, 2001) are two commonly administered neuropsychological tests. These are problem-solving tests that are presumably dependent upon the integrity of the frontal lobes for correct performance. However, when both of these procedures are administered within the same battery of neuropsychological tests, it is common to find performance differences between them. These differences result from two general reasons. First, it is erroneous to assume that all "frontal lobe" tests are the same. These two tests are dependent upon very different cognitive processes, which will be explored in this section. The tests simply do not measure the "same thing." Second, performance of these two tests is dependent upon very different cortical–subcortical networks. From both cognitive and anatomic perspectives, these are multi-factorial or multiply determined tests. As these tests are driven by different anatomies, we can readily see how simply considering them as "frontal lobe" tests would be erroneous.

The Wisconsin Card Sorting Test is, at base, a categorization test. The act of responding differently to objects or events that belong to separate classes or categories is called categorization (Ashby & Ennis, 2006) (see Chapters 2 and 4 for additional information on categorization). Not all categorization tasks are the same, and the WCST would technically be considered a rule-based category learning task. In rule-based categorization tasks, the categories can be learned through an explicit reasoning process. These are essentially hypothesis-testing tasks in which subjects are presented with

stimuli and learn which stimuli belong in which category through trial-and-error. Subjects make a response about category membership and then receive positive or negative feedback in order to learn the categorization dimensions. These types of tasks activate not only the prefrontal cortex, but also the head of the caudate nucleus and other regions of the basal ganglia (Keri, 2008; Konishi et al., 1999; Lombardi et al., 1999; Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Monchi, Petrides, Mejia-Constain, & Strafella, 2007; Rao et al., 1997; Seger, 2008).

The rule-based nature of the WCST illustrates very nicely that the subject's problem-solving paradigm is to determine the stimulus-based characteristics of the task, which is a primary role of the frontostriatal system. The subject generates hypotheses and learns the sorting principles through direct feedback about responses being right or wrong. The stimulus-based characteristics that need to be discovered comprise the categories of color, form, and number. Performing the task not only activates the dorsolateral–prefrontal cortex, but also the head of the caudate nucleus, as well as other cortical and subcortical brain regions. These other regions include the inferior parietal lobule, inferior temporal cortex, and the cerebellum. As indicated previously (see Chapter 2), the parietal and inferior temporal visual association cortices project to the tail and body of the caudate nucleus, respectively. Therefore, although the WCST is a frontostriatal task that taps the dorsolateral executive circuit, the task is dependent upon a brain network and not just the frontal lobes (Berman et al., 1995).

It would be expected that initially thinking through the principles of color, form, and number generates a high demand on working memory because thinking is required to "figure out what to do" on this problem-solving task. Consistent with the functional neuroanatomy described previously (see Chapter 2), this should activate the head of the caudate and the dorsolateral–prefrontal cortex. The model described (in Chapter 2) would also predict that when matching to the correct principle, working memory demand declines, and that this should be observed in less caudate activation. This theory would also predict that activation of the caudate should increase after negative feedback, or after the change in context of a "wrong" response. This is because the incorrect response generates a "cognitive control" episode, requiring thinking, so that the subject has to generate a different response, which again increases demand on working memory. Therefore, striatal activation would be required to selectively reduce Gpi inhibition on the thalamus to activate prefrontal– cortical working memory circuits. There are neuroimaging data to demonstrate that these activations are indeed what happens (Monchi, et al., 2001; Seger, 2008, 2006). Cognitive control episodes occur at times of "switching," in response to negative feedback, which activates the head of the caudate under these conditions of increased working memory demand. Recent neuroimaging data support the important role of dopamine in these cognitive control episodes during completion of this task (Nagano-Saito et al., 2008).

Test Results

WCST scores	Raw scores	Age-corrected Standard scores	*T* scores	%iles
Trials Administered	108			
Total Correct	74			
Total Errors	34	92	45	30
%Errors	31%	91	44	27
Perseverative Responses	20	90	43	25
%Perseverative Responses	19%	88	42	21
Perseverative Errors	19	88	42	21
%Perseverative Errors	18%	85	40	16
Nonperseverative Errors	15	95	47	37
%Nonperseverative Errors	14%	94	46	34
Conceptual Level Responses	64			
%Conceptual Level Responses	59%	89	43	23
Categories Completed	6			> 16
Trials to Complete 1st Category	10			> 16
Failure to Maintain Set	0			> 16
Learning to Learn	−6.36			6–10

The following set of WCST test results illustrates the identification of cognitive control episodes.

The summary scores say little of diagnostic relevance, other than the fact that the subject completed 6 categories in 108 cards which is a respectable general level of performance. A "learning-to-learn" score in the deficit range raises some questions as to the subject's approach to the task. Perseverative responses at the 25th percentile ranking are at least somewhat elevated but the summary statistic says little about the nature of the implied "cognitive episodes" that were required for this individual to complete the task. The perseverative replies are suspicious because it is argued that this type of response does not follow a "normal distribution" if used to identify perseverative thinking within the general population. The issue becomes whether or not this level of perseverative responding is significant within a record that took a relatively few number of cards to complete the test. It, therefore, can be concluded that the significance of perseverative responding on the WCST index needs to be considered on an individual, case-by-case basis.

The actual response record is more informative. The subject initially "guessed" correctly in sorting by color. With the initial correct response, it is not likely that very much "thinking" occurred for the next nine trials. In fact, by observation, the subject performed very quickly. Stimulus card 11 provoked the first cognitive control episode which briefly lasted a total of the next three cards. The second cognitive control episode that was necessary to discover the principle of number began on card 25 and lasted for the next 12 to 13 cards. It was more difficult for the subject to discover this category. The concept of switching back from the principle of number to color was accomplished relatively quickly,

Response Deck 1

Sorting Principle	Correct Seq. Number	Card Number	Column Sorted To	Categories Matched	Perseverative Principle	Perseverative Response	Sorting Principle	Correct Seq. Number	Card Number	Column Sorted To	Categories Matched	Perseverative Principle	Perseverative Response
C	*1*	1.	2	C			**N**	N	33.	4	CF	F	
	2	2.	1	C				N	34.	1	O	F	
	3	3.	4	C				N	35.	2	CF	F	
	4	4.	1	CN				*1*	36.	4	N	F	
	5	5.	2	CF				N	37.	4	CF	F	
	6	6.	3	CF				*1*	38.	3	CN	F	
	7	7.	4	CN				*2*	39.	1	N	F	
	8	8.	1	C				*3*	40.	4	CN	F	
	9	9.	2	C				*4*	41.	1	CFN	F	
	10	10.	3	C				*5*	42.	3	N	F	
F	N	11.	4	C	C	*P*		*6*	43.	4	FN	F	
	1	12.	1	CF	C	*p*		*7*	44.	2	CN	F	
	N	13.	4	C	C	*p*		*8*	45.	3	N	F	
	N	14.	3	C	C	*p*		*9*	46.	2	N	F	
	1	15.	1	F	C			*10*	47.	1	N	F	
	2	16.	4	CFN	C		**C**	*1*	48.	3	CN	N	
	3	17.	2	FN	C			*2*	49.	2	CN	N	
	4	18.	4	F	C			N	50.	4	N	N	*p*
	5	19.	1	CF	C			N	51.	1	FN	N	*p*
	6	20.	4	F	C			N	52.	3	N	N	*p*
	7	21.	2	FN	C			*1*	53.	1	C	N	
	8	22.	3	FN	C			*2*	54.	2	C	N	
	9	23.	2	FN	C			*3*	55.	4	C	N	
	10	24.	1	F	C			*4*	56.	2	C	N	
N	N	25.	2	F	F	*p*		*5*	57.	1	C	N	
	N	26.	1	F	F	*p*		*6*	58.	3	C	N	
	N	27.	4	C	F			*7*	59.	1	C	N	
	1	28.	4	FN	F			*8*	60.	2	CN	N	
	2	29.	2	CFN	F			*9*	61.	4	CN	N	
	N	30.	3	F	F	*p*		*10*	62.	3	CFN	N	
	N	31.	2	C	F		**F**	*1*	63.	1	CF	C	
	1	32.	1	CN	F			N	64.	2	C	C	*p*

after a brief 3–4 card episode. Rediscovering the principles of form and number were more problematic, since the re-application of these concepts again generated more lengthy cognitive control episodes of approximately 12 cards. Therefore, according to this profile, this subject experienced more difficulty in the second half of the test than in the first half of the test. This example reveals a hidden principle of the WCST that can make test interpretation difficult. During the course of task completion, the subject must learn that just because a stimulus category was used previously does preclude that same category being applied again.

The raw data response protocol does provide at least some meaningful information about the nature of the "problem points" experienced during the administration of the task. Although cognitive control episodes on the WCST primarily occur at points of "switching," not all switching issues on this test reflect perseverative thinking. Problems did not occur with regard to concept formation in initially determining the stimulus characteristics of color, form, and number; significant perseverations were not observed in discovering these first three categories. There is no "switching" problem in the way this term is usually understood. The most significant cognitive control episodes were involved when the subject was required to rediscover previously applied concepts and perhaps ignore irrelevant stimulus dimensions. In this regard, the perseverative responses at the 25th percentile ranking do not reflect much of a "shifting" or switching problem at all within this protocol. Granted, these are subtle aspects of the performance. However, the point remains that score comparisons made through a combination of summary score and raw data analysis can be more revealing than either approach used in isolation. Noting the types of cognitive control episodes identified here provides an informal index of how often and how hard the subject had to "think" when taking this test.

Different types of category learning recruit different cortical–striatal networks (see Chapter 4 for a description of the neuroanatomy of categorization). The WCST has its own neuroanatomy. An fMRI study mapped the neural circuits recruited by the WCST (Monchi et al., 2001). The results of this study revealed specific involvement of different prefrontal areas during different phases of the task. Task stages were defined by positive and negative feedback. The dorsolateral–prefrontal cortices (Brodmann areas 9 and 46) increased activity in response to either positive or negative feedback. The authors interpreted this finding as consistent with the ongoing maintenance of task events in working memory. The ventrolateral–prefrontal cortices (areas 12 and 47), the caudate nucleus, and the mediodorsal nucleus of the thalamus all demonstrated increased activity with reception of negative feedback. Therefore, the imaging results identified the recruitment of a prefrontal–basal ganglia loop in response to change in context, and presumably signaling the need for hypothesis generation about a new response.

Activation of the left putamen and left posterior lateral–prefrontal cortex increased when matching correctly after negative feedback, but not when

Response Deck 2

Sorting Principle	Correct Seq. Number	Card Number	Column Sorted To	Categories Matched	Perseverative Principle	Perseverative Response	Sorting Principle	Correct Seq. Number	Card Number	Column Sorted To	Categories Matched	Perseverative Principle	Perseverative Response
F	*1*	1.	1	FN	C		**N**	N	33.	1	O	F	
	N	2.	4	N	C			N	34.	3	CF	F	
	N	3.	2	N	N	*p*		*1*	35.	1	N	F	
	N	4.	1	CN	N	*p*		*2*	36.	4	N	F	
	N	5.	4	N	N	*p*		*3*	37.	2	N	F	
	N	6.	1	N	N	*p*		*4*	38.	3	CN	F	
	N	7.	4	CN	N	*p*		*5*	39.	1	N	F	
	N	8.	3	N	N	*p*		*6*	40.	4	CN	F	
	N	9.	2	C	N			*7*	41.	1	CFN	F	
	N	10.	3	C	N			*8*	42.	3	N	F	
	N	11.	1	N	N	*p*		*9*	43.	4	FN	F	
	N	12.	3	N	N	*p*		*10*	44.	2	CN	F	
	1	13.	3	F	N				45.				
	2	14.	2	F	N				46.				
	3	15.	1	F	N				47.				
	4	16.	4	CFN	N				48.				
	5	17.	2	FN	N				49.				
	6	18.	4	F	N				50.				
	7	19.	1	CF	N				51.				
	8	20.	4	F	N				52.				
	9	21.	2	FN	N				53.				
	10	22.	3	FN	N				54.				
N	*1*	23.	2	FN	F				55.				
	N	24.	1	F	F	*p*			56.				
	1	25.	4	N	F				57.				
	2	26.	2	N	F				58.				
	N	27.	1	O	F				59.				
	N	28.	1	C	F				60.				
	1	29.	2	CFN	F				61.				
	2	30.	1	CN	F				62.				
	N	31.	2	C	F				63.				
	N	32.	4	O	F				64.				

matching after positive reinforcement. These data revealed specialization of the basal ganglia in response to feedback and new rule application. Since the motor requirement throughout the task was obviously constant, the pattern of changing activation within the putamen could not be due to motor demand. The prefrontal cortex and caudate increased activation just prior to the new response, while the putamen was activated in rule application. The authors interpreted these findings to mean that the prefrontal cortex and caudate were activated for the setting of the new rule, or hypothesis generation, while the putamen was involved more during novel than in routine actions in the completion of the WCST. It was also reported that the posterior parietal cortex was activated during all phases of the task. Taken together, these data imply a dynamically changing cortical–subcortical network for the completion of the WCST categorization task, revealing that the WCST is considerably more than a test of "frontal lobe" functioning.

The Tower of London Test (TOL) is a problem-solving task that is not dependent upon rule-based categorization. However, successful performance of the TOL is a function of a person's ability to determine the stimulus-based characteristics of the task (Hodgetts & Jones, 2006). The subject is required to plan ahead in order to determine the order of moves necessary to rearrange three colored balls. The subject works from an initial starting position in which the balls are placed on two of three upright polls and must move the balls to a new predetermined position with the balls on one or more of the polls. Different versions of the test present different numbers of problems to be solved. The task's stimulus-based characteristics relate to the constraints or "rules" placed upon task performance. Only one ball can be moved at a time, the balls always have to be moved from peg to peg and therefore always must be placed on a peg, and the number of balls that can be placed on a post is specified by the length of the polls. For example, on a three-peg TOL, the first peg can hold one ball, the second can hold two balls, and the third peg can hold all three balls. Each problem is to be completed in as few moves as possible. Any problem can be solved in the minimum number of moves if the underlying procedure is discovered. There are different types of tower tests, and differing tests incorporate different procedures. There is a procedure that can be discovered to ensure accurate task performance, but the subject is not required to verbalize this strategy if discovered, nor does the examiner ask the subject about his or her strategy.

This test taxes working memory functions. All the rules of the task must be kept in mind, while thinking needs to be reorganized as the positions are mentally manipulated before engaging the solution. This implies visuospatial rehearsal (Welsh, Satterlee-Cartmell, & Stine, 1999). Subjects can either visualize a sequence of movements, self-verbalize a plan of action, or engage in a combination of both strategies, but it has been proposed that visuospatial working memory plays a stronger role than verbal working memory (Franceschi et al., 2007; Phillips, Wynn, Gilhooly, Della, & Logie, 1999). The task is scored according to the number of moves needed to solve the problems. The test also provides temporal indices such as response planning time,

response execution time (which is an index of how long it took to move the balls from one post to another in solving the problem), and total time, which essentially combines planning time with execution time.

The following scores are presented for a sample interpretation:

Total moves	16th percentile ranking
Planning time	45th percentile ranking
Execution time	30th percentile ranking
Total Time	37th percentile ranking

This subject used just about as much planning time as anyone else in the standardization population. However, this person's problem-solving was highly inefficient, so that seemingly adequate planning time did not generate the same level of accuracy that would be observed within people of his/her age within the general population. The accuracy of solutions was only as the 16th percentile ranking. As a result, a bit more time was required to properly execute solutions. Therefore, it can be inferred from this pattern of results that this subject had difficulty in thinking ahead.

Neuroimaging studies indicate that the TOL activates the dorsolateral–prefrontal cortex, the anterior cingulate, the cuneus and the precuneus, and the insula. Parietal lobe activation is seen in the supramarginal and angular gyri (Lazeron et al., 2000). Cerebellar activation is also found (Schall et al., 2003). However, in mapping planning networks, activity has also been demonstrated within the basal ganglia (Dagher, Owen, Boecker, & Brooks, 1999). A specific TOL planning network has been described as including the lateral premotor cortex, the rostral anterior cingulate, the bilateral dorsolateral–prefrontal cortex, and the right dorsal caudate nucleus. The left anterior putamen was also activated. Activation in the right caudate nucleus correlated with task complexity and independent of that activation, increased activity within the left putamen correlated with number of moves necessary to solve the problem. The activation of the right head of the caudate under the conditions described is consistent with the interpretation of increased striatal activation to meet the demand of increased working memory. It also has been demonstrated that Parkinson's disease patients exhibit little activation of the Gpi during TOL performance, while performing the task significantly below the level of controls. In comparing Parkinson's patients with normal controls, the greatest differences were observed on tasks with increasing cognitive demands, while no differences in Gpi activation were noted between Parkinson's patients and control subjects on very simple motor tasks (Baker, 1996; Owen et al., 1993; Owen, 1997; Owen, Doyon, Dagher, Sadikot, & Evans, 1998). It is very tempting to conclude from these data that a lack of Gpi output to dorsolateral– prefrontal cortex (via the thalamus) prevented the working memory activation that was necessary to perform the task.

Tower tasks have been applied in studies of procedural learning, as reviewed by Ouellet, Beauchamp, Owen, and Doyon (2004). Generally speaking, normal controls become more efficient at performing these tasks as a function of practice. Learning on these types of tasks is observed through improved test

performance. Improved performance is usually measured by a reduction in reaction time or "processing speed," a reduction in the number of errors, and/or a reduction in the number of moves necessary to solve the task. Improved test performance is associated with a dynamically changing neuroanatomy (see Chapter 4 for a discussion of the anatomy of cognitive and motor skill learning). One study demonstrated that initial performance on the TOL is associated with increased blood flow activity in the dorsolateral and orbitofrontal cortices and in the parietal lobe, particularly within the left hemisphere. Bilateral increases in activation were observed in the premotor cortex, the caudate nucleus, and the cerebellum, consistent with what is observed in other procedural learning tasks (see Chapter 4.) As performance improved over time, significant decreases in activation were observed in the frontal cortices, although activity in the left caudate nucleus was maintained throughout the time course of learning (Beauchamp, Dagher, Aston, & Doyon, 2003). These findings demonstrate the importance of the frontostriatal system in mediating processes such as working memory, planning or thinking ahead, and procedural acquisition.

A question emerges concerning how to interpret task "rule violations." Subjects sometimes move two balls at one time, and subjects sometimes try to put more balls on a peg than that peg was designed to hold. Most tower tests have normative data concerning the frequency of occurrence of rule violations according to different age groups. However, subjects make few, if any, rule violations, depending upon subject's age. Since task rule violations occur infrequently and do not follow a normal distribution, we consider rule violations as pathognomonic signs. The typical reason for rule violations concerns disinhibition. This is a type of failure of intention where thought does not guide action. A less frequent reason for rule violation entails a working memory issue in which the subject "forgets" task rules. However, because of the pathognomonic nature of rule violations, the occurrence of this behavior always takes precedence in test interpretation. Therefore, even if the subject earns a problem-solving score that is within normal limits (after a rule violation, the subject proceeds from where they left off, after correction by the examiner), the rule violations remain the all-important finding. Even with good problem-solving accuracy performance, the occurrence of rule violations beyond the norm almost always points to executive deficit implicating pathology within the frontostriatal system. This pathology concerns a disturbance in brain-related intention programs.

Task Comparisons

These data demonstrate that all "frontal lobe" problem-solving tasks are not the same. As we have seen, the cognitive demand characteristics of the WCST and the TOL are different, since the former is a categorization task and the later is a type of procedural learning task that requires specific "think ahead" skill. Nevertheless, there are certain commonalities. Both tasks activate aspects of the

frontostriatal system. It appears that activation of the head of the caudate nucleus is associated with the activation of working memory functions. The putamen appears to be activated in initiating novel responses. The following test score comparisons are reviewed to illustrate the relationships (or lack thereof) between the WCST and TOL.

Wisconsin Card Sorting Test
6 Categories
80 Cards
64 Correct responses
16 Errors
1 Perseverative error
Tower of London
Total moves 33 SS 86 18 PR
Initiation time 1" SS 88 21 PR

This case is presented as an example of a fairly common but dramatic dissociation between WCST and TOL performances. The WCST performance is exemplary. From a clinical point of view, it is difficult to imagine a better performance on this rule-based categorization task. Response to feedback was very efficient. On the other hand, TOL performance was relatively poor, with 82% of this person's peer group performing with greater accuracy of solutions. Poor solutions were a manifestation of premature responding. While total initiation time was at the 21 percentile ranking, a qualitative inspection of the data revealed that two problems were initiated with one second latency times each, while eight problems were approached instantaneously, immediately, with no time to think at all. This interpretation demonstrates the importance of inspecting the response protocol instead of simply reviewing "scores." This person never entertained the demands of the task and never thought about solutions. There was no "thinking ahead." On the TOL, it seems entirely possible that "working memory" functions were never initially activated because there was no "planning time."

While categorization and thinking ahead require different cognitive and neural brain networks, this example also reveals two other differences related to problem-solving tasks. Generally speaking, there are two ways of generating behavior: Through response to environmental structure or cue and through self-controlled or internally directed responding. The WCST categorization task, through the provision of immediate feedback, generates "behavior" in response to external contingencies. The TOL requires self-regulated, internally generated problem-solving behavior. Therefore, once again, comparing and contrasting appropriate measures yields a synergistic finding. The results imply this person would be potentially responsive to external structure and that difficulties would emerge when this individual would be required to rely upon internal capacities to plan, organize, and think things through in the absence of environmental structure or "feedback." This interpretation would

actually be missed if all "frontal lobe" tasks were considered the same and only one of these tasks was administered.

Continuous Performance and Go–No-Go Tasks

The continuous performance test (CPT) paradigm evaluates sustained, focused attention. This test paradigm consists of sequential stimuli presentation, usually strings of numbers or letters. These stimuli are presented over a lengthy period of time, such as six to approximately 20 minutes, depending upon the specific CPT in question. During this time, the subject is required to indicate when a predetermined number or letter is perceived (Lezak, Howieson, & Loring, 2004). Stimuli are usually presented at the rate of one stimulus per second. On computerized versions, the subject presses a button or key when a stimulus is detected, and in manually administered versions, the subject is required to give a response such as tapping (Strub & Black, 2000). CPT tasks can be administered in both auditory and visual versions. However, it is likely that the same neural mechanisms control attention and influence perception across different sensory modalities (Shinn-Cunningham, 2008). In go–no-go paradigms, the subject is required to respond in one way to a predetermined "go" signal and not respond to a similar signal. This paradigm was frequently used by Luria in qualitative interpretation and has also been adapted to a normative approach in the Executive Control Battery (Goldberg, Podell, Bilder, & Jaeger, 2000). However, the essential interpretation is a pathognomonic sign approach, since most normal control subjects do not make errors on this type of task, and when they do, errors are extremely few. Performance within these paradigms is not normally distributed within the general population, so that the translation of performance to standard scores can even be misleading, as the distribution of errors simply does not follow a "bell-shaped" curve. Performances on these tasks follow a dichotomous distribution.

Performance on these tests clearly follows a developmental trajectory. For example, younger children make more errors of omission and commission than older children, but adult performance is achieved between the ages of 12 and 16 years on continuous performance tests (Beck, Bransome, Mirsky, Rosvold, & Sarason, 1956; Kelly, 2000; Rebok et al., 1997). However, even the distribution of errors in children as young as 5 years old does not follow a normal distribution (Mirsky, personal communication, 2008). Adult performance is characterized by making very few to no errors of omission or commission, so that according to this standard, the interpretation of performance requires a pathognomonic sign approach. Simply making more errors than a normal control is a specific indicator of deficit. This finding by itself raises serious question as to whether all commercially available CPT paradigms measure the same phenomenon of inattention and disinhibition. Certain CPT models clearly follow the developmental pattern of almost no errors

with developing age. Other commercially available continuous performance tests tolerate both omission and commission errors in the performance of the task, and then translate these errors into a normal distribution of standard scores. High average, average, low average, and lower ranges are identified, but it is unclear how these classifications relate to the evaluations of alertness and inhibition since these classifications do not reflect the natural developmental trajectory. Performance on go–no-go tasks have also been described as following a developmental trajectory, with adult performance achieved on simple versions of the task by 7 years (Welsh, Pennington, & Groisser, 1991).

These tasks not only require sustained, focused attention, but also response inhibition. The act of "paying attention" always consists of at least two functions, irrespective of which theoretical model of attention might be under consideration. All models of attention include elements of alertness and vigilance, as well as inhibition. Simply put, when a person "pays attention" to one thing, that person has to not pay attention to other things. These "other things" thus require inhibition. These "things" vying to become the contents of attention may comprise either external or internal stimuli. These stimuli are extremely numerous and are in competition for limited attentional resources. Therefore, the ability to "pay attention" to anything requires significant inhibitory capacity.

CPT and go–no-go paradigms thus assess both the capacity to attend and the capacity to inhibit. To perform successfully, the subject is required to detect the proper stimuli while inhibiting response to competing or distracting influences. Errors of omission refer to the subject's failure to attend to stimulus presentations or to "miss" stimuli. Errors of commission refer to the subject's failure to inhibit responses to competing stimuli. Errors of omission reveal inattention along a passive dimension. This type of attention is dependent at least in part on posterior cortices (Robertson, 2004). Errors of commission identify a deficit within the inhibitory component of attentional focus and control. The inhibitory component is dependent upon anterior, frontostriatal brain regions (Cohen, Malloy, & Jenkins, 1998; Fuentes, 2004; Menon, Adleman, White, Glover, & Reiss, 2001; Mesulam, 1985; Ray Li, Yan, Sinha, & Lee, 2008).

We can thus see that the process of attentional focus is mediated by the frontostriatal system. As indicated in Chapter 2, the basal ganglia play a major role in attention and action selection. The basal ganglia "gate" sensory input into motor output. In other words, the basal ganglia are involved in translating sensation (received as output from the cortex) into motor "when" (Denckla & Reiss, 1997). As a result of a deficit within this gating system, attention and action selections are affected. Stimuli that should evoke a response sometimes do not, as demonstrated in errors of omission. Stimuli that should not elicit a response sometimes do, as demonstrated in errors of commission. Therefore, errors of omission can be understood as a manifestation of inattention and errors of commission can be understood as a manifestation of distractibility in addition to the more popular or generic interpretation of impulsivity.

The various testing paradigms that assess these processes have one thing in common. Specifically, the task instructions (press the key when a nine comes after a one, or only when a T comes after another T, or when I do this, you do this) *preset the motor system to respond and then require the frontostriatal system to continuously adjust to an ongoing input stream of sensory information as it arrives*. The individual is required to do this for a prolonged period of time. When this gating system is faulty, it is unable to make "online" adjustments to sensory information as it arrives and this is observed in an error pattern. This is critical to understanding developmental disorders that affect the frontostriatal system, such as Attention Deficit Hyperactivity Disorder.

It has been stated that CPT performance is associated with activation of the frontal system. The right posterior parietal and frontal regions are involved in vigilance, particularly for visual CPT paradigms, as evidenced by selected PET investigations (Posner & Petersen, 1990). The PET studies of normal control subjects reveal higher rates of metabolism in most prefrontal/frontal areas during performance of a CPT and lower metabolic rates in pathological groups (Buchsbaum et al., 1990; Cohen, Malloy, & Jenkins, 1988). Increased rates of metabolism as measured by PET have been found to be associated with good CPT performance (Wu et al., 1991, 1992). Poor CPT performance was associated with decreased metabolic activity in the thalamus, caudate, and the putamen. The magnitude of these relationships was very considerable, supporting an integral role for the basal ganglia in attentional functioning as measured by CPT variables. Studies using fMRI have been equally revealing. Greater right hemisphere activation has been reported in the dorsolateral–prefrontal and medial frontal cortex, the caudate nucleus, and thalamic nuclei (Hager et al., 1998). Therefore, neuroimaging data are very clear in identifying frontal– basal ganglia–thalamic circuitry as an integral node in the cognitive network responsible for the attentional focus and inhibitory control required for CPT performance (Schulz et al., 2004).

While CPT and go–no-go tasks measure inhibitory capacity, all kinds of "inhibition" are not the same. CPT and go–no-go tasks appear to require a similar type of frontostriatal control. However, these tasks do not require the same type of inhibitory control required by the Stroop test described above. Similarly, consider the different types of inhibitory tasks contained within the NEPSY (Korkman, Kirk, & Kemp, 1997). The NEPSY contains a subtest called "Statue." This task requires a child to sustain a posture, with eyes closed, for 75 seconds. At various intervals, an extraneous stimulus (each of them sound-based) is introduced that requires the patient to "not respond" to the distracting influence. This task essentially requires inhibition of orienting responses. According to the anatomy of the basal ganglia described in Chapter 2, not responding to orienting responses requires inhibition over lower-level sensory and motor systems. While CPT and go–no-go tasks are mediated by cortical–basal ganglia loops as described above, the act of inhibiting orienting responses would appear to require the additional mediation of anatomically distinct subcortical–brain stem system loops.

Therefore, although these different types of tasks all require "inhibition," the tasks are subserved by different neuroanatomic notworks. It would seem that dependent upon the distribution of pathology within these different networks, performances on all of these tasks would not be expected to correlate. However, since these tasks are mediated by different anatomies, this could conceivably generate important clues as to either the localized or diffuse nature of the pathology. Similarly, given the differing developmental trajectories of different brain regions and systems, different patterns of performance might be observed at different age levels. To our knowledge, this possibility has not yet been systematically studied.

Different disinhibition syndromes have been described (Starkstein & Kremer, 2001). Dysfunction within highly specific orbirofrontal–subcortical circuits can generate partial disinhibition syndromes. For example, motor disinhibition would imply involvement of the motor cortices and/or ventral striatum. Emotional disinhibition might result from involvement within paralimbic–subcortical circuits. Instinctive disinhibition could result from disruption within circuits from medial-orbital areas to the hypothalamus. Ideational or "intellectual" disinhibition can result from involvement of dorsolateral–subcortical circuitry (Starkstein & Robinson, 1996). Traditional neuropsychological tests do not address each and every one of these circuitries. Therefore, administration of a CPT or go–no-go task could easily yield false negative results, depending upon highly specific areas of involvement. Simply put, neuropsychological tests do not currently measure all processes, however, as has been noted, a number of experimental tasks hold promise for clinical development. For example, a commercial version of the Iowa Gambling Task has recently become available. This task has been used in a variety of experimental studies, and preliminary reviews suggest this instrument is potentially useful in evaluating frontostriatal circuitry. More specifically, this task holds promise for evaluating the reward circuitry of medial–frontal cortices and the ventral striatum.

Different test paradigms define inhibition in different ways. For example, the Stroop Color Word paradigm is often considered a measure of inhibition. It is true that naming a color requires inhibition of the prepotent response of automatically reading the word. An error reveals a loss of inhibitory control. However, a slow performance does not necessarily measure inhibitory deficits. As described above, a slow performance instead reveals the level of effort, or the price paid in time, required to exercise appropriate inhibition for completing the task. Tasks of this type are considered multiple component and assess aspects of the frontostriatal system, but not the type of rapid, "online" gating or selection processes that are necessary for successful CPT or go–no-go task performance. This can be inferred from the frequent lack of clinical correlation between CPT and Stroop performances. The tests assess different processes and require different brain networks. In short, there is little evidence for one unitary construct of inhibition as measured by neuropsychological tests or as might be defined by functional neuroanatomy (Rush, Barch, & Braver, 2006).

Commonly Used Neuropsychological and Cognitive Tests: What Do They Measure?

As might be inferred from the above discussion, tests do not always measure what the specific name of the test or subtest implies. Unfortunately, clinical, cognitive, and neuropsychology practitioners seem to have developed a "habit" of using the same word or term to refer to different concepts, test activities, or behaviors. Sometimes a test construct refers to a test author's idiosyncratic understanding of a concept that has little or nothing to do with brain–behavior relationships. Sometimes a test score or composite quotient refers to a concept that has multiple dimensions.

For example, the concept of a "general memory quotient" essentially comprises a type of average of how a subject performs on multiple learning and memory tests within a given battery. This type of quotient often combines immediate recall and delayed recall, as well as test performances from different modalities. Since immediate recall, learning across trials, delayed recall, and material presented in different modalities all need to be interpreted individually, there is no reason for calculating and applying such a quotient because it is clinically meaningless, although frequently touted as being more "reliable." Such a quotient says nothing about brain–behavior relationships. Any meaningful diagnostic information is buried in the quotient. The so-called "Processing Speed Index" on the Wechsler-type intelligence tests provides another example of this loss of the trees for the forest. This index actually combines two different subtests under one summary concept expressed by a composite quotient. However, from the standpoint of brain–behavior relationships, matching symbols with numbers (Coding subtest) is different from searching for stimuli within an array (Symbol Search subtest), with each line of targets presenting unique stimuli. (see Chapter 9 for a discussion of processing speed). Again, any potentially meaningful information is often buried within this composite score. Generally speaking, composite quotients are inherently meaningless (Lezak, 2004).

Individual neuropsychological or cognitive constructs need to be operationally defined. As indicated above, inhibition on a CPT is not the same type of inhibition required on a Stroop Color Word Test. Inhibition on a Stroop Color Word Test is not the same type of inhibition required on a NEPSY Statue subtest. The "frontal lobe" cognitive demands of the WCST are not the same processes necessary to complete the TOL, even though both are characterized as "frontal lobe" tests. The point is that one word or term can be confusing because in the field of testing human behavior, the same term can be used to refer to dramatically different processes on different tests. We believe that this lack of consistent nomenclature poses a major problem for applied neuropsychology. This is the case because interpreting tests by test name or by category to which the test belongs can be diagnostically misleading, and clinicians without sufficient grounding in neuroanatomy can easily under or over-interpret the data derived from these measures.

Another important issue concerns using cognitive tests for different reasons than they were originally intended. The use of traditional intelligence tests in neuropsychological evaluation is one primary example. These tests were not developed with neuropsychology in mind, and are not organized around the principles of brain–behavior relationships. While intelligence testing provides useful information, data from these tests should not be over-interpreted by neuropsychologists. For instance, the Verbal Comprehension Index of the WISC-IV provides a limited measure of an individual's verbal skill and allows certain kinds of global comparisons and projections. However, the subtests that comprise this index do not measure verbal ability in a systematic way (see Chapter 11 for examples of poor verbal and communicative ability that are not reflected in VCI quotients). These subtests assess aspects of verbal thinking. The Perceptual Reasoning Index (PRI) essentially comprises a problem-solving composite score derived from subtests that can be solved by combining a variety of cognitive approaches. In addition, the individual subtests themselves are multiple-component or multi-factorial in nature, and all items within any given subtest do not necessarily require the same cognitive processes. These tasks do not by any means allow for general statements about a person's "verbal" versus "visual" processing abilities.

For example, on a very superficial level, Picture Concepts (PCn) can be considered a categorization task. However, this subtest cannot be classified according to any of the principles by which the processes of categorization are studied (see Chapter 4 for a description of different types of categorization). In performing this task, reinforcement is not given on a trial-by-trial basis. The stimulus items are not related to each other conceptually, and in fact, content principles change from item to item. Matrix Reasoning follows a similar format. There is no feedback given to the subject, principles change from item to item, and some item principles are easier to verbalize than others. Therefore, from a cognitive viewpoint, successful performance on these subtests requires multiple intact cognitive functions. These are important issues. These types of subtests (including those that were not specifically reviewed here) are time consuming to administer and they provide little information that can be interpreted clearly from a brain–behavior relationship perspective. The administration of an intelligence test is not essential to a comprehensive and competent neuropsychological evaluation, and data from administered IQ testing should only be considered in relation to other more specific data in this context (Baron, 2004).

We also believe that there are solutions to aspects of these problems. We believe that at its core, a neuropsychological assessment should focus upon an evaluation of brain–behavior relationships. This is the most basic tenet of neuropsychology and is not a static proposition. We also believe that practicing neuropsychologists need to develop the ability to determine and fully understand the processes required to perform the tasks measured by neuropsychological tests. Knowledge of brain–behavior relationships is critical to understanding these processes. We should not make assumptions about what tests and subtests

measure based on their names. Neuropsychologists need to evaluate, on their own, the neuroanatomic functions that drive test performance. This type of ability requires a thorough understanding of functional neuroanatomy in addition to the important clinical and observational skills derived through both study and experience. Neuropsychologists must remember that our understanding of functional neuroanatomy remains incomplete and continues to develop over time through constant advances in research. This leads to competent and informed test choices and more useful neuropsychological evaluations.

Summary

This chapter reviewed three functions of the frontostriatal system. These functions were described as assessing the stimulus-based characteristics of novel problem-solving, the selection of an appropriate stimulus-based behavior to meet the requirements of a routine or familiar situation, and automating solutions to problems that were initially novel. Existing clinical neuropsychological tests primarily assess the initial problem-solving functions of this system. Clinical testing does not pay much attention to identifying and measuring automated functions, nor does traditional assessment measure the rate or speed with which the frontostriatal system learns. We believe that neuropsychological evaluation should develop in the direction of assessing these functions in order to remain relevant in the context of rapidly increasing knowledge regarding brain development and function.

A variety of tasks that are subserved by the frontostriatal system were reviewed. These tasks were discussed as dependent upon differing neuroanatomic networks. Some of these tasks actually demonstrate a dynamically changing neuroanatomy during the completion of the tasks. It was emphasized that there is no one "score" or particular level of performance that can speak to the integrity of the frontostriatal system. It was also emphasized that pattern analysis, or comparing certain combinations of test results, was critical to identifying the nature of the functioning of the frontostriatal system. Pattern analysis was described as a synergistic interpretive methodology. Certain test score comparisons can reveal new diagnostic information that would not be known by interpreting each score in isolation or independently.

We also emphasized the important fact that names of tests and subtests frequently convey little—or misleading—information about what a test measures. Sometimes the same word is used to describe a different but related function, and this can be confusing for test interpretation. We indicated that it is thus critical that neuropsychologists develop the skill of analyzing the cognitive requirements of tests. In this regard, there is no substitute for a comprehensive and thorough understanding of functional neuroanatomy as the foundation for neuropsychological test interpretation.

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Chapter 9
Thought in Action: Procedural Learning, Processing Speed, and Automaticity

We never do anything well till we cease to think about the manner of doing it.

William Hazlitt

Practice is the best of all instructors.

Pubilius Syrus

In theory there is no difference between theory and practice. In practice there is.

Yogi Berra

Learning and memory are essential to almost everything we do, from the time we wake in the morning to the time we turn-in for the night. Memory is one of the functions that provides continuity to our existence. We must remember what we have done earlier in order to direct what we are doing now. We often must recollect experience in order to plan for the activities of the future, whether we are thinking five minutes ahead, five hours ahead, five days ahead, or five months ahead. When we engage "working memory," which is the temporary storage of information for the purpose of task completion, we are very often recalling information from longer-term, declarative/episodic recall in order to provide information to assist us in solving the problems of the present. We rely upon what is stored in declarative/episodic memory in order to make plans for the future. We are unable to adapt adequately without these essential functions. Disturbance in these types of memory represent the most frequent complaints for neuropsychological evaluation (Squire & Shimamura, 1996). It is inconceivable to think of a neuropsychological evaluation that does not include an assessment of the ability to learn and remember "new" declarative/episodic information as mediated by the medial–temporal lobe memory system as well as an assessment of executive "working memory" functions. Test publishers offer a range of "tests" that assist in assessing the functions of these memory systems.

In this book, we have argued that procedural learning is just as important to adaptation as higher-order cognitive control. Complaints of difficulties acquiring procedures or in "inhibiting" them are very common in developmental

L.F. Koziol, D.E. Budding, *Subcortical Structures and Cognition*,
DOI 10.1007/978-0-387-84868-6_9, © Springer Science+Business Media, LLC 2009

disorders and in psychiatric conditions in particular. These complaints are not necessarily expressed in the types of concrete terms we have been discussing. Instead, these complaints are generally embedded in the behavioral symptoms that come to clinical attention, and we must learn to "read" them when patients and their families speak of them. For instance, the pediatric clinician very frequently hears of the child with, "a slow personal tempo," who takes a long time to execute chores that should be routine. Some children take forever to get dressed because the routine does not become automatic. Other children never really acquire the overall scholastic routine. They do not master the skills necessary to be successful students, despite possessing intact basic academic skills and sometimes even intelligence measured in the superior to very superior psychometric range.

Many children appear to have problems in acquiring and applying interpersonal skills. From our perspective, social skills need to be understood in part as a skill set that must be learned and automated for successful interpersonal interaction to occur. There are numerous "rule-based" aspects of interactions that are essentially procedures we need to learn in order to "know" what to do when we are initiating, maintaining, and terminating social exchanges. Patients with obsessive-compulsive disorder often engage in the same routine over and over again, such as compulsive washing and checking, as if they have lost the ability to control certain "habits." When patients experience medication side-effects, they can complain of trouble with episodic recall, but they can also experience procedural problems, and forget tasks that require complex behavioral sequences, such as forgetting how to knit. "Procedural" complaints and symptoms can take many forms. All of these types of disruptions in the execution of procedural habits—either too much or too little—implicate the involvement of the frontostriatal system that governs the acquisition and execution of automatic skills.

Previous chapters have presented procedural and automatic behaviors as elegant behavioral repertoires, patterns of organized behaviors that efficiently accomplish various predictable goals. However, procedural learning systems are not assessed in a cortico-centric model of cognition that guides most testing. Neuropsychological reports seldom address an individual's ability to learn and implement instrumental and procedural behaviors, even though these abilities are essential to adaptation. Publishers of tests do not market tasks that assess these functions. The classic text on every neuropsychologist's bookshelf, Neuropsychological Assessment (Lezak, Howieson, & Loring, 2004), does not provide guidance for evaluating these adaptive skills. We feel current neuropsychological evaluations are incomplete because they are rooted in a cortico-centric bias that overlooks the presumably "mindless" behaviors that are manifestations of procedural skill sets and as such, have been limited with regard to ecological validity. This chapter explores some of the issues that are related to the evaluation of procedural skills and presents methodologies that can be tested and further developed to assess these functions.

Processing Speed

Procedures and habits, or the behaviors in which we engage on a daily basis, are often thought of as automatic. Many of these routine behaviors seem to be performed without effort, and usually quickly. A number of theories describe these behaviors as simply being performed faster than higher-order or controlled processing (reviewed in Saling & Phillips, 2007). This raises the issue of processing speed. What is it? How is it measured? What is its anatomic locus? What does it mean? How does it translate to real world behavior?

Processing speed is usually defined as the speed with which different cognitive operations can be performed or executed (Reichenberg & Harvey, 2007). This is a general definition that does not really tell us much. Despite the fact that many clinicians refer to "processing speed" in neuropsychological reports and in descriptions of patients, a more specific and agreed-upon definition does not appear to exist. Based upon the anatomy presented in previous chapters, we believe that the concept of processing speed needs to be defined operationally, in terms of the specific task under consideration. This is necessary because different tasks require the recruitment of different anatomical cognitive networks. Two similar but different tasks do not necessarily require the same cognitive network, although certain regions of the anatomic network might be shared. In addition, while a particular network might be required during the initial phases of learning a task, a different network might be recruited as the task is practiced and becomes automatic. This was reviewed in Chapter 4, which described a dynamically changing neuroanatomy underpinning different types of learning that is dependent upon the basal ganglia. Practice changes activation within the cortical network involved in the task or it produces a functional reorganization, which indicates that the brain regions recruited for the task are altered as a function of this practice (Kubler, Dixon, & Garavan, 2006). Generally speaking, a highly practiced skill very often requires less brain activation than it does before practice (Luu, Tucker, & Stripling, 2007).

There is no "speed center" within the brain. In very general terms, there is a pattern of decreased global activation as well as a shift in activity from cortical to subcortical areas as automaticity is achieved (Saling & Phillips, 2007). In motor skill learning, the pattern of activation not only changes but is dependent upon the type of task. During the initial phases of learning, motor tasks recruit the striatum, cerebellum, and the various relevant motor cortical regions, including frontal brain regions that provide executive control (Kubler et al., 2006). As the task becomes well learned and automatic, the representation of the acquired skill becomes distributed in a network of regions that involve either the cortico-striatal system or the cortico-cerebellar system, depending upon whether the task requires the learning of a new sequence, or requires learning to adapt to environmental perturbations (as in prism adaptation) (Doyon, Penhune, & Ungerleider, 2003; Doyon & Ungerleider, 2002). Decreased activation in cortical brain regions of the network required to perform the task

represents increased neuronal efficiency in processing the task (Beauchamp, Dagher, Aston, & Doyon, 2003).

Therefore, according to this view, automatic processing is performed differently than higher-order or controlled processing. Measuring this on different tests, or as demonstrated by different behaviors, would require observation over a period of time, with repetition, in a way that is analogous to observing performance on a cortically dependent word list learning task. For example, in word list learning tasks, a series of words is presented, usually over the course of five individual consecutive trials, while acquisition is measured by a learning slope and/or by the number of words recalled. How can these concepts be applied to clinical neuropsychological evaluation of procedures? To answer that question, let us first examine how "processing speed" is measured within a traditional cortico-centric model, because on the face of it, this is possibly related to automaticity. The issue of test–retest reliability also needs to be examined with this issue of automaticity in mind, since improved performance on tasks after exposure to test procedures can be associated with the development of automaticity.

The Measurement of Processing Speed

One common way of assessing "processing speed" is through the Processing Speed Index of the Wechsler Intelligence Scales (Wechsler, 1997, 2003). This index consists of two subtests, namely, the Coding/Digit Symbol subtest and the Symbol Search subtest. In the Coding/Digit Symbol subtest, a series of numbers is paired with symbols. The subject is required to draw the symbol that is arbitrarily associated with a corresponding number quickly and correctly. The numbers are not arranged in any particular order but the subject must work sequentially through the presented numbers without skipping any. In the Symbol Search subtest, symbols are arranged in two groups, specifically, a target group and a search group. The subject is required to scan the two groups and indicate whether or not a target symbol appears in the search group (for a complete description of the subtests, see the associated Wechsler Manual). The Processing Speed Index subsequently obtained is a composite score. It comprises a statistical transformation of raw score performances on both subtests essentially representing a type of "average" of the two tasks.

Within this context, "processing speed" is determined on the basis of performance on two different tasks. With regard to the WISC-IV, the group correlation of these two tasks across all age groups is .53(Wechsler, 2003). While these two subtests do have some things in common, they measure different things. This is implied by their modest level of correlation. The discrepant performances frequently demonstrated on these two tasks have puzzled many a clinician, as it is often assumed that the tasks will be performed similarly. The brain–behavior relationships related to these tasks have not been identified and

the neuroanatomical substrates remain relatively unknown. One fMRI study measured activation patterns during performance of the WAIS III Symbol Search task (Sweet et al., 2005). In this study, the task activated regions of occipital, parietal, temporal, and dorsolateral prefrontal cortices. However, slower performance was associated with increased activation particularly in the left dorsolateral prefrontal cortex. This would make sense in that faster performance would rely on less cortical activation in a distributed system model. One thing we do know is that these subtests in general are sensitive to cognitive pathology, since poor performance on one or both of these tasks is frequently seen in patients with documented brain damage. Poor performance is also observed in relation to psychiatric conditions and developmental disorders, including learning disabilities. Aside from these relationships, however, performance on these tasks says little with regard to how brain–behavior relationships influence "processing speed."

It can also be argued that the two tasks make different demands on working memory systems. For example, since the Symbol Search subtest presents trial-unique stimuli for every search, this would seem to place less demand on complex working memory functions. On the other hand, we might hypothesize that good working memory functions would be advantageous in completing the Coding/Digit Symbol subtest, since there are nine pairs of numbers with letters, and quick performance might be facilitated by holding this information "online" in working memory in the course of performing the task. For example, the numbers, symbols, and their associations would be represented and maintained in the reciprocal prefrontal–cortical circuitries described in Chapter 2. These representations and associations would be equivalent to a temporary "plan" of action.

If these associations are made quickly, it would seem to follow that less conscious effort would be required to complete the task. The prefrontal–basal ganglia circuits would execute the task, which essentially consists of gating and updating these representations as the task proceeds. This is essentially a serial-order processing task that theoretically would be well suited for this "looped" cortical–subcortical architecture. This would be consistent with the idea that working memory capacity facilitates speeded performance and the acquisition of procedural learning (Gabrieli, Stebbins, Singh, Willingham, & Goetz, 1997). It could be argued that the Symbol Search task emphasizes the role of cortex in making perceptual discriminations while making less demand on more complex working memory. Considered from this point of view, the pattern of individual subtest performances might be useful in generating hypotheses about a particular patient's potential to acquire new procedures, since the former task theoretically seems more dependent upon serial-order processing than the latter subtest, although these hypotheses could not stand alone and would need support from other data.

Another concern about ascribing meaning to the Processing Speed Index relates to the lack of consideration given to the number and types of errors made during the completion of the subtests. Our intuition tells us that there is likely a

difference between a subject who works quickly but inaccurately, in contrast to a subject who works quickly but accurately, or for that matter, even slowly but accurately. These differences are not reflected in a single subtest performance or in a composite performance score. To our knowledge, whether or not these differences really mean anything in terms of translating to an "extra-test" situation has never been systematically studied. Additionally, the two subtests are scored differently. The number of errors is subtracted from the number correct with regard to Symbol Search, while the total number correct is simply counted in Digit Symbol/Coding. In our opinion, these issues dilute potentially important information that can nevertheless be considered qualitatively through evaluation of raw data.

Processing Speed—A By-Product of Cognitive/Executive Control

Perhaps one way to interpret these subtest data relating to fast and slow performances would be in terms of conscious cognitive effort or concentration. Both of these subtests require the subject to work for 120 seconds and the number of responses made is the index of speed (with the above scoring caveats). The subject who gave more responses during that time period worked faster and the subject who gave fewer responses worked more slowly. These subjects "processed" more and less information during the same time interval. From this it can follow that the subject who worked more slowly had to put forth more conscious cognitive control and effort. This interpretation is consistent with the finding that slower performance is related to recruitment of greater brain area (Sweet et al., 2005; Saling & Phillips, 2007). The person who worked slowly had to concentrate harder. That subject experienced a cognitive control episode. The subject who worked more quickly probably expended less conscious cognitive effort. In this way, the "processing speed" index becomes a measure of the degree or level of efficiency of concentration, or an index of how hard the brain is working.

Thus, the speed with which a task is initially performed might be considered an index of "executive" functioning or "supervisory" control. Speed of performance and executive control are directly tied to the frontostriatal system (Rabbitt et al., 2007). It is no accident that executive function variables are strongly related to perceptual speed abilities (Salthouse, 2005). It is conceded that poor performance can occur for more than one reason, and the "reason" is not always evident in the objective test data. However, characterizing this type of "processing speed" in terms of the standard classifications of "high average," "average," and "low average," and so on and so forth might also be misleading. The idea that this type of a performance follows a normal distribution is an unwarranted assumption.

Cancellation tasks present a similar paradigm for the interpretation of "processing speed." The Trailmaking Tests, the Stroop Color Word Test, rapid naming tests, and the inhibition and "switching" paradigms on the NEPSY (Korkman, Kirk, & Kemp, 1998) and D-KEFS (Delis, Kaplan, & Kramer,

2001) can all be understood within the same interpretive framework. In these neuropsychological test methodologies, conscious cognitive control or the degree of conscious effort required to perform the task is often measured in terms of time, or "processing speed." These are tasks of "executive" control. However, the speed with which these tasks are individually performed would not be expected to correlate with each other because these individual subtests all require different skill sets. Different skills imply the recruitment of different cognitive networks, so that different tasks need to define processing speed in different ways. When considered from this vertex, two important points emerge.

First, processing speed is not a monolithic entity; it is not "one thing." Instead, there are different types of processing speed that are determined by the cognitive operations that are necessary to perform the task. For example, the time required to complete a Block Design subtest, the progress made on Coding/Digit Symbol and Symbol Search subtests, the time required to complete Trailmaking Tests A and B, and response latency/reaction times on a continuous performance test would not be expected to correspond with each other. All of these tasks are different and each task requires a different set of skills. Therefore, speed of performance, or "processing speed" cannot possibly refer to one unitary entity. Instead, it needs to be defined operationally, in terms of task requirements. Although the frontostriatal system is involved in the execution of all novel tasks, the cognitive operations of the task determine the additional brain regions that are recruited.

Second, processing speed can be considered as a manifestation or by-product of cognitive control. The more that cognitive control or conscious cognitive effort is required, the longer it takes to complete the task, or the longer the "processing speed." The less that conscious cognitive effort or control is required for task completion, the faster the "processing speed." Different tasks have different implications for the interpretation of "processing speed." A very fast and accurate Block Design performance might mean the task was easy for the subject and that little conscious effort was required (because the "procedure" was understood), a slow Digit Symbol performance might mean that task completion required considerable conscious control, and fast reaction times on a continuous performance test might imply response disinhibition, or a tendency to respond too quickly, perhaps having little or nothing to do with the degree of concentration or effort. In fact, every aspect of this example, with this type of variability, can occur within the testing protocol of one individual subject. This example suggests it is impossible to interpret processing speed apart from operationalized definitions.

Practice Effect

Practice effect refers to improved performance on cognitive and neuropsychological tests as a result of repeated test administration. It reveals the impact of repeated exposure to an instrument on a subject's performance (McCaffrey,

Duff, & Westervelt, 2000). In general, cognitive and neuropsychological tests with a speeded component, tasks requiring an infrequently practiced response, or tasks featuring a single, easily conceptualized solution have been identified as most susceptible to the effects of practice or prior test exposure (Lezak et al., 2004). Tests of declarative memory mediated by the medial–temporal lobe system are also vulnerable to practice effect from previous testing.

Practitioners are often in a position of having to conduct multiple or serial cognitive or neuropsychological assessments. For example, those working in academic settings perform repeated evaluations on children at certain time intervals in order to qualify the child for the provision of special services or to assess progress as a result of those services. Clinicians often administer re-testing to measure recovery after rehabilitative treatment, to assess the efficacy of medication usage (frequently in cases of dementia in which drugs are prescribed to prevent cognitive deterioration), to monitor disease processes, or to re-evaluate in criminal and litigation cases when issues of criminal responsibility or financial gain are involved. Practitioners in these situations must often entertain the potentially confounding effects of prior test exposure and/or expectations about practice effect. Under any of these circumstances, practice effects can be a "bad thing," representing a potential nightmare for test interpretation. In this regard, "practice effect" is traditionally understood as a source of error (Duff et al., 2007). It is considered something to be avoided.

However, the basic ideas behind practice effect are learning and memory. One way to understand the improved performance of subjects who demonstrate practice effects is to say that these subjects learned, they remembered, and they were able to apply information from prior test exposure to the next testing administration. The subjects were able to benefit from prior test experience. This is related to a fundamental principle described earlier in this book: The purpose or job of the organism is to survive through interaction with the environment. The provision of learning and memory systems provides a decisive advantage for adaptation. This is the case for at least two reasons. First, consciously recalling information learned in the past can be very useful for solving problems in the present. Therefore, memory can assist in determining the context of an ambiguous situation and in determining its stimulus-based characteristics. Second, anterior brain regions play an important role in automating solutions to problems. Said another way, by trying to make solutions to novel problems take on a routine character, the organism benefits from experience, and this greatly increases the chances for survival. The organism does now what it did before because this behavior worked. This is instrumental learning.

We are observing a special instance of these fundamental principles of adaptation in the higher-level phenomenon of "practice effect." The brain is simply doing what it is supposed to do. Although this might sound deceptively simple, the brain is "hard-wired" to benefit from experience. Some of this learning is under conscious awareness, and some of it is not. We need to learn to adapt to novel circumstances, and we also need to respond quickly and

automatically when this is appropriate. Learning or benefiting from prior experience is the default condition of the normally functioning brain.

This discussion has considered at least three types of memory. First, information can be consciously recollected from previously acquired facts and experiences, which is an aspect of the declarative memory function of the medial–temporal lobe system. Second, the storehouse of working memory is required to retrieve information immediately and to hold this information in mind temporarily while manipulating or reorganizing it to apply it to a novel problem. This was described in a previous chapter as dependent upon frontostriatal systems in combination with distributed cortical memory networks (see Chapter 2). Third, in some circumstances, the application of previously effective solutions to similar problems can be understood as related to a type of instrumental or procedural learning that is dependent upon the integrity of frontostriatal networks. Most neuropsychological evaluations routinely assess declarative learning and memory as well as working memory systems. Neuropsychology can also additionally take advantage of the phenomenon of "practice effect" by developing and incorporating measures of procedural learning into evaluations. As we so often find in the sciences and elsewhere, information considered at one time to be, "noise" or "error" is actually highly valuable once we learn how to understand and use it (Faure & Korn, 2001; Schweighofer et al., 2004). In order to do so, a few additional concepts need to be considered.

Types of Practice Effect

Practice effect is not a single entity. Different kinds of practice effect need to be considered according to different task demands. To our knowledge, practice effect has usually been defined in a unitary way, simply referring to the impact of repeated test exposure to an instrument on an examinee's performance (McCaffrey et al., 2000). However, we feel it is useful to break practice effect down into at least two different types. All neuropsychological tests consist of two fundamental elements, which comprise the broad categories of content and procedures (Milberg, Hebben, & Kaplan, 1996). All tasks contain stimulus content and most problem-solving tasks additionally feature procedures that, if known, will facilitate solutions. Therefore, it would be useful to separate practice effects into these two dimensions.

Content practice effects would appear to be heavily dependent upon the medial–temporal lobe memory system. Primary examples of tasks vulnerable to this type of practice effect are word list learning tasks and narrative recall tasks. One would predict that learning the "content" of the word list, or the actual words that comprise the list, would be highly susceptible to repeated test exposure. The same would hold true for thematic narrative recall. This is largely borne out by certain studies on practice effect, although this is clearly dependent upon the types of pathologic conditions in which practice effects are studied

(McCaffrey, et al., 2000). Obviously, we would not expect a patient with impairment of the medial–temporal lobes to demonstrate good learning, memory, or "practice effects" with respect to recalling the actual content of the material. The intact medial–temporal lobe memory system functions to remember consciously experienced information. Single or repeated exposure to material results in that material being learned. Test construction and administration take advantage of this fact. Conscious declarative memory tasks present information over repeated trials during the course of the evaluation in order to measure learning and then, in a delayed condition, memory is evaluated by determining what the subject consciously remembers or recognizes. In a sense, the administration of these types of tasks represents a sort of "controlled" practice effect. Because of the manner in which the medial–temporal lobe system operates, with its default function being to learn and store information, these types of tasks would be subject to practice effect with repeated exposure to the same material on subsequent testing, and lack of practice effect in relation to them is considered evidence of dysfunction and pathology.

The Tower of London is a problem-solving task that emphasizes the discovery, acquisition, and application of a procedure. This task's underlying procedure is constant; it stays the same throughout the course of the task, from item to item. This procedure requires the subject to first place a ball of a given color on a certain peg if that ball is to reside on the bottom of a different identified peg in the model stimulus position. If the procedure is discovered, the subject will always finish each item in the shortest number of moves, regardless of how test content is manipulated from item to item. After the procedure is "known," the content becomes irrelevant. One would expect that if this procedure is acquired, this task would be very vulnerable to practice effect, regardless of alternate forms of the test if only the content and not the procedure is manipulated. If the procedure is discovered early in the task, every item in the series can be performed quickly and accurately, without a second thought. It has been demonstrated that the learning of this task is associated with dynamic functional neuroanatomic changes. As the cognitive skill is acquired, there is a significant decrease in frontal cortical activity, while activity in the left caudate is maintained throughout the course of the task (Beauchamp et al., 2003).

Hubert and associates employed the similar Tower of Toronto task to isolate three phases of procedural learning (Hubert et al., 2007). The initial cognitive stage recruited the prefrontal cortex, cerebellum, and parietal regions. All of these regions became less active as learning progressed. In the second stage, the associative phase, the occipital lobes, the right thalamus, and the caudate nucleus were activated. In the final autonomous phase, the left thalamus and anterior lobes of the cerebellum were activated. The recruitment of parietal and occipital regions during the associative and autonomous phases implies the involvement of visual loops in task acquisition. Therefore, there is a neurodynamically changing anatomy associated with the procedural learning of both of these tasks (This anatomy closely resembles the anatomy of cognitive skill and

motor skill learning described in Chapter 4). Similarly, there is evidence that the procedures of these types of tasks can be learned and remembered without access to declarative memory systems, which emphasizes that not all practice effect is the same (Nissen, 1992).

Explicit, declarative knowledge can seem essential to the acquisition of cognitive skills. However, some cognitive skills can be learned through nonconscious or implicit processes, and a subject need not go through a "declarative" stage to acquire cognitive skills. Although extent of lesion in the PFC does impact upon procedural learning, it has been suggested that the integrity of the dorsolateral PFC is not mandatory for normal cognitive procedural learning (Schmidtke, Manner, Kaufmann, & Schmolck, 2002). Some data demonstrate that on rule-learning tasks, striatal activation increases while activity declines in the declarative, hippocampal system (Seger & Cincotta, 2006). In fact, patients with deterioration in declarative memory systems can learn tower tasks at a rate that is comparable to normal controls. Problem-solving tasks such as the Tower of London and Tower of Hanoi have clearly demonstrated that individuals exhibit procedural learning on these tasks (Ouellet, Beauchamp, Owen, & Doyon, 2004). As indicated above, subjects improve their performance on the TOL with practice, and this is associated with dynamic functional anatomic changes. This implies that exposure to these types of problems can trigger changes in an individual's capacity to use the mental operations necessary to solve the problems simply as a manifestation of task participation or exposure.

Other tasks can be defined in terms of both procedural and content elements, where knowing about the subtest content provides little useful information about learning the procedure, and knowing the procedure provides few clues as to how to manipulate the content. A primary example of this is the Wechsler Block Design subtest. First, consider only those designs that can be completed with four blocks. Once the procedure that the blocks need to be manipulated within a square matrix is "known," the problem-solving component concerns manipulating the "content," or the angles of the mosaic blocks, which essentially comprises a task of how the subject's frontal systems use featural–visuospatial information in problem–solving. After a few design presentations, the procedure changes by requiring the subject to construct the blocks in a larger matrix. Therefore, the procedure actually changes in the middle of the task.

If an individual has good visuospatial skills for manipulating the blocks, the content becomes less important, since the subject should theoretically be able to complete any block design once the procedures are known. The task is made more difficult by rotating the stimulus models or by changing the "border" characteristics of the designs. However, it is clear that Block Design is a multiple component task, dependent upon applying certain procedures that change during the course of the task, with changing content as well, so that this subtest would be vulnerable to both procedural and content "practice effects." By the same token, because both content and procedures are manipulated during the

course of the task, a poor performance provides limited information about the reason for that poor performance, and a lack of practice effect with repeated administrations might be similarly difficult to interpret without additional more specific data. In any case, it is important to understand that all tests manipulate content and procedural variables to some degree.

Procedural Learning in Neuropsychological Evaluation

Neuropsychological assessment already measures "content" practice effects in a controlled way by administering conscious declarative learning instruments. These types of tasks include both verbal and visual–perceptual–spatial learning and memory tests. In general terms, a subject is presented with content stimulus material over a prescribed number of trials, and that information is recalled in a delayed condition. This is learning, memory, or controlled "practice effect." These assessment concepts need to be extended and applied to tests that can demonstrate the learning and performance of activities in order to evaluate procedural learning. This methodology is currently absent from contemporary neuropsychological assessment. However, this methodology can easily be developed and incorporated into the neuropsychological examination. A variety of tasks will be reviewed to illustrate how these procedures can be developed. This discussion should be considered hypothetically, as a proposal. We view this presentation as a first step in an attempt to develop a more comprehensive neuropsychological evaluation that includes assessing functional aspects of the procedural learning system's dynamic anatomy.

As we have seen, a general anatomic pattern of procedural learning can be identified. Grossly speaking, there is a shift from executive and visual corticostriatal loops to the motor loop across the time course of learning (Seger, 2008). This dynamic activity appears to represent a transfer of information within patterns of interaction between these corticostriatal loops. The most typical pattern is characterized by a marked gradient from ventral, anterior, and medial regions of frontostriatal circuits out to the most superior, posterior, and lateral regions. In other words, activation proceeds from the dorsal and ventral striatum out to the putamen, with the visual loop lying in the middle of the gradient. Motor skill learning has also been summarized as shifting from the executive loop to the motor loop. This pattern presumably reflects the executive loop being involved in the initial acquisition of the task and the motor loop being involved in task execution (Nakahara, Doya, & Hikosaka, 2001; Poldrack et al., 2005). Given that procedures generally comprise ways of "doing" things, activation of motor loops would be anticipated in relation to most tasks of these types. With this general but dynamic anatomy in mind, a variety of known neuropsychological tasks can theoretically be applied to evaluate the integrity of the procedural learning system. The circuitry of this system is depicted in Fig. 9.1.

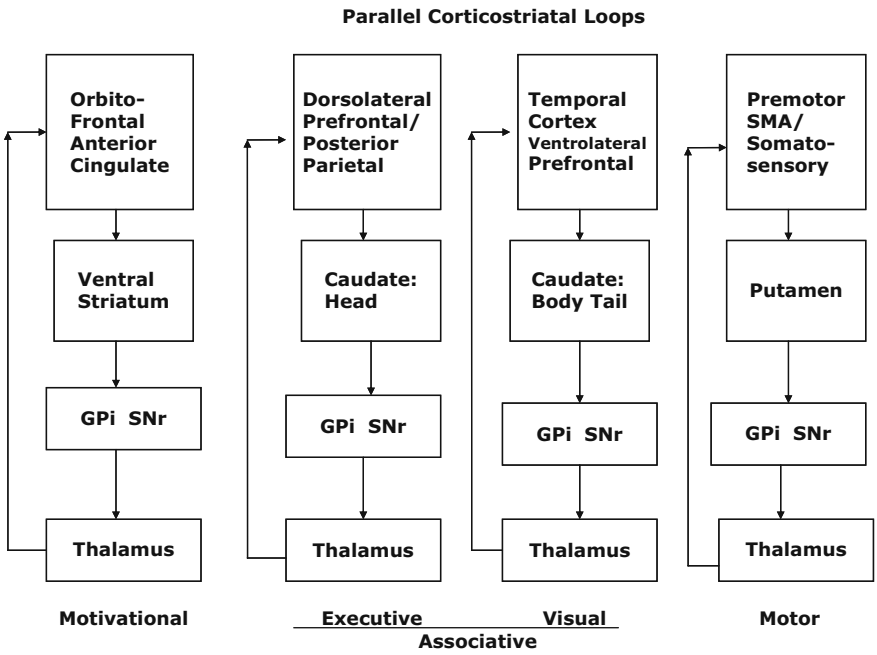

Fig. 9.1 Illustration of cortico-striatal loops. Learning proceeds from motivational and associative loops to motor loops. From Seger, 2008 with permission

The Wechsler Mazes

The WISC-R and the WISC-III contained optional maze subtests. These mazes are not included in the WISC-IV revision, nor have these mazes ever been a part of the Wechsler Adult Intelligence Scale series (the Elithorn Maze task included in the WISC-IV PI is not the same task as previously offered). These mazes would theoretically be excellent sample tests to use for assessing procedural learning for several reasons. The removal of this subtest from recent versions of the Wechsler batteries raises the sometimes thorny issue clinicians face in relation to staying current with available tests; how do we provide sufficiently competent and comprehensive evaluations in the context of test publishing decisions that are usually out of our hands? Unfortunately such questions are outside the scope of this book, but remain salient topics of discussion.

In any case, the tasks obviously include a "visual" component, which would activate visual loops. Both the oculomotor and SMA motor loops would be involved because of the visual search and motor tracing demands of the task. The executive loop would also be recruited, since the task has an obvious inhibition and planning component. In order to perform the maze tasks well, executive activity would be required to "think ahead," executive activity would presumably interact with the visual and oculomotor loops to execute the proper

search, and integration with the motor loop would be required for task execution. Therefore, the Wechsler Maze tasks would, in theory, recruit all of the brain regions that are activated during the time course of procedural learning as described above. The mazes are thus theoretically adaptable to procedural learning.

However, the task administration would be different from what was proposed for the original Mazes subtest. To measure procedural learning, several different formats could be followed. One format would consist of using just one single maze of at least moderate difficulty level. Using one maze would be an essential requirement in order to keep the procedure constant. The task would be scored for both errors and time to completion. The same maze would be administered over the course of five trials (which seems to be somewhat of a tradition in neuropsychological assessment). Given that procedural learning is slower than declarative learning, the number of trials might need to be increased. However, procedural learning consists of both "fast" acquisition and slower consolidation phases, and there is absolutely no reason why the fast acquisition phase could not be measured during the course of an evaluation. If administered within this framework, reduction in time and decrease in errors relative to trial 1 of the maze performance would be a rough index of procedural learning for that task. An alternate administration would consist of administering the same maze, over and over again, until error-free performance was achieved. The total number of trials, along with decrease in speed to task completion, would serve as the index of procedural learning. In all of these ways, learning would be measured by improved performance. One would expect a physical ceiling on speed effects, so that trials to error-free completion might represent the best index of learning. As the task was learned or became automatic, the subject's eyes and hand would almost "move by themselves" as procedural learning occurs. This would presumably be a manifestation of the neuroanatomic activation pattern described above. By the same token, failure to learn the maze, failure to demonstrate decrease in time with improved performance, and failure to reduce errors would all reflect failures in learning, or failure to benefit from procedural experience.

Trailmaking Tests

The Trailmaking Tests would appear to represent a potentially useful paradigm for measuring the frontostriatal system's procedural learning, particularly Trailmaking part B. This test requires a visual search pattern as well as a motor response pattern, both of which can be learned. Because of the task characteristics, it would seem fair to say that the visual and motor loops are both required for successful task completion. This test also includes an executive component. The task actually requires an individual to combine previously learned material in a new way. The test takes advantage of the fact that the

numeric and alphabetic sequences are both automated. The task requires the frontostriatal learning system in order to "gate" the new alternating sequence of going from numbers to letters and letters to numbers. Therefore, Trailmaking part B requires several cognitive skill processes. The executive direction of the task requires "working memory" because of the integration of the two sequences, the mental updating required of one's performance, and coupling these aspects of the task with visual search and the motor response. Learning would be measured by administering the task over the course of consecutive repeated trials. Faster performance would be expected over multiple trials. The previously reviewed data on sequence and procedural learning suggests that over the course of several trials, the subject would learn to anticipate a response based on the constant locations of the numbers and letters. As performance became faster over several trials, this would very likely reflect the shift from "controlled" to "automatic" processes, or in anatomic terms, from executive to motor loops as described above.

This test has been described as subject to practice effect after only brief periods of time (McCaffrey et al., 2000). This actually implies it would be a good candidate to apply to a procedural learning paradigm in neuropsychological testing because it would be time-efficient to incorporate into a test battery. There is also at least limited data on practice effect with certain patient populations that might serve as a "rule of thumb" in guiding expectations. For example, patients taking certain psychotropic medications do not show the same practice effect as normal controls (McCaffrey, 2000). In addition, this test is so commonly used in test batteries that one might expect contamination to occur quite frequently with repeated or serial neuropsychological assessment. Therefore, perhaps this test should be used in developing a procedural learning paradigm, given its apparent popularity. As a corollary, clinicians might then refrain from additional use in future repeated assessments, as is the case in avoiding repetition of the same declarative learning and memory task.

Perceptual–Motor Skill Learning

Tasks such as mirror tracing and rotary pursuit are perceptual–motor learning tasks that are applied in experimental paradigms. These test paradigms are available through certain publishers that sell experimental equipment, but normative data on control subjects and clinical populations are not available. The mirror-tracing task involves the tracing of the outline of a geometric figure (such as a star) by looking in a mirror (Banich, 2004). This motor skill task involves acquiring the skill of moving one's hand/pencil in the opposite direction of what is viewed in the mirror. Theoretically, this task should activate executive, visual, and motor loops. Across multiple trials, the number of times the subject's drawing falls outside the outline of the figure and the time required to complete the task decreases, which is the measure of

perceptual–motor skill learning. This should theoretically reflect the "training" occurring within visual and motor loops.

Amnestic patients with disturbances in the medial–temporal lobe memory system, such as patients with Alzheimer's disease and global amnesia perform normally on this task (Gabrieli, Corkin, Mickel, & Growdon, 1993). In the rotary pursuit task, the subject is required to use a stylus to track a circularly moving target (as reviewed in Banich, 2004). Again, with repetition, normal controls and amnestic subjects perform in a similar manner (Willingham, 1992). However, patients with Huntington's disease demonstrate differential impairment on rotary pursuit learning in contrast to intact mirror tracing motor skill learning. Although both tasks would appear to recruit visual and motor loops, these two tasks do not measure the same processes and the performance pattern implies that different forms of motor skill learning are mediated by separable neural circuits (Gabrieli et al., 1997).

Although these tasks are experimental procedures, they can be applied to clinical populations. In other words, these are methodologies that are testable for the purpose of developing norms for potential clinical application. Skill learning appears to be mediated by discrete changes within motor learning systems that are driven by experience or practice. These changes appear to occur within specific neural networks that mediate task performance. Skilled motor performance appears to be acquired in different stages or phases (Karni et al., 1998). There appears to be a "fast" learning, initial improvement stage. This is followed by a time of consolidation of several hours duration, followed by a period of "slower" learning in which incremental gains are made with further practice over a longer period of time. Motor skill learning has been described as robust, but as often taking considerable time for acquisition of the skill. However, these data regarding fast and slower learning imply that motor skill acquisition can occur within a brief time. This makes it feasible to assess during a relatively brief neuropsychological evaluation.

Subcircuit Differentiation

Corticostriatal circuit dysfunction is not all the same. Foerde and colleagues have demonstrated that different types of skill learning are related to separable corticostriatal loops (Foerde et al., 2008). Schizophrenic patients were impaired relative to normal controls on the cognitive Probabilistic Classification Task (PCT). The improved performance of controls occurred within the first session, while the patient group never reached the performance level of control subjects. Both groups performed equivalently on the Serial Reaction Time (SRT) task which was considered a form of motor skill learning. The findings imply that the functioning of specific corticostriatal circuits are dissociable using neuropsychological tests and that patients with schizophrenia have an abnormality in a specific corticostriatal subcircuit that mediates cognitive skill learning.

Clinical neuropsychological evaluations often include a rule-based categorization task, but the data reviewed on implicit categorization reveal that this important type of instrumental learning has an anatomy that is specifically driven by the basal ganglia. Incorporating a probabilistic category learning task in clinical evaluation would provide unique information about intuitive thinking that is often important to cognition. Coupling this type of task with a motor skill acquisition task would provide information about potentially dissociable circuitries. Both the PCT and SRT could conceivably be developed for computerized administration during a single evaluation session.

Motor Adaptation

As reviewed above, the cortico-striatal and cerebro-cerebellar systems play different roles in motor skill sequence and environmental adaptation learning respectively. Therefore, paradigms need to be developed to assess both systems. In motor skill adaptation learning, the individual is required to adapt to environmental manipulations or perturbations. Frequently used tasks of this type involve the adaptation of arm movements to laterally displacing prism glasses. A subject is required to perform a limb movement, then to adapt that movement to displacement while wearing prism glasses, and then to readapt to the original movement after the prism glasses are removed. The visual–motor adaptation to the lateral displacement of vision by prism glasses has been studied in normal control populations and various patient populations. These patient populations include individuals with Parkinson's disease, patients with lateralized cortical lesions, patients with dementia, psychiatric disturbances, and patients with cerebellar dysfunction (Weiner, Hallett, & Funkenstein, 1983). The cerebellum has been identified as an essential component in the neural network for prism adaptation, and disturbances in the performance of this task are primarily seen in patients with cerebellar involvement (Bigelow et al., 2006; Fernandez-Ruiz, Hall, Vergara, & Diiaz, 2000; Fernandez-Ruiz et al., 2003; Morton & Bastian, 2004; Weiner et al., 1983). This type of task could be developed for computerized administration within a "virtual reality" paradigm for neuropsychological assessment.

As we have seen, neuropsychological evaluation within a cortico-centric model of cognition does not pay much attention to cerebellar or basal ganglia function unless a specific lesion to one of these areas is involved in the referral question. However, this book proposes that the cortex, basal ganglia, and cerebellum all operate in concert, in parallel, during the course of most, if not all, adaptive activity. The chapter on clinical disorders also reviewed several neurological and psychiatric conditions in which the cerebellum has been identified as involved in the pathogenesis of the disorder. Involvement of the cerebellum has also been implicated in learning disabilities, specifically, reading disorder (Nicolson, 2000). We believe that neuropsychology also needs to

consider including an assessment of cerebellar functioning in its evaluations. A comprehensive motor examination would include observations about coordination, as well as making distinctions between a patient's ability to learn new motor programs and sequences and the ability to automate those sequences. This would be done while observing the rate, rhythm, and force of the measured behavior in the process of its implementation. This implies the need for careful observation since these observations are qualitative and are not easily quantifiable. These observations would likely follow a pathognomonic or specific sign approach for interpretation rather than index scores that suggest a normal statistical distribution (Reitan & Wolfson, 2008). This type of approach using a dichotomous distribution stems from a focus upon identification of a problem in contrast to the aim of representing and measuring a full range of behavioral characteristics, and would be performed in concert with assessment of those areas of function amenable to assessment in relation to a normal distribution.

Summary

This chapter reviewed the concept of procedural learning as it applies to clinical neuropsychological evaluation. Procedural learning is currently not addressed in neuropsychological assessment, even though impairment in procedural learning systems is often central to a patient's clinical presentation. In order to lay the background for the development of clinical tests within this domain, this chapter reviewed and redefined the traditional concepts of processing speed and practice effect. These constructs are not unitary entities. Understanding these constructs as processes dependent upon anatomic brain–behavior relationships is critical to the development of tests able to assess procedural learning systems. Learning, in all its forms, represents the default condition of the brain. The chapter discussed how a variety of simple methodologies might be developed for clinical application.

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Chapter 10
The Basal Ganglia and Neuropsychological Testing

Chaos is inherent in all compounded things. Strive on with diligence.

Buddha

The distributed frontal–subcortical system consists of connected cortical and subcortical structures. While this can be referred to as the frontostriatal system, the anatomic connections originate in the prefrontal and frontal cortices, and project to the striatum, the globus pallidus, the thalamus, and back to the cortex (see Chapters 2 and 3). The term frontostriatal system sometimes represents a convenient shorthand label for this entire circuitry that extends beyond the striatum. Very similar behaviors, signs, and symptoms will be seen in disorders that affect the frontal cortices, the subcortical white matter projections, the striatum, the globus pallidus, or the thalamus (Chow & Cummings, 2007; Stewart, 2006). This chapter presents a series of cases that illustrate the manner in which currently available neuropsychological tests can begin to assess the functioning of this extended region.

All of the test data in these cases are organized very specifically according to cognitive domain or module. These domains reflect a systematic way to organize brain–behavior relationships. For example, the visual–perceptual–spatial domain data are organized and interpreted in the same way in which these processes are represented within the brain. Object recognition functions are subsumed by posterior ventral pathways, and object location functions are subserved by dorsal pathways. Constructional functions are viewed as anterior in localization while requiring the support of these posterior perceptual processes (Capruso, Hamsher, & Benton, 1998). In this anatomical frame of reference, the central sulcus separates anterior from posterior cortices. All brain regions posterior to the central sulcus are considered posterior cortices, and regions anterior to this fissure are considered anterior. Therefore, the occipital, parietal, and temporal lobes are considered posterior; the frontal lobes and basal forebrain region are considered anterior brain systems. Tests

L.F. Koziol, D.E. Budding, *Subcortical Structures and Cognition*,
DOI 10.1007/978-0-387-84868-6_10, © Springer Science+Business Media, LLC 2009

and results are grouped into the appropriate domain and into the appropriate function within each domain.

This interpretive methodology greatly facilitates the integration of test data. This type of integration is important because it assists practitioners in making anatomic sense of test data while forcing us to notice and evaluate any inconsistencies in results. However, in organizing evaluation data this way, it is readily apparent that neuropsychological tests and instruments are not necessarily constructed along the lines of anatomic brain–behavior relationships. A test's name often does not reflect a brain-related anatomic organization. Therefore, the clinician's understanding of functional neuroanatomy, cognitive processes, and judgment are required in grouping various tests within domains. A number of tests are considered multi-factorial to the extent that they might be placed in more than one domain simultaneously. For example, a sentence repetition test might be considered as a language function, as a measure of immediate recall, and as a measure of an element of attention.

The language domain is divided into receptive and expressive processes. The level of organization proposed here respects the brain-related representations of posterior/receptive and anterior/expressive functions. It is of relevance to consider language as comprising both cortical and subcortical processes within this domain as well. However, there are no commercially available cognitive, neuropsychological, or language tests that make any attempt at all to separate or recognize the organization of the declarative and procedural language systems. (see Chapter 6 for a description of the Declarative–Procedural language model.) Any separation of function of this type thus currently results from qualitative test interpretation and behavioral observation. However, in clinical evaluation, a qualitative approach is justifiable.

The domain of attention is organized according to the model proposed by Mirsky (Duncan & Mirsky, 2004; Mirsky, 1996; Mirsky & Duncan, 2004). We use this model because of its simplicity and convenience in systematically evaluating attentional functions. We fully recognize that other models are justifiable (Cohen, Malloy, & Jenkins, 1998). A number of different models of attention can be employed, so long as attentional functions are measured in a systematic way. The "Mirsky model" divides attention into the dimensions of initial registration or encoding of information, sustained attention, shifting attention, and the focus/execute element. Within the element of sustained attention, we have subdivided the dimensions of stimulus selection and response inhibition (Fuster, 1997) which are not components of Mirsky's original proposal. This allows for a finer breakdown of function as related to the inhibitory component of attentional focus and control as mediated by the frontostriatal system. The focus-execute subdomain features test data that are considered to be related in some capacity to what is commonly referred to as "processing speed," insofar as "processing speed" refers to the amount of material processed per unit of time. As we have seen, "processing speed" is not "one thing" (see Chapter 9). It is thus common to find variability in the scores placed within this domain.

The executive domain is categorized according to four functions, specifically, working memory, inhibition, attentional shifting, and planning (Bennetto & Pennington, 2003; Pennington, 1997). It is realized that the attention and executive domains, therefore, overlap. However, it always needs to be understood and remembered that the categories of different domains can and do share certain features. Thus, the divisions provided here should serve as a reminder that cognitive functions are integrated, and that division into categories is always somewhat arbitrary and never completely clean or absolute. This actually helps to avoid fragmented thinking about patients during the process of test interpretation.

It can easily be argued that inhibition and working memory are the abilities that developmentally support all executive functions (Denckla, 1994, 1996). Without an ability to "not respond" to the immediate, we cannot develop the capacity to "think" about anything other than that which is right before us. Without working memory, we cannot develop the capacity for higher-order, self-directed control over behavior. For example, the ability to change attentional focus and shift from thinking about one concept to another, as well as the ability to plan ahead hinge upon background functions of working memory and inhibitory control (Asato, Sweeney, & Luna, 2006). Further, inhibition and working memory are two functions that are rooted in the "serial order processing" of cognitive and motor control as described in Chapter 2. For example, we drew parallels between motor plans, working memory, and higher-order cognitive control. The architecture of frontal–basal ganglia "loops" allows both inhibition and working memory, and it is this anatomic organization that generates the viewpoint that higher-order cognitive executive control is the evolutionary extension of the motor control system (see Chapter 2 for a review).

We follow Squire's model in relation to assessing the declarative learning and memory domain (Squire & Shimamura, 1996). Learning is defined as the acquisition of information and memory is defined as the persistence of that learning over time. Therefore, memory is very narrowly defined as the retention of newly presented information. This is considered a posterior function, initially dependent upon the hippocampal formation within the medial–temporal lobes, which is best measured by recognition paradigms. The retrieval functions are considered to be mediated by the frontostriatal system (Squire, Stark, & Clark, 2004; Yener & Zaffos, 1999).

The final domain consists of sensory and motor functioning. We believe it is preferable and advisable to interpret sensory and motor systems separately. We adhere to this distinction for two reasons. First, this methodology respects functional anatomic organization. Sensory–perceptual processes are mediated by posterior sensory brain regions, and motor functions are subserved by anterior brain regions in coordination with subcortical areas as previously discussed. It is true that every motor action requires sensory input. However, sensory perception can be assessed without requiring significant motor response. This allows for discriminations as to whether deficits lie on the sensory or on the motor side of the sensory–motor equation. This assists in

neuroanatomic localization. Second, this division relates to adaptive function. Sensory–perceptual processes are passive–receptive functions that in isolation do not require executive, higher-order control. They require recognition functions and they assist in object identification and object location. On the other hand, motor control and executive function are intimately related.

To reiterate a theme of this book, cognitive control can be understood as an "extension" of the same frontal and basal ganglia interactions that control movement (Hazy, Frank, & O'Reilly, 2007). This translates movement to thought. The process of child development can be conceptualized as the acquisition of increasing control over the motor system (Slattery, Garvey, & Swedo, 2001). Controlled motor function, by definition, is executive control. Motor development clearly corresponds with the development of higher-order executive control processes (Diamond, 2000). Therefore, we believe that combining sensory–motor functioning as a unitary concept usually results in a critical loss of interpretable data that can guide diagnostic decision-making and treatment planning. This distinction is of critical significance in pediatric cases, in which dissociations between sensory and motor function are common and are of differential diagnostic importance.

Interpretation Paradigm

All of the cases that will be reviewed also follow a systematic interpretation strategy within each domain. This interpretative methodology was initially developed by Reitan (1974, 1975). However, the methodology can be applied to any cognitive data, without relying on any of the specific tests of the Halsted-Reitan assessment approach. We believe that it is important to apply the same systematic interpretative methodology to every case, every time, in order to ensure a comprehensive understanding of the data. Non-systematic approaches can lead to superficial interpretations and false negative and false positive findings.

The three most important inferential methods in this system are directly related to cognition. These methods of interpretation comprise evaluating a person's level of performance in relation to normative data, comparison of performances across cognitive tests of relevant dimensions (also referred to as pattern analysis), and assessment of pathognomonic signs. A fourth level of inferential analysis comprises body-side comparison, though this fourth methodology might not always reflect cognitive status, since in certain cases, sensory and motor functioning can be affected by pathology peripheral to brain functioning. In addition, certain sensory and motor information usually considered in body-side comparisons can be used in other comparisons, in other domains, and sometimes even in a pathognomonic manner. For instance, impaired competing programs go–no-go motor task performance is often interpreted as a specific sign of deficit within the executive domain of "inhibition." However,

unfortunately, while every case for clinical evaluation consists of cognitive data, not every case includes the type of sensory and motor data necessary for body-side interpretive comparisons. This stems from the popular but misleading notion that sensory and motor functions are "non-cognitive" in terms of interpretative implications.

Level of Performance

The first and most basic inferential method is the level of performance. In this method, a test score is compared to an objective normative standard. A "good" level of performance typically implies healthy brain-related ability for the function in question. However, this is not always the case, since an interpretation at this level can be modified through test pattern analysis when comparing a particular performance to other test data. For example, against the background of test scores within a superior range, an "average" test performance might actually be indicative of a cognitive deficit. This type of interpretation has also been referred to as an individual comparison standard (Lezak et al., 2004). A "poor" level of performance in isolation never provides any information concerning the reason for that poor performance (Anastasi & Urbina, 1997). Therefore, a poor performance on any single test might be a manifestation of any one of multiple factors. Simply comparing a performance on any single test to a normative standard does not necessarily speak towards the integrity of a brain function, even if test score standards were derived from populations with documented brain damage.

Test Score Comparisons/Pattern Analysis

Test score comparisons are often much more useful than simple level of performance criteria, and this represents the second level of inference in analyzing test data. A comparison of test scores often generates synergistic interpretive information because it provides data that would not be available through simply interpreting scores in isolation. For example, scores on semantic/category fluency tasks and scores on letter/phonemic fluency tasks might not say very much when interpreted individually, but comparing category and letter fluency scores with each other can often generate information about the integrity of posterior versus anterior brain-related language and executive processes. Many diagnostically powerful neuropsychological inferences are generated by this synergistic methodology. We believe that organizing test data according to the concept of functional domains assists the examiner in structuring relevant test score comparisons. Examples of the synergistic power of test score comparisons were reviewed in Chapter 8.

Pathognomonic Signs

When neuropsychological test metrics are described in terms of standard scores, it is tempting to conclude that the measured function follows a normal probability distribution. However, a number of abilities and skills do not follow a normal distribution of scores within the general population, even though the test publisher may have assigned ranges of performance with standard scores. There is also a difference in approach between trying to measure a full range of behavioral characteristics versus trying to identify a problem or disease characteristic. The former range often approximates a "bell-shaped curve," while the later focus on the identification of a disease process typically results in detecting behavioral "signs" that follow a dichotomous distribution (Reitan & Wolfson, 2008). These latter types of test data are simply not normally distributed and need to be interpreted within the context of pathognomonic or specific signs. This means that almost each and every time the performance is observed, it points to a lack of integrity in brain-related functions. For example, disorientation in an adult patient, dysphonetic spelling errors in school-aged children and errors of commission on certain specific continuous performance and go–no-go tasks comprise a few samples of behavior that are considered pathological simply on the basis of their occurrence. All cases that are reviewed below will include an examination of certain functions within this framework.

Body-Side Comparisons

In body-side comparisons, the functioning of the dominant and non-dominant hands is compared in sensory and motor domains. Comparing the functioning of one body side with another can implicate the contralateral cerebral hemisphere when a sensory or motor deficit is observed. In addition, deficits in sensory–perceptual functioning (on tasks such as finger localization) typically implicate involvement of posterior brain regions while deficits in motor functioning typically imply involvement of anterior brain regions. We tend to view sensory body side comparison data as significant mostly when these results correspond with cognitive pathology identified by other aspects of test data. In other words, these data are viewed as supportive of interpretations generated from direct cognitive test results. This is because data concerning motor functioning can also be affected by factors that are peripheral to cognitive processes, such as fracture or other damage to a limb.

We favor a motor examination that systematically evaluates and hierarchically "layers" motor functions. The guiding principle concerns the fact that higher-level motor functions must be expressed through lower level systems. It is anatomically impossible to execute an "intact" higher-level motor skill through a deficient lower-level motor system. For example, a task such as finger tapping is relatively straightforward and "taps" the "lower-level" motor systems of "posterior" regions

of frontal motor cortices, such as the pre-central gyrus, commonly referred to as the primary motor cortex or the vernacular "motor strip." Tasks such as "finger sequencing," or touching each finger, in order, over repetitive trials recruit frontal regions anterior to primary motor cortex, in the premotor and supplementary motor areas. More complex tasks, such as learning new motor movements involving multiple limb movement combinations, or tasks that involve the executive coordination of bi-lateral limb movements, involve even more anterior frontal cortices, and can include dorsolateral– prefrontal cortices. Therefore, the motor system can be evaluated very systematically. Based upon the premise that motor control is the "precursor" of higher-order control, this methodology has implications for executive function, which is frequently the focus of neuropsychological evaluation. However, this methodology is not frequently employed in traditional American neuropsychology.

Clinical Case Examples

The following cases offer an introduction to aspects of our approach to test data interpretation. We employ a flexible battery approach. The cases presented here made use of a variety of commercially available and public domain measures. These included the following: Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983); various versions of the California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987, 1994, 2000); Wechsler Intelligence, Memory and Academic measures (Wechsler, 1997a, 1999, 2001, 2003); Rey Auditory Verbal Learning Test (Schmidt, 1996); Rey Complex Figure Test and Recognition Trial (Meyers & Meyers, 1995); Tower of London (Culbertson & Zillmer, 2001); NEPSY Neurodevelopmental Battery (Korkman, Kirk, & Kemp, 1998); The Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, 1998); Minnesota Multiphasic Personality Inventory, Second Edition (Butcher, Dahlstrom, Graham, Tellegen, & Kaemmer, 1989); Stroop Color and Word Test (Golden, 1978); Grooved Pegboard (Trites, 1997); Benton Finger Localization (Benton, 1983); Wisconsin Card Sorting Technique (Heaton, Chelume, Talley, Kay, & Curtis, 1993); Gordon Diagnostic System (Gordon, 1983); Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001); Gray Oral Reading Tests (Wiederholt & Blalock, 2001); Wide Range Achievement Test (Wilkinson & Robertson, 2006). Tests such as Auditory Consonant Trigrams (Brown-Peterson Technique) and Trail Making Tests are featured, with norms, in Spreen and Strauss (1998); Strauss, Sherman, and Spreen (2006).

Case 1

The first case is a 67-year-old right-handed male who has completed 18 years of formal education. Approximately 1 year prior to this assessment, he was

hospitalized in relation to a diagnosis of Bipolar Affective Disorder. He has not been "normal" since that time. His wife reports that he is afraid to drive, that he does not socialize with others, and that he has not returned to work. He needs to be prompted to engage in activities. His thinking is described as slow, he lacks spontaneity, he has flat, bland affect, and a mask-like facial expression. He earned a Bachelor's degree in business administration and a Master's degree in economics. He is in good health other than his psychiatric symptoms. Prior to his current illness, he was socially active and enjoyed a wide range of interests and activities.

Case 1 GENDER: M AGE: 67 EDUCATION: 18 HANDEDNESS: R

GLOBAL FUNCTIONING

WASI

	Sum of T Scores	IQ	Percentile
Verbal	127	122	93
Performance	93	94	34
Full Scale	220	108	70

WASI Subtests

Subtest	Raw Score	T Score	Percentile
Vocabulary	69	62	88
Block Design	19	42	21
Similarities	42	65	93
Matrix Reasoning	18	51	54
Digit Span Forward	06		
Digit Span Backward	06		

ATTENTION DOMAIN

Encoding

	Raw Score	SS	Percentile
Digits Forwards	06		
RAVLT Trail 1	06		
RAVLT-B	04		
	Raw Score	MEAN	
Sentence Repetition	15	16	

Sustain

GDS Vigilance Subtest

Summary Data		Selection Position		Tracking Data
Total Correct	30	1	–	19X
Block 1	10	2	–	XX9
Omissions	00	3	–	XX1
Commissions	00	4	–	X1X

(continued)

Summary Data		Selection Position		Tracking Data
Block 2	10	5	–	X9X
Omissions	00	6	–	XXX
Commissions	00	7	46	Block 1 Latency
Block 3	10	8	50	Block 2 Latency
Omissions	00	9	49	Block 3 Latency
Commissions	00	0	48	

Overall	Number	Classification	Percentile
Total Correct	30	Normal	
Commissions	00	–	xx
Omissions	00	–	xx

GDS DISTRACTIBILITY SUBTEST

Summary Data		Selection Position		Tracking Data
Total Correct	14	1		19X
Block 1	05	2		XX9
Omissions	05	3		XX1
Commissions	03	4		X1X
Block 2	06	5		X9X
Omissions	04	6		XXX
Commissions	00	7	51	Block 1 Latency
Block 3	03	8	43	Block 2 Latency
Omissions	07	9	43	Block 3 Latency
Commissions	00	0	46	

Overall	Number	Classification	Percentile
Total Correct	14	Impaired	
Commissions	03		xx
Omissions	16	Impaired	xx

Shifting

WCST 64	Raw Score	SS	Percentile
Trials Administered	128	–	–
Total Correct	65	–	–
Total Errors	63	76	05
Perseverative Responses	44	80	09
Perseverative Errors	34	82	12
Non-Perseverative Errors	29	73	04
Categories Completed	01	–	11–16
Trials to 1st completion	61	–	6–10
Failure to Maintain Set	03	–	6–10
Learning to Learn	N/A	–	–

Focus/Execute

TMT	Raw Score	T Score	Percentile
A	82	39	14
B	87	47	38
Stroop Test			
Word	88	40	
Color	65	40	
C/W	43	48	

LANGUAGE DOMAIN

Receptive- Comprehension

Token Test—Short Form	Raw Score	Mean	Percentile	Significance
Total Score	43/44	43		Expected

Expressive Language

WASI	Raw Score	T score	Percentile
Vocab	69	62	88
Similarities	42	65	93

Confrontational Naming

	Raw Score	Mean	SD
Boston Naming Test	59/60	53.3	2.3

	Raw Score	Scale Score
FAS	16	4
Animals	11	4

LEARNING & MEMORY DOMAIN

RAVLT

Trials	Raw Score	Mean	SD
Trial 1	06	5.9	1.6
Trial 2	07	8.4	2.0
Trial 3	06	9.8	2.3
Trial 4	08	10.9	2.3
Trial 5	09	11.3	2.3
Trial B	04	5.1	1.3
Immediate Recall	04	9.3	2.9
Delay Recall	00	8.8	3.0
Recognition	10	13.5	1.3
False Positives	00	–	
Trial I –V Total	36	43	7.7
Intrusions–Recognition Trial	05	–	

2 foils identified, 3 intrusions from list B

Rey Complex Figure Test

	Raw Score	T Score	Percentile
Copy	32	–	>16
Imm Recall	11.5	43	24
30 min Delay Recall	07	31	03
Recognition	17	32	04

Executive Functioning

Working Memory: Auditory Consonant Trigrams

Delay	Raw Score	Age Norms50–69 norms
0:0	15	
09 sec	15	11.47 sd 2.33
18 sec	13	10.23 sd 2.46
36 sec	15	8.67 sd 2.85

Planning: did not complete stopped after 3 problems

Tower of London	Raw Score	SS	Percentile
Total Moves	29		
Total Correct			
Total Rule Violation	03		
Time Violation Score	04		
Total Initiation time			
Total Executive time	269		
Total Problem Solving time			

Inhibition

	Raw Score	T score	Percentile
Stroop C/W Score		48	
TOL Rule Violations	03		

Concept Formation

	Raw Score		Percentile
WCST Categories Completed	01		
Vocab T Score		T = 62	
Sim T Score		T = 65	

VISUAL—SPATIAL DOMAIN

Object Identification/Recognition Functions

	Raw Score	SS	Percentile
BNT	59/60		

Objection Location Functions

	Raw Score	Mean	Percentile
Judgment of Line	25	22.7	

VISUAL—MOTOR/SENSORIMOTOR

Construction Functions

	Raw Score	SS	percentile
RCFT-Copy Phase	32		>16
Block Design T score		T score 42	21

Motor Functions

	Raw Score (Total)	SS	Percentile
Finger Tapping Test	Did not assess		
Dom Hand			
Non-Dom Hand			
Grooved Peg Board			
Dom Hand	150	02	25
Non-Dom Hand	171	02	25

ACHIEVEMENT

WIAT-II Abbreviated

Subtest	Standard Scores	Percentile
Word Reading	116	86
Math Reasoning	111	87
Spelling	114	82
Reading Comprehension	108	70

MMPI -2

Clinical/Supplemental Scales		Content Scales		Restructured Scales	
Scale	T Score	Scale	T Score	Scale	T Score
VRIN	46	Anxiety	35	Demoralization	47
TRIN	50	Fears	35	Somatic Complaints	48
F Scale	42	Obsessions	50	Low Pos. Emotion	50
FB Scale	46	Depression	48	Cynicism	47
Fp Scale	41	Health Concerns	48	Antisocial Beh	44
L Scale	48	Bizarre Mention	39	Ideas of Persecution	41

(continued)

Clinical/Supplemental Scales		Content Scales		Restructured Scales	
K Scale	66	Anger	40	Dysfun Neg Emotions	42
S Scale	63	Cynicism	44	Aberrant Experiences	52
Scale 1 Hs	62	Antisocial Practices	46	Hypomanic Activation	33
Scale 2 Dep.	57	Type A	41		
Scale 3 Hy.	45	Low Self-Esteem	45		
Scale 4 Pd.	54	Social Discomfort	52		
Scale 5 MF	46	Family Problems	47		
Scale 6 Pa	49	Work Interference	44		
Scale 7 Pt	55	Neg. Treatment Ind.	47		
Scale 8 Sc	62				
Scale 9 Ma	47				
Scale 10 Si	53				
MAC R	51				
APS	38				
AAS	48				
PK	42				
Ho	42				
MDS	42				

***Scores at or exceeding T 65 are clinically significant**

On an abbreviated IQ test, this man obtained a Full Scale IQ (FSIQ) of 108, and this is considered consistent with expectation in view of his background. It is true that certain data reveal people with a Master's degree have high average range intelligence. However, his Verbal IQ (VIQ) of 122 is certainly quite respectable, which is one of the Wechsler indices that correlates with scholastic accomplishment. It is tempting to intuitively conclude that his Performance IQ (PIQ) of 94 represents a deterioration in cognitive–adaptive capability. However, from the perspective of "blind diagnosis," it is certainly possible that the VIQ–PIQ difference is a feature of his premorbid functioning. In this regard, it is impossible to infer cognitive deterioration with certainty in a range of scores of this type when the skills are presumably normally distributed (Reitan & Wolfson, 2008; Lezak, et al., 2004). In reviewing his cognitive scores altogether, his general level of performance is best summarized as poor. There are a few good scores, but most others are well below expectation for a person of his educational background. This fact, by itself, cannot be interpreted without comparison to other

data. All that can be said with clinical confidence (from the perspective of "blind diagnosis" while considering the cognitive results as an independent source of "stand alone" data) is that cognitive–adaptive capability is significantly affected.

Within the domain of attention, his initial encoding/registration of information is considered adequate. For example, he performed within the range of normal limits on immediate recall tasks such as Digit Span forward, RAVLT Trial 1, and Sentence Repetition. Therefore, he seems able to initially register or "take in" the same range of information as others his age within the general population. However, specific deficits were noted within the elements of sustained attention. He performed in an error-free manner on a simple, slow-paced version of the task. However, when the task required him to attend to multiple stimuli simultaneously for successful task completion, he made significant errors of omission. This means he "missed" or failed to identify stimulus presentations. Errors of commission were at least suspicious at the 25th PR, so that he was sometimes unable to inhibit responding to distracting influences. Keep in mind that this is a "pathognomonic sign" interpretation, since errors of commission are not normally distributed on this particular task.

On a task that required him to shift the focus of attention from one thing to another, he was unable to make any meaningful progress at all. He discovered one category and perseverative responses (also not normally distributed) were significantly elevated. As previously reviewed (see Chapters 2 and 8), this is a categorization task that requires an interaction between prefrontal and subcortical (basal ganglia) functions. His poor performance, as indexed by perseverations, says nothing as to anatomically localizing the reason for this inability to shift the focus of attention and thinking (Nagano-Saito, et al., 2008). In addition to requiring prefrontal processes, this task activates the caudate. The head of the caudate is initially activated, and as learning occurs, activation shifts to the body and tail of the caudate. In fact, this pattern of dynamically changing activation separates good learners from poor category learners.

These WCST test results, although very poor, implicate the frontostriatal system without greater anatomic specificity. Lesions might be localized within the prefrontal cortex, the white matter tracts, or within the striatum. The focus/execute element is essentially an index of the speed with which cognitive operations can be performed. Although the anatomy of this component of attention has never been identified through neuroimaging, the putative neuroanatomy concerns the interaction of prefrontal, posterior perceptual cortices, and subcortical regions (Mirsky, 1996). The patient performed very poorly within this dimension, implicating prefrontal–subcortical systems (please review other domains which imply visual–perceptual processes are intact, which, therefore, enables the interpretation of anterior localization). Since we interpret this type of "processing speed" as a by-product of executive control, these results implicate deficits in higher-order control processes.

Therefore, since attentional functions are affected, executive functioning must be involved as well. However, his impairment within the executive domain is fractionated. His working memory, as measured by the extremely sensitive

Auditory Consonant Trigrams Task (the Brown-Peterson Technique), is very solid. This implies that "maintenance" functions are intact. However, the failures to maintain cognitive set on the WCST are pathognomonic signs of cognitive impairment and it can be argued that this implies orbitofrontol/medial involvement. Similarly, these failures to maintain cognitive set might imply a failure in working memory "updating" functions mediated by the processes of the basal ganglia (see Chapter 2) (Moustafa, Sherman, & Frank, 2008).

One would predict that pathology within the dorsolateral–prefrontal cortex and/or within parietal/temporal regions would have a significant deleterious impact upon general test performance for the WCST. His generally poor test performance can imply pathology in any of these areas and does not allow for more specific interpretation. The "shifting" aspect of executive cognition is obviously affected, but as previously stated, this might be a manifestation of pathology within the striatum. Functions of inhibition are affected, with commission errors on a demanding version of the continuous performance task and with numerous "rule violations" on the TOL, despite his understanding of task demands and his working memory maintenance capacity. Planning or "think ahead" capacity is notably affected. He made no progress at all on the TOL. He could not "think things through." This is a frontostriatal task that typically recruits the right frontostriatal system. Therefore, the executive functions of inhibition, shifting, and planning are affected, while aspects of this particular pattern makes it tempting to infer involvement of medial and orbitofrontal– subcortical circuitries. However, more generally speaking, this individual experienced difficulties on tasks requiring higher-order cognitive control.

Within the language domain, there are certainly no indications of deficit concerning receptive comprehension functions. For instance, his performance on the Token Test was at the expected mean level. His WASI Vocabulary and Similarities subtest scores certainly imply an absence of deficit in abilities dependent upon posterior-mediated declarative language functions. In this regard, confrontational naming is also intact. However, by comparison, obvious deficits are observed in expressive language functioning. Performances were approximately two standard deviations below the mean on both categorical (animal) and letter (FAS) spontaneous word fluency tasks. When left to his own resources, he was unable to demonstrate appropriate levels of verbal output or productivity. His poor performances on both tasks imply a deficit in free/voluntary word retrieval functions. This implicates the frontostriatal system, while this pattern occurs in the varieties of frontal lobe dementia as well as in subcortical dementias such as Parkinson's and Huntington's diseases. In any event, pattern analysis of language data clearly implicate anterior brain regions in the pathogenesis of this patient's presentation.

The data on visual–perceptual–spatial domain illustrate some of the problems in trying to organize the interpretation of neuropsychological tests according to neuroanatomical principles. Object recognition functions are localized within ventral posterior brain regions while object location functions

are localized within dorsal posterior brain regions. To test these functions in a "pure" way, a test format organized around a response recognition format is preferable. Test paradigms that require the self-generation of a constructional response (as in Block Design and drawing tasks) contaminate the perceptual processes of object recognition and location by recruiting frontal system problem-solving processes. However, this patient's intact confrontational naming certainly implies that object identification functions (ventral information processing) are intact. The unremarkable Rey Complex Figure drawing also implies that posterior dorsal functions that support constructional skills are not involved in the patient's pathology. The poor figure recall implies memory is affected.

In this regard, the verbal learning test data reveal a typical pattern of involvement of the frontostriatal system. Although immediate word list recall is intact, the learning slope is shallow. The patient was slow to learn as indexed by trial-to-trial free recall, and the patient did not acquire as much information as his peers, by a factor of a standard deviation. List B recall was low, suggesting "interference" as a manifestation of involvement of anterior processes, while delayed recall was extremely poor since the patient was unable to voluntarily remember anything at all. Recognition recall was considerably improved and indicated that the patient retained substantial material. This pattern always implies a retrieval deficit that is based in the frontostriatal system. The patient is unable to remember things spontaneously, but he did acquire a solid range of information while retaining it. The intrusion responses which originated from List B stimulus material reveal a problem with the temporal ordering of information which again represents a frontostriatal, anterior system function.

On a sensory–motor task that required the patient to place pegs in holes on a formboard, performance was consistent across body sides, at the 25 PR. These are considered supportive data for interpreting anterior brain region involvement. These are limited motor test data that do not significantly enhance the diagnostic formulation. Personality measures feature few subjective complaints, as well as a moderately "defensive" response set consistent with the limited self awareness often found in patient populations featuring prefrontal–subcortical deficits (Butcher et al., 1989).

These overall test results are very clear in implicating anterior brain regions in the pathogenesis of this patient's condition. These test results very specifically imply involvement of the frontostriatal system. From a strict neuropsychological point of view, it is best to characterize this presentation as a frontal– subcortical or frontal system dementia. It is impossible to make distinctions regarding involvement of either frontal, white matter, or striatal levels of involvement. This dementia can have multiple etiologies. Some of the data might imply more medial than dorsolateral involvement. This is also suggested by the patient's lack of initiation and loss of interest that imply involvement of medial–motivational brain regions. The case interpretation illustrates that a systematic approach to analyzing test data, relying on level of performance, patterns of performance, and pathognomonic

signs allows for meaningful integration and diagnostic formulation. This particular interpretive methodology allows for the management of a considerable volume of test data in an organized and efficient way. However, it also reveals one of the weaknesses of cognitive test data in that the results do not allow a differentiation between cortical and basal ganglia pathology.

Case 2

Consider the following data, from the perspective of "blind" neuropsychological test interpretation.

Case 2 GENDER: M AGE: 57 EDUCATION: 13 HANDEDNESS: R
GLOBAL FUNCTIONING:

WASI

	Sum of T Scores	IQ	Percentile
Verbal	106	105	63
Performance	86	89	23
Full Scale	192	97	42

WASI Subtests

Subtest	Raw Score	T Score	Percentile
Vocabulary	64	57	76
Block Design	20	33	04
Similarities	32	49	46
Matrix Reasoning	21	53	62

ATTENTION DOMAIN

Encoding

	Raw Score	Mean	SD
RAVLT Trial 1	03	5.8	
RAVLT B	04	6.2	
Sentence Repetition	13	16.46	2.48

Sustain
GDS VIGILANCE SUBTEST

Summary Data		Selection Position		Tracking Data
Total Correct	29	1	0	19X
Block 1	10	2	0	XX9
Omissions	00	3	0	XX1
Commissions	00	4	0	X1X

(continued)

Summary Data		Selection Position		Tracking Data
Block 2	09	5	0	X9X
Omissions	01	6	0	XXX
Commissions	00	7	44	Block 1 Latency
Block 3	10	8	38	Block 2 Latency
Omissions	00	9	36	Block 3 Latency
Commissions	00	0	40	

Overall	Number	Mean	SD	Percentile
Total Correct	29	29.7	.52	25
Commissions	00	.72	1.5	xx
Omissions	01	–	–	xx

GDS DISTRACTIBILITY SUBTEST

Summary Data		Selection Position		Tracking Data
Total Correct	24	1	0	19X
Block 1	08	2	0	XX9
Omissions	02	3	0	XX1
Commissions	01	4	1	X1X
Block 2	07	5	0	X9X
Omissions	03	6	0	XXX
Commissions	00	7	46	Block 1 Latency
Block 3	09	8	40	Block 2 Latency
Omissions	01	9	40	Block 3 Latency
Commissions	00	0	42	

Overall	Number	Mean	SD	Percentile
Total Correct	24	26.45	4.5	38
Commissions	01	2	2.94	xx
Omissions	06	–	–	xx

Shifting

WCST	Raw Score	SS	Percentile
Trials Administered	128	–	–
Total Correct	67	–	–
Total Errors	61	74	04
Perseverative Responses	25	87	19
Perseverative Errors	23	86	18
Non-perseverative Errors	38	64	01
Conceptual Level Response	43	73	04
Categories Completed	01	–	2–5
Trials to 1st completion	118	–	2–5
Failure to Maintain Set	02	–	>16
Learning to Learn	N/A	–	–

Attention: Focus/Execute

TMT	Raw Score	T Score	Percentile
A	77	33	05
B	145	28	01

Made an error on trail 5 (self corrected on Trail 5)

LANGUAGE DOMAIN

Expressive Language

WASI	Raw Score	T Score	Percentile
Vocab		57	
Similarities		49	

Confrontational Naming

Boston Naming Test	Raw Score	Mean	SD
# Total Correct	55	55.2	4.0
# of Stimulus cues given	06		
# correct after cue	01		
# phonemic cues given	05		
# correct after cue	04		
# multiple choice	01		
# correct	01		

Verbal Fluency

	Raw Score	SS	Percentile
F	18		
A	09		
S	10		
FAS TOTAL	37	10	48
Animals	18	09	45

LEARNING & MEMORY DOMAIN

RAVLT

Trials	Raw Score	Mean	SD
Trial 1	03	5.8	1.7
Trial 2	05	8.9	2.0
Trial 3	06	10.2	2.0
Trial 4	10	11.3	1.9
Trial 5	10	12.0	2.0
Trial B	04	6.2	2.3
Immediate Recall	05	10.2	3.6
Delay Recall	04	9.9	3.3
Recognition	14	13.9	1.6
False Positives	04		
Trial I–V Total	34	47.6	8.5
Intrusions- Recognition Trial	05		

Intrusion Errors: Window, home, flower, desk (list B), children

Sentence Repetition

	Raw Score	Mean	SD
SRT	13	16.46	2.48

Rey Complex Figure Test

	Raw Score	T Score	Percentile
Copy	31	–	6–10
Imm Recall	23	61	86
30 min Delay Recall	22	59	82
Recognition	17	31	03

Working Memory
Auditory Consonant Trigrams

Delay	Raw Score	Age Norms 50–69	
0:0	15		
09 sec	10	11.47 SD 2.33	NS
18 sec	06	10.23 SD 2.46	> 1.5 SD
36 sec	04	8.57 SD 2.85	> 1.5 SD

EXECUTIVE FUNCTIONING

Planning

Tower of London	Raw Score	SS	Percentile
Total Moves	49	84	14
Total Correct	03	94	34
Total Rule Violation	04	<60	<1
Time Violation Score	02	78	07
Total Initiation time	26	92	31
Total Execution time	314	86	18
Total Problem Solving time	340	92	31

Initiation Times

	1	2	3	4	5	6	7	8	9	10
1st move	7	3	1	3	1	1	3	2	2	3

Execution Times

	1	2	3	4	5	6	7	8	9	10
Time	66	04	06	43	06	31	42	35	62	19

Inhibition: COLOR BLIND DID NOT ASSESS

	Raw Score	SS	Percentile
Stroop C/W Score			
TOL Rule Violations			

VISUAL—SPATIAL DOMAIN

Object Identification/Recognition Functions

	Raw Score	SS	Percentile
Face Recognition	–	–	
BNT	55 Normal		

Construction Functions

	Raw Score	TS	Percentile
RCFT-Copy Phase	31		6–10
Block Design		53	62

Motor Functions: DID NOT ASSESS

This 57-year-old man with 13 years of formal schooling performed within the expected average psychometric range of intelligence. His abbreviated PIQ remains suspicious. With respect to the elements of attention, his initial registration of information was never better than the 36%ile ranking and this implies he was unable to initially register the same range of information as other people. On tasks of sustained attention, errors of omission were between the 25 and 38%ile implying he was not as alert or as vigilant as his peer group. On a task of attentional or cognitive shifting, he made no progress at all. Although elevated perseverative responses imply cognitive rigidity, difficulties were evident at the level of concept formation because it took him 118 cards to discover the first category. On Focus/Execute, speed of performance tasks, his performances were always slow indicating he had to concentrate very hard to perform these tasks despite their relative simplicity. Therefore, attention is affected within all dimensions.

Deficits in the executive functions of working memory and planning were also evident. For instance, he had significant difficulties with the Auditory Consonant Trigrams Task that required him to keep information in mind while performing some other cognitive activity. His performance on the TOL that required "think ahead" capacity was very poor, only at the 14th%ile ranking, while he made numerous pathognomonic rule violations. Since he clearly understood the requirements of the task, we consider these rule violations as a disturbance of intention. While response initiation time was averaged to fall at the 31st%ile ranking, an inspection of the data reveals that all but one problem consisted of a response time of 1–3 seconds. Therefore, he barely gave himself any time to think things through.

There were no indications of any language deficit in terms of naming and spontaneous word retrieval functions. The limited visual–perceptual–spatial functions that were assessed are intact. For example, his very solid copying of a complex figure implies visuospatial processing is intact, as does the respectable performance on the Matrix Reasoning subtest. His poor Block Design performance is likely attributable to problem-solving functions.

With respect to learning and memory functions, the acquisition of new information as assessed by the RAVLT was slow. By inspection, the learning slope was shallow. Free recall in delayed conditions was always poor, but recognition recall was well within the expected range, revealing good information retention but poor volitional access, implicating frontal–subcortical systems.

The point of this "blind" test interpretation is to demonstrate the lack of localization specificity of neuropsychological tests. These test results could easily be interpreted as a "frontal lobe" profile. However, this patient's actual pathology is within the basal ganglia. He had an infarct in the right globus pallidus and putamen. Both CT and MRI data revealed a well-defined lesion in these regions, with no edema, and no evidence of cortical involvement. Subcortical lesions generate cognitive impairment and on neuropsychological testing, the findings are indistinguishable from what is observed in patients with cortical lesions (Su, Chen, Kwan, Lin, & Guo, 2007). The patient was seen for evaluation because his primary symptoms were cognitive. He returned to work and was having difficulties in attending to detail and in keeping several things in mind at once. His test results provide clear support for these complaints, with pathology being very focal and localized to the right-sided basal ganglia.

Case 3

The following case is of a 66-year-old man who suffered a CVA 4 to 5 weeks before this neuropsychological evaluation. He has a high school education. He worked in a skilled occupation for 42 years. He has always enjoyed good health and he does not have a history of psychiatric treatment. He obtained the following scores on a battery of neuropsychological tests:

BG CASE 3 GENDER: M AGE: 66 EDUCATION: 12 HANDEDNESS: R

GLOBAL FUNCTIONING

WAIS-III	IQ/Index	Percentile
Verbal	84	14
Performance	85	16
Full Scale	84	14
Verb. Comp. Index	88	21
Percep. Reas. Index	88	21
Working Mem. Index	73	4
Proc. Speed Index	86	18

Verbal Subtests	Scale Score	Performance Subtests	Scale Score
Vocabulary	9	Picture Competition	7
Similarities	6	Coding	7
Arithmetic	8	Block Design	10

(continued)

Verbal Subtests	Scale Score	Performance Subtests	Scale Score
Digit Span	6	Matrix Reasoning	7
Comprehension		Picture Arrangement	
Information	8	Symbol Search	8
Letter-Number Seq.	3	Object Assembly	

ATTENTION DOMAIN

Encoding/Registration

	Raw Score	SD
CVLT Trial 1	02	–3
CVLT B	04	–1

Focus/Execute

	Scale Score	Standard Score	Percentile
Trail A		72	3
Trail B		67	1
WAIS Coding	7		
WAIS Symbol Search	8		

Sustain

GDS Vigilance Subtest (Adult Version)

Summary Data		Selection Position		Tracking Data
Total Correct	26	1	1	19X
Block 1	09	2	0	XX9
Omissions	01	3	3	XX1
Commissions	02	4	2	X1X
Block 2	08	5	0	X9X
Omissions	02	6	0	XXX
Commissions	02	7	34	Block 1 Latency
Block 3	09	8	34	Block 2 Latency
Omissions	01	9	43	Block 3 Latency
Commissions	02	0		

Overall	Number	Mean	SD	Percentile
Total Correct	26	29.5	.96	1
Commissions	06	.84	1.4	1
Omissions	04	–	–	

GDS Distractibility Subtest (Adult Version)

Summary Data		Selection Position		Tracking Data
Total Correct	13	1	0	19X
Block 1	05	2	0	XX9
Omissions	05	3	19	XX1

(continued)

Summary Data		Selection Position		Tracking Data
Commissions	15	4	12	X1X
Block 2	03	5	4	X9X
Omissions	07	6	8	XXX
Commissions	17	7	38	Block 1 Latency
Block 3	05	8	64	Block 2 Latency
Omissions	05	9	53	Block 3 Latency
Commissions	13	0		

Overall	Number	Mean	SD	Percentile
Total Correct	13	23.	6.0	1
Commissions	43	2	3.0	1
Omissions	17	–	–	1

Shifting
WCST

	Raw Score	SS	Percentile
Trials Administered	128	–	–
Total Correct	83	–	–
Total Errors	45	92	30
Perseverative Responses	37	88	21
Perseverative Errors	33	87	19
Non-perseverative Errors			
Categories Completed	05	–	>16
Trials to 1st completion	12	–	>16
Failure to Maintain Set	00	–	>16

LEARNING & MEMORY

WMS-III

Subtest	Percentile
Logical Memory I	14
Logical Memory II	1
Recognition	Raw 25/30

CVLT-2

Trials	Raw Score
Trial 1	02
Trial 2	04
Trial 3	05
Trial 4	04
Trial 5	05
List B	04
Short Delay Free Recall	0

(continued)

Trials	Raw Score
Short Delay Cued Recall	0
Long Delay Free Recall	0
Delayed Cued Recall	0
Intrusions	17
Repetitions	3
Recognition	8/16
False positive	18

LANGUAGE

Receptive-Comprehension

	Index Score	Percentile
WAIS VCI	88	21

Confrontational Naming

RBANS Object Naming	10/10

Rapid Naming

	T Score
Stroop Word Reading	30
Stroop Color Naming	25

Verbal Fluency

	Raw Score	Percentile
FAS	17	<10
Animals	17	50

EXECUTIVE FUNCTIONING

Planning

Tower of London	SS
Total Moves	114
Total Correct	98
Total Rule Violation	<60
Time Violation Score	108
Total Initiation time	86
Total Execution time	104
Total Problem Solving time	108

Inhibition

GDS	Raw Score	Percentile
Vigilance Commissions	6	1
Distract. Commissions	43	1

STROOP COLOR WORD	T Score
Stroop Word Reading	30
Stroop Color Naming	25
Interference	31

Working Memory

	Scale Score
Digit Span	6
LN Sequen.	3
Arithmetc	8

VISUAL–PERCEPTUAL–CONSTRUCTIONAL DOMAIN

	Raw Score	
JLO/RBANS	13/20	−1SD
Figure Copy RBANS	17/20	WNL
WAIS Block Design		Ss10

This patient functions within the low average psychometric range of intelligence as demonstrated by his WAIS-III IQ values. All index scores, with the exception of the WMI, are statistically comparable. Given the normal distribution of IQ scores within the general population, it is impossible to infer cognitive loss or decline from these limited data. However, the WMI of 73 is certainly significant, with obvious implications for executive cognitive and behavioral control. Nevertheless, the poor score itself does not localize the pathology. Deficits might be in either maintenance or updating functions, and the site of pathology can include cortex, basal ganglia, or for that matter, even the cerebellum (Chang, Crottaz-Herbette, & Menon, 2007; Gerton et al., 2004). In perusing the data altogether, the overall level of performance is extremely variable, characterized by good scores, adequate scores, and some very poor test performances.

Obvious deficits are noted with respect to this patient's initial registration or encoding of information. He was never able to perform anywhere near expected levels on any immediate recall subtest. His continuous performance test scores reveal that he is both inattentive and distractible, as suggested by both errors of omission and errors of commission. Although his discovery of five categories on the WCST reflects adequate performance in categorization in response to informational feedback, perseverative errors and responses are notably elevated. He is slow to shift the focus of his attention and thinking from one feature of the task to another, and as a result, one would predict that it is difficult for him to adjust to the changing demands of tasks as these develop or unfold. The focus/execute component of attention is very much

affected. On each and every task that required him to demonstrate perceptual discriminations by making a simple motor response, he performed slowly. It took him much more effort, concentration-or conscious cognitive control-than would be expected of others his age within the general population.

His response latency times on continuous performance tests were also variable, further revealing instability within his attentional system. Therefore, attention is affected within each and every dimension that was evaluated according to the Mirsky methodology (Duncan & Mirsky, 2004). His deficits in executive functioning are characterized by impairment in inhibitory processes, by working memory deficits, and by his inclination towards perseverative responding. His rule violations on the TOL are particularly revealing. Not only are his numerous rule violations (of moving two balls at the same time) pathognomonic of impairment by virtue of their occurrence, but his behavior during the administration of this task is significant. For example, he frequently verbalized the rules to himself as he was working on the task (while the task rules were repeated to him as well), implying that his "thoughts" were unable to guide his behavior, as if experiencing a disturbance in intention. Therefore, his "good" performance with respect to the accuracy of his solutions does not really reflect intact "planning" ability, even though his scores along this parameter are within the "average" to "high average" ranges, depending on whether one is considering the total move or total correct scores. The pattern of data reveals an impairment in self-control.

The data for language functioning do not reveal deficit upon object confrontation. There were no spontaneous word retrieval deficits when generating words semantically, by the way in which words are presumably naturally stored. However, retrieving words by starting letter was problematic. He was unable to be appropriately productive, with performance below the 10th PR, implicating involvement of anterior executive systems. Performances on visual–perceptual–spatial cognition tasks were mixed. Intact object naming implies intact ventral object identification pathways. Although his performance on a task judging the orientation of lines was poor, perhaps implying a deficit in spatial cognition, his unremarkable Block Design performance implies that his line judgment performance might have been affected by factors other than visuospatial ability.

There is no question about impaired learning and memory functions. His learning slope on a word list learning task is essentially flat. Free recall was poor, regardless of task (CVLT and WMS-LM), while recognition performance was always better. While WMS recognition was "clean," his intrusions and false positive errors in relation to word list learning suggests that his memory for newly presented information is unreliable.

Therefore, these test results reveal two very general areas of deficit. First, the results imply frontostriatal system involvement. Second, there is evidence of impairment in learning and memory. Although disturbances in memory, aside from deficits in retrieval, are not usually primary manifestations of basal ganglia pathology, the striatum has been described as demonstrating a functional

compartmentalization (Cervenka, Backman, Cselenyi, Halldin, & Farde, 2008). The limbic striatum, a region essential to reward processing, has been implicated in episodic memory function. Case studies of patients with lesions confined to the caudate include severe disorders of episodic, immediate, and longer-term memory functions for both verbal and visual–perceptual material (Benke, Delazer, Bartha, & Auer, 2003).

The issue of "blind diagnosis" is particularly difficult in this case. His CVA pathology actually consists of a very focal "stroke" or infarction of the right caudate nucleus. One would never be able to "pinpoint" that specific neuroanatomic area of involvement on the basis of this set of test results. In a traditional cortico-centric model of cognition, his memory disturbance would likely be interpreted as a manifestation of medial–temporal lobe pathology. The point here is that many neuropsychological tests are multifactorial in composition, which makes specific localization difficult. However, the loss of intention and accompanying need for verbalization while problem solving (TOL) represents a subtle suggestion of basal ganglia pathology, as the basal ganglia are so central to intention programming. The test data also underscore the multiply determined nature of working memory functions, while revealing the role of the basal ganglia in information maintenance in cortical working memory systems as well as in the inhibition of response to distracting influences.

Case 4

This is another case of basal ganglia pathology, this time within the left lentiform nucleus of a 71-year-old right-handed man. His test scores are listed in Case 4.

Case 4 GENDER: M AGE: 71 EDUCATION: 12
HANDEDNESS: R
GLOBAL FUNCTIONING

WASI

	IQ	Percentile
Verbal	108	70
Performance	94	34
Full Scale	101	53

Subtest	T Score	Scale Score
Vocabulary	58	12
Block Design	52	11
Similarities	53	11
Matrix Reasoning	41	7
WMS Digit Span		8

WAIS-III

	Scale Score
Coding	9
Symbol Search	11

ATTENTION

Registration/Encoding

	Raw Score	SS	
Digits Forwards	5–6		
CVLT Short Form Trial 1	2		–3 SD
WMS LM 1 Story A	3/25		
WMS LM 1 Story B	3/25		
WMS Faces 1	28/48	7	

Sustain

GDS Vigilance Subtest (Adult Version)

Summary Data		Selection Position		Tracking Data
Total Correct	15	1	1	19X
Block 1	08	2	0	XX9
Omissions	02	3	0	XX1
Commissions	01	4	0	X1X
Block 2	04	5	0	X9X
Omissions	06	6	0	XXX
Commissions	00	7	54	Block 1 Latency
Block 3	03	8	46	Block 2 Latency
Omissions	07	9	59	Block 3 Latency
Commissions	00	0		

Overall	Number	Mean	SD	Percentile
Total Correct	15	29.5	.96	<1
Commissions	01	.84	1.4	25
Omissions	15	–	–	

GDS Distractibility Subtest (Adult Version)

Summary Data		Selection Position		Tracking Data
Total Correct	02	1	0	19X
Block 1	01	2	0	XX9
Omissions	09	3	0	XX1
Commissions	00	4	0	X1X
Block 2	00	5	0	X9X
Omissions	10	6	0	XXX
Commissions	00	7	51	Block 1 Latency
Block 3	01	8	0	Block 2 Latency
Omissions	09	9	29	Block 3 Latency
Commissions	00	0		

Overall	Number	Mean	SD	Percentile
Total Correct	02	23.	6.0	<1
Commissions	0	2	3.0	100
Omissions	17	–	–	

Shifting

WCST	Raw Score	SS
Trials Administered	128	–
Total Correct	82	–
Total Errors	46	96
Perseverative Responses	26	100
Perseverative Errors	24	99
Non-perseverative Errors	22	89
Categories Completed	03	>16%
Trials to 1st completion	52	2–5%
Failure to Maintain Set	03	2–5%
Learning to Learn	–7.69	>16%

Focus/Execute

	Scale Score
DKEFS Visual Scanning	13
Number Sequencing	8
Letter Sequencing	6
Letter/Number Switch	6
WAIS Coding	9
Symbol Search	11

LANGUAGE DOMAIN

Receptive-Comprehension

Token Test—Short Form	Raw Score	Mean	Percentile	Significance
Total Score	43/44	43		Expected

Expressive Language

WASI	T score	Scale Score
Vocab	58	12
Similarities	53	11

Confrontational Naming

	Raw Score
BNT Short Form	11/15

Rapid Naming

D-KEFS CWI	Scale Score
Color Naming	6
Word Reading	7

Verbal Fluency

D-KEFS Verbal Fluency	Scale Score
Letter Fluency	6
Category Fluency	6

LEARNING & MEMORY

WMS-III	Raw Score	Scale Score
LM I	11 (A = 3/25;B1 = 3/25;B2 = 5/25)	2
LM II	2 (A = 1/25;B = 1/25)	3
Recognition	19/30 (6 false +)	
Faces I	28/48 (8 false +)	7
Faces II	31/48 (6 false +)	9

CVLT-2 Short Form	Raw Score	Standard Deviation
Trial 1	2	–3
Trial 2	3	–2
Trial 3	2	–3
Trial 4	5	–1.5
Trials 1–4 total	20	T 20
SD Free Recall	1	–2.5
LD Free Recall	0	–2
LD Cued Recall	1	–2.5
Recognition	5	–3
False Positive	1	0
Forced Choice	9/9	

Rey Complex Figure Test and Recognition

	Raw Score	T Score	Percentile
Copy	34	–	>16
Imm Recall	3.5	<20	<1
30 min Delay Recall	1	<20	<1
Recognition	14/24	<20	<1
False Positive	6/12		<1
False Negative	4/12		>16

EXECUTIVE FUNCTIONING

Working Memory

	Raw Score	Age Norms
Auditory Consonant Trigrams	Unable to complete	
Digits backward	3	

Planning

Tower of London	Standard Score
Total Moves	98
Total Correct	98
Total Rule Violation	<60
Time Violation Score	100
Total Initiation time	94
Total Execution time	94
Total Problem Solving time	96

Inhibition

	Scale Score	Standard Score
DKEFS CWI Inhibition	6	
TOL Rule Violations		<60
GDS Commissions 1/0		

Concept Formation

	Raw Score	Percentile
WCST Categories Completed	03	
Vocab T Score	T = 58	
Sim T Score	T = 53	

VISUAL–PERCEPTUAL–SPATIAL

	Raw Score	SS	Percentile
Benton JOLO	19/30		9
Block Design		11	
Matrix Reasoning		7	
RCFT Copy	34/36		>16

SENSORY AND MOTOR FUNCTIONS

	Raw Score (Total)	SS	Percentile
Finger Recognition			
Dom Hand	3 errors		19
Non-Dom Hand	3 errors		13
Grooved Peg Board			
Dom Hand	94” 3 drops	91	
Non-Dom Hand	88” 3 drops	100	

PERSONALITY FUNCTION
PAI
Uninterpretable due to Inconsistent Responding

Intellectual functioning is unremarkable. Once again, each and every element of attention is affected. His initial registration of information is clearly affected, and this extends to all modalities in which it was measured. He was quite inattentive on a vigilance task, making numerous errors of omission. Response latency times were also prolonged. In fact, these two factors may have combined to reduce the number of possible commission errors, since he responded slowly and infrequently. He was slow to acquire conceptual information on the WCST, although he was able to discover the task's primary categories. This is consistent with a role for the basal ganglia in reasoning (Melrose, Poulin, & Stern, 2007). His performances were variable on focus/execute tasks. Poor performances were observed on tasks requiring greater cognitive demand, such as in "sequencing" paradigms. Coding and Symbol Search are well retained. These results certainly speak to our view that "processing speed," or the speed with which various cognitive operations are performed, is not a unitary construct (see Chapter 9 for a discussion of processing speed).

Performances on other executive control tasks were also variable. Of particular note is the fact that his TOL performance is intact in terms of accuracy. This is consistent with the interpretation that this task is more dependent upon right than left hemisphere processes (Dagher, et al., 1999.) However, the most striking aspect of his functioning-which nullifies his TOL "accuracy" performance-concerns his numerous rule violations, again implying a disorder of intention programs since he clearly understood task requirements.

He was unable to perform productively on any spontaneous word fluency task, also implying frontal system involvement for general retrieval processes. Expressive language problems are suggested not only by poor fluency performances, but also by confrontation naming difficulties on the Boston Naming Test (BNT). He had no constructional deficits in copying a complex figure suggesting that fundamental visual–perceptual–spatial skills are intact.

The data give evidence of impairment in learning and memory functions. For instance, he performed quite poorly on the WMS Logical Memory subtest (Wechsler, 1997b). He made little progress on the short form of the CVLT-II (Delis et al., 2000). He acquired little information, but what he learned was retained. These results are also consistent with reported learning and memory deficits in patients with focal impairment of the basal ganglia (Benke et al., 2003). It has been demonstrated that focal infarction within the globus pallidus can present with inattention, decreased verbal fluency, and amnesia (Kim et al., 2008).

The patient was administered repeated MRI studies. None of these studies ever revealed cortical involvement. In fact, these studies specifically commented that the imaging data were not consistent with the MRI pattern often observed in Alzheimer's disease. Therefore, once again, regardless of region of lateralization, these data demonstrate that neuropsychological testing of patients with basal ganglia abnormality can mimic what is observed in primary cortical pathology.

Case 5

The next case of a 12-year-old right-handed boy is also approached for teaching purposes from the perspective of "blind diagnosis," without the benefit of history, to assist in developing skills for interpreting test data and recognizing its strengths and limitations.

Case 5 12 yo RH Male
ss = Scale Score SS = Standard Score T = T-score SD = Standard Deviation

INTELLECTUAL FUNCTIONG
Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV)

Verbal Comprehension	Perceptual Reasoning
Verbal Comprehension	SS 99
Perceptual Reasoning	SS 94
Working Memory	SS 97
Processing Speed	SS 103
Full Scale IQ	SS 97
Similarities ss 13	Block Design ss 8
Vocabulary ss 9	Pic Concepts ss 10
Comprehen ss 8	Mat. Reason. ss 9

Working Memory	Processing Speed
Digit Span ss 9	Coding ss 10
LN Sequen. ss 10	Sym.Srch ss 11

ATTENTION/CONCENTRATION

Initial Registration	
*WISC Digit Span forwards	longest = 5
*CVLT Trial 1	words 2
*CVLT List B	words 5

Focus-Execute	
*WISC Coding	ss 10
*WISC Symbol Search	ss 11
*NEPSY Auditory Attn & Response	ss 9
*NEPSY Visual Attention	ss 11
Shifting	
*WCST PSV Rsp 34	S 83
*WCST Errors 26	S 86
Sustaining	
*GDS Vigilance 39 Correct	7 percentile
Commissions 19	<1 percentile

MEMORY AND LEARNING

*CVLT	Raw Score	
List A Trial 1	2	
Trial 2	5	
Trial 3	5	
Trial 4	2	
Trial 5	12	
List B	5	
SD Free Recall	9	–.5 SD
SD Cued Recall	8	
LD Free Recall	8	
LD Cued Recall	8	–1 SD
Recall Perseverations	2	–1 SD
Free Recall Intrusions	0	
Cued Recall Intrusions	1	
Recognition	14/15	
False Positives	0	

EXECUTIVE FUNCTIONS

Planning / Conceptualization	
*Tower of London	
Total Move Score	SS 96
Total Correct	SS 90
Total Initiation Time	SS 92
Total Rule Violations	SS 72
Inhibition	
*NEPSY Knock and Tap	3–10th percentile
*NEPSY Statue	3–10th percentile
Shifting	
*WCST	
128 Trials 77 correct	
Total Errors 51	SS 85
PSV Rspns 34	SS 83
PSV Errors 26	SS 86
Categories 2	6–10 percentile
Trials to 1st	11–16 percentile
Set Failures 4	2–5 percentiles
Idea Generation	
*NEPSY Verbal Fluency	ss 10
Semantic	>75th percentile
Phonemic	11–25th percentile
*NEPSY Design Fluency	ss 12

(continued)

Working Memory	
*WISC Digit Span backward longest: 3	
*WISC LN Sequence	ss 11
LANGUAGE	
Comprehension	
*NEPSY Comprehension of Instructions	ss 5
Repetition	
*NEPSY Rep. Of Nonsense Words	ss 12
Phonological Awarenesss	
*NEPSY Phonological Processing	ss 9
*NEPSY Rep. Of Nonsense Words	ss 12
Naming	
*NEPSY Speeded Naming	ss 11
*NEPSY Verbal Fluency	ss 10
Semantic	>75th percentile
Phonemic	11–25th percentile
Sensorimotor	
*NEPSY Finger Discrimination R L	26–75th percentile 26–75th percentile
*NEPSY Fingertip Tapping	ss 9
*NEPSY Imitating Hand Positions	ss 5
*NEPSY Visuomotor Precision	ss 3
*NEPSY Manual Motor Sequences	3–10th percentiles
*NEPSY Oromotor Sequences	11–25th percentiles
Visual Perceptual/Visual Spatial	
*NEPSY Design Copy	ss 12
*NEPSY Arrows	ss 15
*NEPSY Block Construction	ss 5
*NEPSY Route Finding	26–75th percentiles
*WISC Block Design	ss 8
*WISC Matrix Reasoning	ss 9

This patient's level of performance is variable, characterized by good scores and some scores that are poorer than expected in comparison to normative standards. This patient's Wechsler scores are completely unremarkable from the point of view of composite quotients, while individual subtest performances cannot be analyzed without running the risk of over-interpretation. In many cases, Wechsler Intelligence Test data are not very informative with respect to identifying the integrity of brain-related cognitive processes.

In assessing the various elements of attention, the patient's initial registration of information was inclined to fluctuate. This inference was made on the basis of his variable performances on immediate recall measures. He did adequately on immediate recall language tasks, which present an inherent structure, but he fared poorly on immediate word list recall, presumably because of difficulties with self-organization and direction of attentional resources. His ability to shift attention from one thing to another is affected as measured by relatively elevated perseverative responses. Perseverative errors and responses do not follow a "normal distribution," in which case this patient's score at the 13th PR is very clearly problematic. The significant failures to maintain set also imply a notable distractibility about him. In this regard, problems with sustained attention were very clearly evident. On the continuous performance vigilance task, errors of omission at the 7th PR indicate that he often failed to identify or "missed" stimulus presentations. Errors of commission near the 1st PR demonstrate that he was unable to inhibit responding to distracting influences. A performance between the 3 and 10 PR was observed on the Knock and Tap subtest, and he performed at the same level on the Statue subtest, which indicates he had difficulties in inhibiting extraneous movements and even lower-level orienting responses.

Within the focus/execute dimension, the patient performed within normal limits with respect to the Coding and Symbol Search subtests. However, the NEPSY Auditory Attention and Response Set performance, features a commission error that technically falls within a "borderline" psychometric range. There is also a commission error on the "Cats" NEPSY Visual Attention cancellation subtest. Errors of commission on this subtest occur so rarely within this age range that the result is considered a pathognomonic sign of disinhibition. Therefore, this set of test results as they pertain to attention are characterized by variable performances that include pathognomonic signs of impairment (Mirsky & Duncan, 2004). The perseverative responses, the set failures, the problems with making appropriate attentional selections and the deficits in inhibitory control all point to pathological involvement of the frontostriatal system.

This involvement by definition would include deficits in other executive functions. The patient's planning skills seem unremarkable, as inferred from his performance on a task that required age-appropriate "think ahead" capability (Tower of London). However, this level of performance is misleading, as is often the case when applying level of performance as a single level of inference in isolation. The real issue concerns his rule violations, which essentially serve as an index of his disinhibition. Therefore, this youngster has great difficulty "not responding" to influences that compete with successful tasks completion. This was evident on multiple tasks, and in this way his test results identify his potential for distractibility in the extra-test situation. Working memory is also suspect as inferred from his performance on the NEPSY Comprehension of Instructions subtest. His inconsistency of functioning, with errors on "easy" items and successful execution of more difficult items implies that he sometimes forgot aspects of directions.

Receptive language functions appear intact, although this ability is confounded by inattention and/or inconsistency in working memory function. His solid ability to repeat non-words certainly argues against any fundamental deficit in speech sound discrimination. His WISC-IV Similarities subtest score implies that verbal semantic concept formation is intact. At the expressive level, he obviously had no difficulty in reproducing novel speech sounds as evidenced again by his strong performance in repeating non-words. His average Verbal Fluency scaled score again implies that expressive word finding is intact. However, once again, the pattern of performance is far more revealing than a composite index that can only be interpreted from a simple level of performance dimension. While semantic fluency was always very solid, phonemic or letter fluency was somewhat suspect. This suggests a difficulty with the self-organization of expressive language processes. Speeded Naming was solid, Phonological Processing was at least adequate, so that the test results did not immediately reveal risk factors for spelling and reading whole words in isolation.

Visual–perceptual–spatial information processing skills are intact. His error-free performance on a facial recognition subtest very clearly implies that ventral, object discrimination pathways are intact. His solid performances in judging the directionality of arrows and on the Route Finding location task imply that dorsal object location pathways are intact. Design Copy was another strong performance. However, as constructional tasks became more complex as in mosaic and three-dimensional block design, his performances quickly deteriorated. This pattern of performing well on visuospatial recognition tasks with declining performances on less structured constructional tasks implies involvement of frontal systems. Once again, the overall interpretation is based upon a layering of tasks which allows for test performance comparisons instead of viewing each test score in isolation and comparing to a simple population average. The pattern analysis approach which is advocated here provides information that is truly synergistic. The pattern of performances literally reveals something unique about the patient that a single test score in isolation cannot exhibit. In addition, this approach generates an integrated and comprehensive understanding of the patient, in contrast to a fragmented, loosely organized view that can often emerge from simple level of performance criteria.

When "memory" is very strictly, narrowly, and operationally defined as the ability to retain newly presented information with the passage of time, then this patient has no memory deficit. For example, on a memory for names subtest, the patient performed in an error-free manner in a delayed condition. His performance on the CVLT-C is just as revealing with respect to his correctly recognizing 14 of 15 stimulus words, performing at the same level as any other 12-year old. Similarly, his recognition performance was "clean," without any false positive responses. These test results obviously do not reveal any signs of forgetting whatsoever. He retained everything he learned. Therefore, according to these test results, the medial–temporal lobe, hippocampal declarative memory system is intact.

However, the process of learning is a much different matter and is an obvious area of concern for this patient. This is apparent from his pattern of performance on the CVLT-C. For the first four trials of the test, his learning slope was essentially flat, but with inconsistencies. On trial five, his learning slope skewed upward with his recall of 12 of 15 words. His short delay recall of nine was a half standard deviation below the mean and his long delay recall of eight was a full standard deviation below the average level. The process of "cueing" replies never produced more than eight responses. This is an important pattern. The data demonstrate that this youngster had notable difficulties in organizing the complex activity necessary for efficient learning, memorization, and recall. He had difficulties in imposing stimulus-based characteristics upon the material to facilitate acquisition. Free or voluntary retrieval was incomplete, and he needed a recognition paradigm because he was unable to independently access what he learned and retained. He had difficulties in organizing the material in a way that would facilitate conscious recollection. This learning and memory pattern implies involvement of anterior brain regions, specifically, the frontostriatal system. Once again, the pattern of performance generates this interpretation and not a comparison to group norms on any one summary score or index viewed in isolation.

The patient's solid performances across body sides on a task of finger discrimination argues against any fundamental sensory dysfunction that would be mediated by the somatosensory cortex. This suggests that the posterior sensory cortices are intact, while nothing in this data corresponds with localized dysfunction in the posterior contralateral hemispheres. He did not perform nearly as well in imitating novel hand positions. On this task, performance within the general population follows a skewed distribution, so this patient's performance of 19 out of 24 items converts to a summary score that falls approximately two standard deviations below the mean. The patient performed quickly, with one error of inattention on his non-dominant left hand, and dexterity issues were evident in his difficulties executing the last two complex items across body sides. This does not imply a "true" sensory deficit that would implicate somatosensory cortices.

Motor ability represents a deficit area. Fingertip tapping was unremarkable. However, visuomotor precision was quite poor, characterized by fast, inaccurate performances. These performances were a manifestation of poor inhibitory control. The tasks were started and executed very quickly, with time to completion always above the 75 PR. The patient never seemed to consider task difficulty level, and as a result, made numerous errors, technically falling between the 3 and 10 PR. This corresponds with sloppy pencil-and-paper work in the extra-test situation. Significant difficulties were observed with the patient's attempts at modeling and implementing new motor programs, with a summary performance between the 3 and 10 PR. Therefore, in analyzing the pattern of sensorimotor performances, the patient clearly had difficulties on the motor side of the equation. This is significant because it is consistent with the cognitive data which imply involvement of anterior or "frontal system" brain

regions. These results also illustrate the point that in pediatric populations, executive, higher-order control often mirrors the development of the motor control system.

All of the data in this case are entirely consistent. From the perspective of "blind diagnosis," considerable information about cognition and behavior can be gleaned from these test results. The data give evidence of attention/executive dysfunction as a manifestation of frontostriatal system involvement. Behavioral complaints actually include distractibility, interrupting and intruding upon others, and difficulty awaiting turns. He is described as having difficulties in staying on task, with trouble completing tasks and activities. All of these common complaints of attention deficit disorder are mediated by the frontostriatal system. It is interesting to observe that hyperactivity is not one of the presenting complaints. There are no current or historic complaints of motor over activity. Hyperactivity was not observed during the course of the evaluation.

Summary

This chapter applied assessment methods for evaluating the frontostriatal system. A systematic way of organizing test data was introduced. This interpretive methodology is composed of organizing test data according to functional domains, while considering results within the inferential methods of level of performance, test score pattern analysis, and pathognomonic, or specific signs of impairment. This methodology represents a powerful neuropsychological tool for identifying frontal system deficits, although the results do not necessarily allow for greater specificity of localization within frontal–subcortical circuitries. The emphasis in assessing the frontostriatal system is on cognitive performance. This is related to dorsolateral circuitry. However, certain methodologies for evaluating inhibitory control allow for the generation of hypotheses concerning more medial–frontostriatal functions.

The patient with frontal system dementia exhibited the most impairment on neuropsychological testing. The surprising feature of that patient's results was relatively intact working memory function. Two of the patients with basal ganglia infarct were more selectively impaired because certain aspects of problem-solving were relatively spared. However, disinhibition was always prominent and revealed disturbances in cognitive intention programs. The case of Attention Deficit Disorder was characterized by marked disinhibition and selective cognitive impairment, primarily evident in relation to learning new information but not with respect to impairment in retention. The cases serve to demonstrate that different types of pathology impose different types of character upon neuropsychological test data. However, from the perspective of "blind diagnosis," the type of cognitive impairment observed in test data is not differentiating with respect to specific pathology within the frontostriatal

system. For this reason, clinical evaluation, which incorporates test results, clinical presentation, and historical information, is likely to be the most diagnostically informative.

None of these test results reveal how the frontal system acquires procedures or routines. The test data in all these cases identify the cognitive features of the frontostriatal system as a "snapshot" of how it is functioning at the time. None of these test data identify how the frontostriatal system is learning. This is important. Most of the "tests" go through dorsolateral channels. Emphasis is thus placed on the dorsolateral "loop." The data do not provide information on how the system acquires procedures or how the system might assist in automating. At first glance, this point might not seem relevant in cases of frontal system dementia. However, it has been demonstrated that practice effects and lack of practice effects on neuropsychological tests are related to patient outcome. This has been illustrated in adults with mild cognitive impairment, in HIV+ patients, and in individuals with Huntington's disease (Duff et al., 2007). Those who demonstrate practice effects or "learning" might be in a better position to benefit from interventions. It has also been demonstrated that the dorsolateral loop is not mandatory for procedural learning (Schmidtke, Manner, Kaufmann, & Schmolck, 2002). This implies that assessing other circuitries or loops of the frontostriatal system would be useful in devising treatment techniques and perhaps in predicting outcome in patient populations with particular difficulties in learning certain adaptive or routine activities and procedures, including patients with developmental disorders such as AD(H)D.

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Chapter 11
The Cerebellum in Neuropsychological Testing

It is the quality rather than the quantity that matters.
Seneca

As we have seen, the cerebellum plays a role in a variety of cognitive processes. These domains include attention and executive functioning, speech and language, visuospatial functioning, and learning and memory, as discussed in Chapter 5 (Schmahmann, 2004). These functions are all routinely assessed in a standard neuropsychological assessment. The cerebro-cerebellar circuit is considered the neuroanatomic substrate subserving the cerebellum's participation in these functions (Schmahmann & Pandya, 1997). The cerebellum also plays a central role in classical conditioning, temporal processing, and procedural learning, but these functions are very seldom, if ever, addressed during the course of a traditional neuropsychological evaluation. As reviewed by Justus and Ivry, cerebellar involvement can readily be demonstrated in four general areas of cognition, namely, speech and language, temporal processing, implicit learning and memory, and visuospatial processing and attention (Justus & Ivry, 2001).

Clearly, cognitive functioning can be classified according to different domains and systems. In trying to identify the cerebellum's role in non-motor functions, perhaps the most important issue to understand is that the cerebellum receives projections from nearly every region of cortex (with the exception of projections from the inferior temporal lobes) while sending efferents back to the same cortical regions from which the afferent fibers originated. The cerebellum's projection system back to the cortex, via the thalamus, allows the cerebellum to influence activity in those regions from which it receives projections. Essentially, *the cerebellum plays an important role in deciding what information is and is not returned to cortex* (Andreasen & Pierson, 2008). Although the cerebellum is technically not an initial "processor" of the sensory and action selections of the brain, the cerebellum effects and in many ways regulates activity in other brain regions. This is at the heart of the cerebellar contribution to cognition, and for that matter, to emotional and personality functioning as well (see Chapter 5). For example,

L.F. Koziol, D.E. Budding, *Subcortical Structures and Cognition*,
DOI 10.1007/978-0-387-84868-6_11, © Springer Science+Business Media, LLC 2009

Catani and colleagues recently demonstrated that impairment in cerebellar output prevents the cerebral cortex from receiving the cerebellar feedback necessary for adaptive social behavior (Catani et al., 2008).

The human brain functions as a system (Hatta et al., 2004). This system consists of the cortex, the basal ganglia, and the cerebellum. As discussed in the previous chapters, this has very significant implications for clinical neuropsychological testing, especially when the evaluation is reduced to a simple level of performance interpretive approach. In this very basic approach, a subject's performance is compared to a normative or population standard. A poor level of performance can never identify the reason for that performance. A poor or suboptimal performance by itself can never identify whether the affected brain region that generates the performance is cortical or subcortical. Even in cases where there is very focal involvement of the cerebellum, a modular deficit in cognition can never be attributed to specific involvement of the cerebellum based upon neuropsychological testing alone when interpreted in isolation. Cognitive tests are simply not that sensitive to specific brain region (Hirata, Tanaka, Zeng, Hozumi, & Arai, 2006).

In the previous chapter, we attended to qualitative features of the test data as related to the basal's ganglia's role in intention programs, such as in the interpretation of rule violations. We also stressed "blind diagnosis" in order to illustrate the limitations of purely numeric and statistical approaches to test data interpretation. This chapter builds on that approach. However, in this chapter we include the interpretation of the actual quality of the patient's verbatim responses in order to illustrate how these replies modify the interpretation of test results. We also include historic information (particularly in Case 4) to illustrate how this material can be used as an interpretive framework.

Clinical Case Examples

As with the previous chapter, cases will be presented using the systematic approach described in the beginning of Chapter 10. The following cases feature data from children, adolescents, and adults. Again, we use a flexible battery approach. See the previous chapter for a list of the tests used.

Case 1

The following set of test results were obtained from an 8-year-old boy with the differential diagnostic question of high-functioning Autism versus Asperger's disorder, two conditions in which the cerebellum has been thought to play a role.

Case 1 8.9 yo RH Male

ss = Scale Score SS = Standard Score T = T-score SD = Standard Deviation

INTELLECTUAL FUNCTIONG

Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV)

Verbal Comprehension	SS 112
Perceptual Reasoning	SS 115
Working Memory	SS 94
Processing Speed	SS 97
Full Scale IQ	SS 108

Verbal Comprehension	**Perceptual Reasoning**
Similarities ss 14	Block Design ss 13
Vocabulary ss 12	Pic Concepts ss 7
Comprehen ss 11	Mat. Reason. ss 17
(Information) ss	(Pic Complet.) ss
Working Memory	**Processing Speed**
Digit Span ss 9	Coding ss 7
LN Sequen. ss 9	Sym.Srch ss 12

ATTENTION/CONCENTRATION

Initial Registration

***WISC Digit Span forwards**	longest = 5	
***CVLT Trial 1**	words 5	–.5 SD
***CVLT List B**	words 7	1 SD

FOCUS-EXECUTE

***WISC Coding**	ss 7
***WISC Symbol Search**	ss 12
***NEPSY Auditory Attn & Response**	ss 11
***NEPSY Visual Attention**	ss 10

MEMORY AND LEARNING

***CVLT**

List A Trial 1	5	–.5 SD
Trial 2	8	
Trial 3	12	
Trial 4	12	
Trial 5	13	1.5 SD
List B	7	1 SD
SD Free Recall	8	0 SD
SD Cued Recall	11	1 SD
LD Free Recall	11	1 SD
LD Cued Recall	11	1 SD
Recognition	14/15 (shorts)	
False Positives	0	

EXECUTIVE FUNCTIONS

Planning / Conceptualization

***Tower of London**

Total Move Score	SS 66
Total Initiation Time	SS 86
Total Execution Time	SS 74
Total Problem-Solving Time	SS 76

Inhibition

***NEPSY Knock and Tap**	11–25th percentile
***NEPSY Statue**	11–25th percentile

Shifting

Idea Generation

***NEPSY Verbal Fluency**	ss 12
Semantic	>75th percentile
Phonemic	<2nd percentile
***NEPSY Design Fluency**	ss 9

Working Memory

***WISC Digit Span** backward longest: 3

***WISC LN Sequence**	ss 9

LANGUAGE

Comprehension

***NEPSY Comprehension of Instructions**	ss 14

Repetition

***NEPSY Rep. Of Nonsense Words**	ss 11

Phonological Awarenesss

***NEPSY Phonological Processing**	ss 9
***NEPSY Rep. Of Nonsense Words**	ss 11

Naming

***NEPSY Speeded Naming**	ss 12
***NEPSY Verbal Fluency**	ss 12
Semantic	>75th percentile
Phonemic	<2nd percentile

SENSORIMOTOR

***NEPSY Finger Discrimination**	R 17/18	26–75th percentile
	L 17/18	26–75th percentile
***NEPSY Fingertip Tapping**		ss 11
***NEPSY Imitating Hand Positions**		ss 8
***NEPSY Visuomotor Precision**		ss 11
***NEPSY Manual Motor Sequences**		3–10th percentile

VISUAL PERCEPTUAL/VISUAL SPATIAL

***NEPSY Design Copy**	ss 9
***NEPSY Arrows**	ss 9
***NEPSY Block Construction**	ss 10
***NEPSY Route Finding**	26–75th percentiles
***WISC Block Design**	ss 13
***WISC Matrix Reasoning**	ss 17

A simple level of performance approach to analyzing these test results is not very informative with respect to any possible localizing significance. To begin with, the WISC-IV index scores demonstrate solidly developed verbal skills as measured by this instrument, and there are no indications of problem-solving deficits on the Perceptual Reasoning Index. The peculiar Picture Concepts scaled score is impossible to interpret because the subtest composition is multifactorial. On the face of it, by quick glance, this looks like a capable child.

The Working Memory Index and Processing Speed Index are unremarkable when considered from a strict level of performance viewpoint. However, in terms of pattern analysis, these index scores might be considered suspicious. These index scores are lower than the very solid range verbal and perceptual reasoning scores. The issue becomes whether or not someone with "high average" intelligence as measured by VCI and PRI index scores should have better working memory and "speed" functions as assessed by WISC-IV. This issue has not been systematically studied, but an argument can be made that performances in this case are not as strong as they should be (Denckla, 1996). Scaled score comparisons are not very revealing. It is impossible to confidently interpret the significance of Coding versus a much higher Symbol Search performance. The suggestion is that a working memory factor contributes to the differential in scores. However, against "working memory" scaled scores of 9 on both Digit Span and Letter-number Sequencing, there is really no clinically persuasive interpretation about pathology or its possible locus to be found in this data. Perhaps the most that can be said about the WISC-IV profile is that the Coding subtest, which is objectively very sensitive to cognitive pathology, is certainly well within a range that is suggestive of cognitive difficulty in extra-test situations. To our way of thinking, this implies an executive control difficulty (see Chapter 9.)

At first glance, the NEPSY Language profile looks unremarkable. However, once again, a simple level of performance or "achievement" approach proves inferior to pattern analysis in this regard. The Verbal Fluency scaled score is deceiving. This child performed at around the 75 PR on semantic or categorical fluency but below the 2 PR on Letter/Phonemic Fluency, despite a VCI of 112 with a Vocabulary scaled score performance of 12. Once again, the category-letter fluency comparison generates a synergistic interpretation, which implies anterior brain involvement. The differential of good categorical fluency versus poor letter fluency implies a deficit with the anterior localized functions of strategy generation. This youngster could not "figure out" how to be productive when required to retrieve words by using a strategy other than the way

words are semantically stored or retained. This pattern clearly implies involvement of the frontostriatal system, and perhaps even more specifically, the left hemisphere dorsolateral–prefrontal cortex.

However, the problem for neuropsychological interpretation is that people with focal involvement of the right posterior–inferior cerebellar hemisphere can demonstrate the same pattern of differential performance on word retrieval tasks (Justus & Ivry, 2001). It is hypothesized that a dysfunction within the right posterior cerebellum results in inadequate regulation of neuronal activity within the left hemisphere prefrontal cortex, as manifest by decreased productivity on the letter fluency task. In this regard, the interpretive level of pattern analysis might "get us in the ballpark" of the underlying pathology, but we are still stuck with data that can be interpreted in two ways, that is, a primary deficit within the frontostriatal system versus inadequate prefrontal regulation by the cerebellum. Perhaps this is the best neuropsychology can do with these types of traditional tests. The "executive" language deficit can be identified, but its neuroanatomic localization is elusive. If behavior is really a manifestation of brain networks, then we cannot identify a multiple component network on the basis of one or two test scores.

The NEPSY Attention/Executive domain looks quite unremarkable, with the exception of performance on the Statue and Knock and Tap subtests. Many clinicians might interpret these performances as "borderline" and equivocal because they are within the 11–25 PR range. However, performances on these tasks follow a dichotomous, skewed distribution and not a "bell-shaped" curve, and from a clinical (in contrast to a statistical) point of view, there is really nothing "borderline" about them. These performances reflect inhibitory deficits. This youngster has difficulties in "not responding" to competing or distracting influences. The performance on the Statue subtest implies disinhibition of orienting responses, suggesting involvement of lower level systems, specifically basal ganglia–subcortical circuitry (see Chapter 2). The Knock and Tap performance implies involvement of the frontostriatal system. Therefore, the basal ganglia represent the interface of these two systems. Interpretations of this nature require examiners to be aware of subtleties. Given the popularity of standard scores in level of performance interpretations, it is very tempting to minimize the significance of these findings. In this case, treating these scores as if they were normally distributed would generate a misleading false negative interpretation. Instead, these results need to be interpreted in terms of a pathognomonic sign approach. Performances on these tasks fall into a "have–have-not" skill set category.

These functions comprise an aspect of frontostriatal control networks that develop from childhood to mid-adulthood (Rubia et al., 2006). The significance of these findings concerns their relationship to a lack of cognitive control that can generate distractibility. These data imply a deficit within frontostriatal gating mechanisms. After pre-setting motor control systems with task instructions, this youngster is having difficulty adjusting to sensory input as it arrives in the present (Denckla & Reiss, 1997). These results reveal a deficit within the

inhibitory component of attentional focus and control. In an extra-test situation, these findings would be expected to correlate with complaints such as distractibility, and having difficulties in staying on task when required to work independently.

Although the Knock and Tap test performance has an element of timing and might reflect involvement of the cerebellum, the lack of suppression to orienting stimuli on the Statue subtest implies a problem in selection processes under the mediation of the basal ganglia, which interfaces the frontal–basal ganglia and basal ganglia–subcortical motor systems. Nevertheless, it has been suggested that the cerebellum plays an important role in releasing behaviors with the appropriate timing for the situational context (Hirata et al., 2006). Dysfunction of the cerebellum has been associated with an impairment of the inhibitory system. For example, while cerebellar abnormality contributes to frontal dysfunction, a neuropsychological study has suggested that this dysfunction is characterized by impairment within an inhibitory system under the mediation of frontal-cerebellar circuitry (Tanaka, Harada, Arai, & Hirata, 2003).

The Tower of London level of performance is quite poor concerning accuracy of solutions. He clearly had difficulties when the task required "age-appropriate" think ahead planning ability relative to the 7–8 year-old reference group. Much of this difficulty was associated with premature responding, since response initiation time was only at the 18 PR. The hasty initiation of solutions resulted in essentially "trial-and-error" responding, which required an increased number of moves to solve the problems, which in turn generated increased execution and total problem-solving time. Therefore, these test results leave little question concerning "executive" deficits, while disinhibition appears to represent the primary area of executive difficulty. What remains open to question concerns the specific anatomic locus of the deficit. These test results can be described in cognitive and behavioral terms, but not in anatomic terms.

The Visuospatial Processing data are completely unremarkable. These data would indicate that the ventral and dorsal, or the "what" and "where" information processing pathways are both intact. Solid Block Construction (NEPSY)/Design (WISC) scores certainly reveal an absence of constructional deficits.

As measured by the CVLT-C, the mechanisms that support learning and its persistence in memory are intact. There was no difficulty in expanding upon initial recall capacity, with the expected incremental learning slope, and information was retained very nicely in delayed conditions, after the passage of a 20–25-minute interval. There were certainly no signs of medial temporal lobe dysfunction in these aspects of the test data. It has been argued that this type of performance implies intact cortical function in pediatric populations (Nicolson & Fawcett, 2006, 2007).

With respect to sensory functioning, the performances on the Finger Discrimination subtest were solid and identical across body sides, implying a lack of basic sensory processing deficits for tactile information. These findings, coupled with the above listed language, visuospatial, and even memory

performances, imply that posterior hemispheric processes are intact. Therefore, an integration of findings across different domains implies an absence of "posterior" pathology while implicating "anterior system" involvement, although once again, it remains possible that cerebellar regions contribute to the deficit pattern by returning "defective" information to the cortex through selective cerebrocerebellar circuits. The performance in imitating hand positions is not at all pathological, since only the most difficult stimulus presentations were missed, while the reason for mistakes according to behavioral observation concerned a lack of finger dexterity. In view of the data described below, it is parsimonious to attribute this to a motor issue.

Motor functioning is noteworthy. Finger tapping was well within normal limits for both NEPSY repetitions and sequences. Visuomotor Precision was technically within expectation. However, from an observational standpoint, the patient gripped the pencil very awkwardly. He held the pencil in a manner so that it touched all fingertips, with his thumb pressing the pencil against his fingertips, so that this grip required him to control the pencil with whole arm movements. Thus, if a child has appropriate neatness as measured by a visuomotor precision sample, does this negate the possibility of motoric difficulty based upon the nature of the pencil grip? The awkward grip is actually a potential "window" to the notion that this youngster experienced developmental motor problems. Motoric difficulties were clearly evident on motor programming tasks. The early NEPSY items were completed easily, with the exception of increased speed, force, and frequent rate changes. Subsequent items revealed programming difficulties as well as the continuing rate and force issues. The NEPSY interpretation manual has not systematically examined whether or not disturbances in rate, rhythm, and force on this subtest are characteristics of cerebellar or any other particular developmental involvement. However, from a theoretical point of view, a cerebellar contribution could very easily be responsible for the ultimate generation of all of the issues that emerged during the course of novel motor programming.

In the above interpretation of the data, not only level of performance or achievement was analyzed, but also performance patterns and pathognomonic signs. The significant interpretations about brain–behavior relationships were generated mostly by the pattern analysis and specific sign approaches. However, the interpretation does not end here. Throughout the course of an evaluation, the patient behaves. These behaviors are generated by brain systems, and as such, observations and information about the quality of responses provide informative data. Tests themselves provide quantitative data, but this does not negate the importance of response quality. In fact, in "going by the numbers" alone, the WISC-IV results are misleading. This is because the quality of this child's responses was extremely informative from a clinical point of view and this could never be captured by raw score or scaled score numbers in isolation. As has been pointed out by Lezak (2004), formal test scores might be viewed as a "skeleton," while the actual responses might be viewed as the "flesh."

Reviewing this child's "raw data" responses reveal that the WISC VCI is misleading, since this youngster's verbalizations were anything but "high average." For example, in stating how a lion and a tiger were similar, this child stated, "both are types of living things, but a tiger is like a cat, but bigger, and a lion has more hair, but both can eat you." In stating how a saw and a hammer are alike, he said, "both are tools that you use and they're different because a saw is for making wood smaller and a hammer is for putting a nail in wood." In fact, even after being told earlier in the subtest to reply with similarities only and not differences, he was compelled to state differences for most of his Similarities subtest responses. In stating how an hour and week are alike, he responded, "because there is a type of time where hours makes days and days make weeks, and they're different because an hour can be short and a week is long." (These simulated Similarities items were obtained from the Psychological Corporation and are reproduced with permission following the quality of his actual responses) (Wechsler, 2003a).

His definitions of vocabulary words were equally revealing. For example, in defining the word "cat," he stated, "an animal or pet that lives in your house and everyone plays with, if you're not allergic to cats, and it is also a pet that can stay inside or go outside." In defining the word "chief," he replied, "a person that is a leader, also known as a leader of a tribe for Indians or a president of a country for people, then there are good ones and bad ones . . ." and the remainder of the prolific answer could not be recorded because he spoke more quickly than the examiner could write. He defined the word "cave" as, "a type of place that is below the ground, which includes tunnels, caverns, and there are some big underground holes and some small ones," and again, the entire reply could not be recorded because the patient spoke too rapidly (Simulated Vocabulary subtest items were obtained from the Psychological Corporation, reprinted with permission, 2003).

Qualitatively, these responses feature a tendency to overshoot the "target." Although aspects of the responses reflect verbal disinhibition, this disinhibition demonstrates a particular quality of circumstantially going around the response, undershooting and overshooting, as if exhibiting the verbal equivalent of "intention tremor" or cognitive dysmetria (Andreasen, Paradiso, & O'Leary, 1998; Andreasen et al., 1999).

From the standpoint of theory, these responses might imply right hemisphere cerebellar involvement, particularly within the posterior, inferior region. Involvement of this type would affect executive and expressive language functions. Even if it were argued that whatever generated these test results was purely cortical in etiology, there would be no disputing that the quality of these replies is far from what would be expected in relation to "high average" verbal ability, and in this regard, response scores and response quality represent two different diagnostic dimensions. "High average" VCI scores might ordinarily imply potential for academic achievement. However, in this case, the executive dysfunction evident in the response quality implies the potential for social, communicative, and, therefore, academic difficulty that would never be seen

or predicted by numeric scores alone. All of the pertinent diagnostic data in this case point to executive function deficits, the understanding of which is enriched by taking a "brain systems" point of view.

Case 2

Interpreting test results of cases with known cerebellar pathology in the left posterior hemisphere takes on its own character, including a limitation on the degree to which qualitative aspects of responses can be utilized. This is because involvement of the left cerebellar hemisphere may not generate linguistic deficits, thus limiting the population of responses open to qualitative interpretation (see Chapter 5 for a review of the cerebellar contribution to language and visuospatial functions). If anything, the following patient's verbal responses were typically very brief, but of sufficient productivity to answer the referral questions that were asked. Consider the profile of this 43-year-old female who experienced a left hemisphere cerebellar stroke approximately 5 years prior to this evaluation.

CB CASE 2 GENDER: F AGE: 43 EDUCATION: GED HANDEDNESS: R

GLOBAL FUNCTIONING

WAIS-III

	IQ/Index	Percentile
Verbal	105	63
Performance	85	16
Full Scale	97	42
Verb. Comp. Index	116	86
Percep. Reas. Index	89	23
Working Mem. Index	92	30
Proc. Speed Index	76	5

Subtests

Verbal Subtests	Scale Score	Performance Subtests	Scale Score
Vocabulary	15	Picture Competition	9
Similarities	14	Coding	6
Arithmetic	7	Block Design	8
Digit Span	9	Matrix Reasoning	8
Comprehension	NA	Picture Arrangement	NA
Information	10	Symbol Search	5
Letter-Number Seq.	10		

ATTENTION DOMAIN

Encoding/Registration

	Raw Score	Mean	SD
CVLT Trial 1	05		–1.5
CVLT B	02		–2
Digit Span Forward	5 digits		

Focus/Execute

	Scale Score	Standard Score	Percentile
Trails A		<55	<1
Trails B		70	2
WAIS Coding	6		
WAIS Symbol Search	5		

Sustain

GDS Vigilance Subtest (Adult Version)

Summary Data		Selection Position		Tracking Data
Total Correct	22	1	4	19X
Block 1	08	2	0	XX9
Omissions	02	3	0	XX1
Commissions	01	4	0	X1X
Block 2	07	5	0	X9X
Omissions	03	6	0	XXX
Commissions	01	7	97	Block 1 Latency
Block 3	07	8	87	Block 2 Latency
Omissions	03	9	82	Block 3 Latency
Commissions	02	0		

Overall	Number	Mean	SD	Percentile
Total Correct	22	29.7	.52	
Commissions	04	.72	1.5	
Omissions	08	–	–	

GDS Distractibility Subtest (Adult Version)

Summary Data		Selection Position		Tracking Data
Total Correct	02	1	1	19X
Block 1	00	2	0	XX9
Omissions	10	3	0	XX1
Commissions	00	4	2	X1X
Block 2	00	5	4	X9X
Omissions	10	6	4	XXX
Commissions	00	7	0	Block 1 Latency
Block 3	02	8	0	Block 2 Latency
Omissions	08	9	22	Block 3 Latency
Commissions	11	0	42	

Overall	Number	Mean	SD	Percentile
Total Correct	02	26.45	4.5	
Commissions	11	2	2.94	
Omissions	28	–	–	

Shifting

WCST	Raw Score	SS	Percentile
Discontinued after 64 cards			
No categories obtained			
"Can't figure it out"			

LEARNING & MEMORY DOMAIN

WMS-III

Subtest	Scale Score
Logical Memory I	10
Logical Memory II	12
Recognition	Raw 25/30

CVLT-2

Trials	Raw Score	SD
Trial 1	05	–1.5
Trial 2	10	0
Trial 3	09	–1.5
Trial 4	11	–1
Trial 5	09	–2
Trial B	02	–2
Immediate Free Recall	08	–1.5
Immediate Cued Recall	13	0
Delayed Free Recall	07	–2.5
Delayed Cued Recall	07	–3
Trial I–V Total	44	T 38
Recognition	10/16	–5
False positive	1	

Rey Complex Figure Test

	Raw Score	T Score	Percentile
Copy	15	–	<1
Imm Recall	10	–	<1
30 min Delay Recall	12	–	<1
Recognition			14

LANGUAGE DOMAIN

Receptive-Comprehension

	Index Score	Percentile
WAIS VCI	116	86

Expressive Language

Confrontational Naming

Boston Naming Test-2	
# **Total Correct**	**57/60**
# of Stimulus cues given	02
# correct after cue	02
# phonemic cues given	00
# correct after cue	00
# multiple choice	00

Rapid Naming

	T Score
Stroop Color Naming	25
Stroop Word Reading	24

Verbal Fluency

	Raw Score	Percentile
FAS	36	30th
Animals	15	10th

EXECUTIVE FUNCTIONING

Planning

Tower of London	SS
Total Moves	72
Total Correct	82
Total Rule Violation	104
Time Violation Score	108
Total Initiation time	104
Total Execution time	84
Total Problem Solving time	84

Inhibition

GDS Delay Task	Score	Percentile
Total ER	.72	11
Total Responses	74	
Total Correct	54	

Stroop Color Word	T Score
Stroop Color Naming	25
Stroop Word Reading	24
Interference	48

Working Memory: Auditory Consonant Trigrams

Delay	Raw Score	Age Norms
0:0	15	
09 sec	9	12 SD 2.5
18 sec	1	10.5 SD 3.11
36 sec	4	9.9 SD 3.04

VISUAL—SPATIAL DOMAIN

	Raw Score	ss	Percentile
Judgment of Line	13/20	–	
WAIS BD		8	
RCFT Copy			<1
WAIS MR		8	

Motor Functions: DID NOT ASSESS

The Full Scale IQ value of 97, within the average range, is consistent with expectation in view of her completing 3.5 years of high school (and GED) and 2 years of community college. Her Verbal Comprehension Index (VCI) is considerably stronger than her Perceptual Organization Index (POI). This type of disparity has historically been considered a measure of left cerebral hemisphere versus right cerebral hemisphere information processing differences in some interpretative models. However, it seems more appropriate here to consider the POI as an index of problem-solving requiring an individual to contend with novelty, while both right and left hemisphere information processing strategies are necessary for successful performance (Milberg, Hebben, & Kaplan, 1996). The WMI is relatively low, while the PSI of only 76 identifies an obvious concern. This index predicts cognitive difficulty in the extra-test situation although as we have noted, this index has never been directly tied to a specific anatomic locus.

With respect to attentional functions, her initial registration of information as described in the model of attention proposed by Mirsky is variable at best (Mirsky, 1996). Immediate recall on the LM subtest was average, but all other

performances within this dimension of attention were 1–2 standard deviations below the mean. Therefore, the conclusion is offered that this individual does not typically "take in" or register the same range of information as other people within the general population. Further, verbal working memory as measured by the ACT clearly indicates she is unable to keep information in mind while directing her attention and thinking to something else. The ACT required her to keep consonants in mind while counting backwards by three's for a certain length of time, then required her to recall the consonants. Her very poor performance indicates she often forgot the status of the original information. Therefore, attention-related functions are affected within a mnemonic dimension (which extends to include verbal working memory). Encoding, maintenance, and updating functions all appear to be affected.

This patient also demonstrated difficulties with the functions of sustained attention. Her performances were consistently well below expected levels concerning errors of omission. This essentially means she had difficulties with stimulus selection, since she often failed to identify stimulus presentations. Errors of commission were also significantly elevated, which means she had difficulty "not responding" to competing influences. Therefore, she can be considered distractible in relation to this apparent deficit within the inhibitory component of attentional focus and control. Response latency or reaction times were also very prolonged. In all, these results imply considerable instability within her attentional system.

The Mirsky model of attention considers WAIS-type "processing speed" tasks within a dimension of attention labeled "focus/execute." This individual performed very slowly on every test that this model considers to be contained within that dimension. Digit Symbol, Trailmaking, the Stroop CW test, as well as Symbol Search all feature very slow performances. Therefore, from our perspective, these tasks generated "cognitive control" episodes, and this patient adjusts very slowly to novel tasks requiring higher-order control. She has to concentrate and put forth much more conscious cognitive effort than others (see Chapters 9 and 10). She does not easily focus upon and execute these types of novel tasks. The Mirsky model element of "shifting" attention could not be evaluated because the patient had such conceptual difficulty with the task used to measure this function. Therefore, this patient performed poorly within every dimension of attention considered by this model.

The patient performed very poorly in problem-solving. The WCST was discontinued after the first set of 64 cards because she was unable to discover any categories for sorting. The Tower of London test performance was quite poor, with a total move standard score of 72, at the 3rd PR. Therefore, she had obvious difficulties when the task required think ahead capacity.

Although verbal ability was not systematically evaluated, she performed at an average level upon object confrontation naming. Her performance on categorical, or animal, naming was near the 10th PR, and letter/phonemic fluency was measured between the 20 and 30 PR. These findings are obviously below expectation and take on particular significance when viewed in comparison to

her solid WAIS verbal scores. This pattern implies a difficulty with verbal self-generation, and this is actually correlated with her lack of spontaneity and brief verbalizations observed during the course of the evaluation.

With respect to visual–perceptual–spatial functions, her level of performance was approximately 1 standard deviation below the mean on a judgment of line orientation task. Her performance on the Rey Complex Figure was very poor in all phases. These findings are consistent with what has been described by Schmahmann in reference to the cerebellar cognitive affective syndrome (Schmahmann, 2004).

Verbal learning and memory were also affected. On the CVLT-II, the patient performed well over a standard deviation below the mean on the immediate recall trial, and she had obvious difficulty expanding upon immediate recall capacity. Her learning "slope" was characterized by her recalling words inconsistently from one trial to the next, while she did not acquire as much information as would others her age. Delayed free recall was poor, and miminal improvement was observed within a recognition paradigm. She did not necessarily "forget" what she learned, but she had difficulty with retrieval and contaminated her recall with many intrusion responses. On the other hand, she performed well on the language structured WMS LM test, with scaled scores of 10 and 12 in immediate and delayed conditions respectively. These learning and memory test results do not give evidence of an anterograde amnesia, but indicate that learning is slow and inefficient, particularly when defined in terms of those acquisition conditions where she is left to her own organizational resources. The pattern implies the involvement of anterior brain systems. However, the patient has no known cortical lesions. The only abnormality noted was a left hemisphere cerebellar "stroke" secondary to dissection of the left vertebral artery.

This patient's test results are characterized by three primary areas of deficit. First, there is evidence of notable frontostriatal system impairment. This is evident in poor WCST and TOL performance, very poor performance on tasks of sustained attention (continuous performance test paradigms), as well as deficits in complex working memory functions. Word fluency deficits also imply difficulties with appropriate productivity in self-generated behaviors. Therefore, these results reveal executive function disorder. Second, the results document impairment in visual–constructional skills. This is primarily evident in the very poor performance in the copying of the Rey Complex Figure. This conclusion is further supported by the relatively poor Block Design score. Third, there is evidence of difficulty with the acquisition and recollection of new verbal information, primarily when input from the frontostriatal system is involved, as suggested by the differential performances between CVLT-II and LM from the WMS-II.

Therefore, these results reveal multiple systems involvement. The patient does not demonstrate strictly lateralized test findings. However, while the TOL has been demonstrated to be more sensitive to right hemisphere lesions, many studies have failed to demonstrate lateralized deficits on the WCST in patients with frontal lobe lesions (Podell, Lovell, & Goldberg, 2001). Similarly, patients with medial–frontal lobe involvement have been described as exhibiting

moderate deficits on verbal fluency tasks, regardless of side of hemispheric involvement (Lezak et al., 2004). While frontal systems play an important role in strategic memory processes, patients with frontal lobe involvement have been observed to demonstrate elevated intrusion responses on word list learning (Baldo, Delis, Kramer, & Shimamura, 2002). Therefore, it is tempting to explain these test results on the basis of disruption in cerebro-cerebellar circuitry, particularly between the left cerebellar hemisphere and the right cerebral hemisphere as a manifestation of a damaged left posterior cerebellum.

However, it is clear that the neuropsychological test results are not persuasive in localizing the region of pathology in this patient. One recent study found cognitive impairment primarily in patients with right cerebellar hemisphere infarct (Kalashnikova, Zueva, Pugacheva, & Korsakova, 2005). Others have also reported a tendency towards lateralized findings although descriptions of lateralized deficits on neuropsychological testing were not necessarily clear-cut (Schmahmann, 2004; Schmahmann & Sherman, 1998). When interpreting these test results blindly, in the absence of data from external sources, the test data do not "stand alone" as a localizer in differentiating frontal from subcortical, cerebellar pathology. Again, the results need to be described in cognitive and behavioral terms, rather than in anatomic terms. Disturbances within specific functional zones of the cerebellum can generate neuropsychological test results that mimic the findings observed in patients with primary cortical involvement.

Case 3

The following 13-year-old right-handed male carries three behaviorally defined diagnoses, namely, ADHD, OCD, and Bipolar disorder. He has been treated with a variety of psychiatric medicines over the years. Improvement has always been minimal. After he experienced several episodes of extreme lethargy, he was given an MRI and was found to have a Chiari I malformation affecting the right cerebellar tonsil as well as a posterior fossa arachnoid cyst, without significant mass effect upon the adjacent cerebellum. He experiences a range of ADHD symptoms, notable contamination fears, and severe mood swings. He obtained the following scores on a battery of neuropsychological tests:

CASE 3 Age: 13 RH Male

INTELLECTUAL FUNCTIONG

Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV)

Verbal Comprehension		**Perceptual Reasoning**	
Similarities	14	Block Design	9
Vocabulary	12	Pic Concepts	12
Comprehen	12	Mat. Reason	10
(Information)	11	(Pic Complet.)	11

Verbal Comprehension	114 (82%ile)
Perceptual Reasoning	102 (55%ile)
Working Memory	97 (42%ile)
Processing Speed	75 (5%ile)
Full Scale IQ	99 (47%ile)

Working Memory	**Processing Speed**
Digit Span 10	Coding 3
# fwd 6–7	Sym.Srch 8
# bkwd 3	
LN Sequen. 9	
(Arithmetic) 6	

ATTENTION/CONCENTRATION

Registration/Encoding

***WISC Digit Span forwards**	longest = 6–7	ss12
***CVLT Trial 1**	words 4	–1.5 SD
***CVLT List B**	words 3	–2 SD
***CMS Stories**	raw A 39/44 B 5/44	
***Sentence Repetition**	13/22	SS92
***CMS Faces I**	raw 38/48	ss8

Focus-Execute

***WISC Coding**	ss3
***WISC Symbol Search**	ss8

Shifting

***WCST PSV RSP**	SS98
***WCST PSV Errors**	SS95

Sustaining

***Gordon Diagnostic System**

GDS	**VIGILANCE SUBTEST (12–16 yo norms)**			
Summary Data		Selection Position		Tracking Data
Total Correct	41	1	4	19X
Block 1	14	2	1	XX9
Omissions	01	3	8	XX1
Commissions	08	4	1	X1X
Block 2	15	5	3	X9X
Omissions	00	6	1	XXX
Commissions	02	7	49	Block 1 Latency
Block 3	12	8	47	Block 2 Latency
Omissions	03	9	45	Block 3 Latency
Commissions	08	0	47	

Overall	Number	Classification	Percentile
Total Correct	41	Borderline	20
Commissions	18	Impaired	<1
Omissions	04	–	

GDS DISTRACTIBILITY SUBTEST (12–16 yo norms)

Summary Data		Selection Position		Tracking Data
Total Correct	43	1	2	19X
Block 1	15	2	2	XX9
Omissions	00	3	1	XX1
Commissions	04	4	5	X1X
Block 2	13	5	2	X9X
Omissions	02	6	1	XXX
Commissions	01	7	44	Block 1 Latency
Block 3	15	8	42	Block 2 Latency
Omissions	00	9	40	Block 3 Latency
Commissions	08	0	42	

Overall	Number	Classification	Percentile
Total Correct	43	Normal	98
Commissions	13	Impaired	2
Omissions	02		

*__WCST__ set losses 1 (1 cat)

EXECUTIVE FUNCTIONS

Planning

*__Tower of London__

Total Move Score	SS92
Total Correct Score	86
Total rule Violation	104
Total Time Violation	94
Total Initiation Time	90
Total Execution Time	96
Total Problem-Solving Time	104

Inhibition

*__Gordon Delay__

Total Correct	38
Total Rspns	109
Total ER	.34(<1%)

***DKEFS Color Word Interference**

Color Naming	ss 5
Word Reading	ss 8
Inhibition	ss 5

Shifting

***WCST**

128 Trials	47 Correct	
81 total errors	SS 67	1%
17 PSV RSP	SS 98	45%
17 PSV Err	SS 95	37%
64 Nonpsv	SS 55	<1%
12% Concept.	SS 63	1%
1 cat. Completed	<1%	
23 trials to first	11–16%	
1 set failure	>16%	

Idea Generation

***Verbal Fluency**		
F (12) A(12) S (16) = 40		SS 120
Animals = 6		SS 68
***DKEFS Figural Fluency**	Total Correct	ss 8

Working Memory

***WISC Digit Span** backward longest: 3	ss7
***WISC Arithmetic**	ss6
***WISC LN Sequence**	ss9
***Auditory Consonant Trigrams**	
0" delay 15 correct	
3" delay 12 correct	SS 98
9"delay 7 correct	SS 84
18"delay 3 correct	SS 70

LEARNING AND MEMORY

***CVLT**

List A Trial 1	4	–1.5 SD
Trial 2	7	
Trial 3	8	
Trial 4	9	
Trial 5	11	–.5 SD

List B	3	–2 SD
Total		T 34
Short Delay Free Recall	8	–1 SD
Short Delay Cued Recall	10	–.5 SD
Long Delay Free Recall	10	–.5 SD
Long Delay Cued Recall	10	–.5 SD
Recognition	12/15	–1 SD

***Rey Osterrieth Complex Figure and Recognition**

Copy	24/36	1%
Immediate Recall	17.5/36	40T (>16%ile)
Delayed Recall	13.5/36	33 (4%ile)
Recognition	19/24	40T (>16%ile)
False Positives	2/12	(>16%ile)
False Negatives	3/12	(>16%ile)

***CMS**

Story A	39/44		
Story B	5/44	Immediate	11
Story A	2/44		
Story B	3/44	Delay	3
Recognition	22/30	(_False+, _False–)	7
Faces	38/48	Immediate	8
	32/48	Delay	4

LANGUAGE

Comprehension

***WISC VCI**	SS114

Repetition

***Sentences Repetition**	13/22	SS92

Phonological Awarenesss

***NEPSY Phonological Processing**	ss 12

Naming

***Boston Naming Test**		NA
***Verbal Fluency**		
F (12) + A(12) + S(16) = 40		SS 120
Animals	6	SS 68
***DKEFS Word Naming**		ss8
***DKEFS Color Naming**		ss5

VISUAL PERCEPTUAL/ SPATIAL/VISUAL MOTOR

***WISC Block Design**	ss9
***WISC Matrix Reasoning**	ss10
***Rey Osterrieth** copy 24/36	16 percentile

ACHIEVEMENT

***Gray Oral Reading Tests-Fourth Edition (Form A)**

	ss
Rate	7
Accuracy	7
Comprehension	9

***Wide Range Achievement Test- Third Edition**

Spelling	Grade Equiv. HS	SS102
Reading	Grade Equiv. 5	97
Arithmetic	Grade Equiv. 4	71

The patient's level of performance on the WISC-IV indices was variable, but the most striking aspect of this variability is observed on the PSI, which is a standard score of only 75, equivalent to the 5th PR. Once again, the anatomic locus of this index has never been identified, but the poor performance is certainly within a range that predicts cognitive difficulty in extra-test situations, probably because of a relationship with higher-order, executive control (Salthouse, 2005). Considering the WISC-IV data generates interesting hypothetical questions. For example, let us assume that the VCI, PRI, and WMI indices all reflect the level of cortical integrity. The question then becomes, if cortex is functioning well for these indices, why is it not functioning well for the PSI? The answer may be that the PSI features a substantial subcortical contribution (see Chapter 9 for a discussion of issues related to processing speed).

For example, the basic functions of ventral pathway discrimination and dorsal pathway location must be supporting the adequate Matrix Reasoning and Block Design performances, while these same basic pathways should theoretically be able to support Coding and Symbol Search as well. Therefore, the poor performances on these tasks obviously relates to some additional and different function that is not common to the other WISC-IV subtests. The low intercorrelations between the PSI subtests and the other WISC-IV subtests support this conclusion (Wechsler, 2003b). Might these differences reflect a subcortical contribution to the network of brain regions necessary to perform these tasks? For example, do aspects of the PSI tasks reflect the speed with which the striatum can make action selections? Might aspects of these tasks make a different demand on the timing functions of the cerebellum? Do these tasks reveal the level of cooperation or integration between cortical and subcortical brain regions?

Answers to these questions have not been generated, but given these WISC-IV data, these seem logical and appropriate questions to ask. If our goal is to understand brain–behavior relationships and to make predictions about cognition in the extra-test situation, then these types of questions must be asked and answered. While discrepancies in scores allow for these questions to be justifiably generated, current clinical neuropsychological testing methodologies do not allow for these questions to be answered. However, answering these questions will most certainly lead to the development of useful ways of defining and characterizing "processing speed."

Again relying upon the Mirsky model of attention for an organizing framework, we see that the patient's initial encoding or registration of information is variable. Fluctuation in performance can be understood in terms of task demands. The patient performs as well as his peers on Sentence Repetition, which is a task that allows for a natural reliance on language structure, as in conversational discourse. Digit Span, which primes or structures attention along the type of format of successive increase in stimuli, is also reasonably strong. The patient knows what to expect as digit length increases and he responds well. However, when the task demand requires the patient to rely upon his own structuring resources to attend to novel material, his performances are consistently 1–2 standard deviations below the mean. From these data, a hypothesis might be generated that he can look more adequately attentive in structured situations that do not require him to self-direct attentional resources.

Important inferences are also derived from the patient's performances on the GDS Vigilance and Distractibility tasks. The patient's poorest performances were observed under conditions of cognitive monotony as assessed by the standard Vigilance task. He was inattentive as indexed by errors of omission, and distractible as indexed by errors of commission. Stimuli that should have elicited his response often did not and stimuli that should not have evoked his response often did. In terms of percentile rankings, he was more attentive on the cognitively demanding distractibility task insofar as he did not "miss" or fail to identify stimulus presentations. However, errors of commission were a continuing problem. Therefore, deficits within the inhibitory component of attentional focus and control were consistently identified.

He performed poorly on a task administered to assess his capacity to shift attention from one thing to another in response to informational feedback. However, his poor performance was actually a manifestation of poor concept formation. He discovered only one category on the WCST and perseverative errors and responses were not obviously elevated. Therefore, he was unable to determine the stimulus-based characteristics of the task. He was slow to "catch-on" to the task (also supported by the index of trials to 1st category completion) but he did not necessarily respond in the same way, over and over again anyway, despite the provision of informational feedback. It is impossible to determine any one specific brain region as the anatomic "locus of control" of this performance.

For instance, categorization tasks routinely recruit the prefrontal cortex and basal ganglia (Seger, 2008), while interactions between the frontal and parietal cortices and the caudate nucleus have been described as aspects of the network mediating conscious cognitive reasoning (Melrose, Poulin, & Stern, 2007). As indicated above, he performed slowly within the focus/execute dimension of attention. He had to concentrate harder than his peers, exerting more cognitive effort and control, so that on the WISC-IV PSI subtests, he was unable to "process" the same amount of information per unit of time as others his age within the general population. Consistent with this interpretation, he performed very slowly on all phases of the Color-Word Interference test. Therefore, several dimensions of attention that effect controlled cognitive processing are affected.

Other executive disturbance includes working memory deficits. This is evident in at least two ways. First, his longest digit series recitation backwards comprised only three numbers, which is equivalent to a scaled score of seven. Second, he had difficulties performing the Auditory Consonant Trigrams task (also known as the Brown-Peterson technique). For the 9 and 18 second time delay intervals, his performances were at least a standard deviation below the mean. This essentially means that when he was required to keep small bits of information in mind while forced to do something else, he often forgot the status of the original information. One would expect to find a relationship between this type of working memory deficit and the self-regulation of behavior.

In this regard, we need to keep in mind that there are only two ways of generating a behavior. On one hand, there is response to environmental stimulus or external influence. On the other, there is self-generated, goal directed responding. This second type of responding controls and directs behavior through the generation, manipulation, and maintenance of mental representations or ideas. This, in essence, is "working memory." Therefore, one would predict that as working memory capacity diminishes, dependence on the external environment increases, as the person necessarily becomes more dependent upon the external world to prompt or direct behavior in the here-and-now. When coupled with deficits in inhibitory control, this generates the recipe for impulsivity as well. In this regard, within cognitive or neuropsychological evaluation, it becomes critical to evaluate attention and executive function in sufficient detail to be able to explain and predict reported and observed behavior.

Returning to our 13-year-old "Chiari" subject, his performance on the TOL that required "think ahead" capacity was adequate but unimpressive. Formal index scores reveal that 70% of his age-matched peers were more accurate in generating solutions than he was able to demonstrate. In fact, his ability to solve problems in the fewest number of moves fell at the 18th PR compared to same-age peers. To some extent, this was a function of his premature responding, since 75% of the people within his age-range in the standardization population took more time than he did to plan and organize solutions before responding.

Therefore, he did not give himself much of an opportunity to think things through before responding, and this presumably had an impact on the accuracy of his solutions. Perhaps he can be characterized as more of a "doer" than a "thinker." This hypothesis would be consistent with the above description of the relationship between working memory and inhibition.

Language functioning in this case was not systematically evaluated. However, certain qualitative aspects of his response pattern are revealing. Although he achieved a VCI of 114, his verbal functioning is anything but "high average." When he was asked to indicate how a circle and a triangle are alike, he stated, "something that has geometric shape, surfaces, you use them every day." When explaining how an hour and a week are alike, he replied, "they are elements of time, almost every day they're almost exactly alike, but for keeping track of an hour you need a watch, and to keep track of a week, you need a calendar." In responding to how a parakeet and an eagle are alike, he indicated, "they are almost exactly alike because they're both animals that exist. They evolved from other animals. It's possible that Godzilla could exist, or possible that life forms like ET exist." In defining the word urge he stated, "to want to do something, to have an impulse, to have an action take form, to morph an activity, to have an activity take form," and in explaining "rumble," he replied, "thunder, instead of being quiet, there is a barrage of sound. Things make sounds according to their activity and they reverberate." (All Similarities and Vocabulary subtest questions are simulated items obtained from the Psychological Corporation, reprinted with permission, 2003, and reworded to approximate the quality of his actual responses).

There is certainly nothing "high average" about the level of appropriateness or adaptability of these responses. The responses are off the point and include oddities in thinking. There is the quality of "dysmetria" in his verbalization (Andreasen & Pierson, 2008; Andreasen et al., 1999, 1998). As reviewed previously (see Chapter 5), this type of response pattern might represent a manifestation of failure to encode and/or detect error within the olivo-cerebellar system. In any case, the quality of his response pattern very clearly qualifies the level of performance or psychometric event of his achieving a "high average" WISC-IV VCI.

Visual–perceptual–spatial functioning was considered intact. For example, Matrix Reasoning and Block Design performances were unremarkable, so it was inferred that the perceptual and spatial cognition that support these performances are intact. The Rey CFT performance was obviously poor, and the comparison of CFT with Block Design and Matrix Reasoning suggests anterior, frontostriatal involvement mediating organizational skill rather than a primary deficit in perceptual or spatial cognition (Denckla, 1994, 1996). These aspects of the data also reveal the inherent limitations of cognitive and neuropsychological tests that are not organized along the parameters of known brain–behavior relationships, in this case, concerning object identification and location functions. There were no data that directly speak to these processes. This is because brain–behavior relationships in the visual–perceptual– spatial domain

are organized one way, according to the ventral (object identification) and dorsal (object location) streams of information processing while most cognitive and neuropsychological tests do not obey that anatomic organization. Therefore, indirect inferences have to be made.

With respect to learning and memory functions, the CVLT-C performance revealed deficits in learning but not memory. His learning slope was shallow, which means acquisition was very gradual but incremental. Across the five trials, recall gradually improved from 4 to 7 to 8 to 9 to 11 words, while his summary total T-score of 34 reveals he did not acquire as much information as others his age. Relative to his own performance, free recall was "in the ballpark" of expectation and recognition performance improved by a factor of one word. Therefore, he did not forget anything he acquired but he did not learn as much as his peers either. The pattern implies that attention and concentration impact upon acquisition but that storage functions are intact. His response to the CMS stories would be interpreted in a similar way. His immediate recall of 39 out of 44 units on Story A implies intact initial recall capacity, but the recall of 5 out of 44 units on Story B implies an inability to function consistently at optimal level. Free recall was poor in delayed conditions, with recognition much improved as weighed against the background of his notable variability in immediate recollection. There is no anterograde amnesia, but learning and retrieval functions are inefficient. One would expect that in the extra-test situation, this corresponds with considerable day-to-day inconsistency in learning within the school situation. However, this remains experiential clinical inference that has not been systematically investigated in controlled studies.

Chiari II malformation is associated with hydrocephalus, and this can occur with Chiari I malformation as well. In cases with hydrocephalus, there is no question that cognitive deficits occur, and it is easy to understand these deficits, even on the basis of a cortico-centric model of cognition. Whether or not Chiari I malformation without hydrocephalus is responsible for cognitive deficits remains a very controversial issue. This is exactly why this case was chosen to include for interpretation and review. It was not chosen because it is "easy" or "clear-cut," but instead, because it can be interpreted in more than one way. This is the type of case that a practicing clinician frequently faces, instead of the relatively "pure" case that is attributable to classic or unambiguous pathology. Proving or settling the diagnostic matter of localization cannot be accomplished through neuropsychological testing alone. However, children with this condition (Chiari I) have been described as demonstrating subtle difficulties with attention, executive functions, language, and behavior as in obsessions and compulsions. These are the types of problems that are in the direction of what has been described in children with posterior fossa tumors as well as in what has been termed the cerebellar cognitive affective syndrome (Schmahmann, 2004).

The deficits in the case presented above are not nearly as severe, although this youngster remains quite obviously impaired in his thinking. If one adheres

to a rigid model of cortico-centric cognition, then the neuroscience that establishes the groundwork for a cerebellar contribution to cognitive functioning must be ignored. However, within the context of a more integrated view of brain function and behavior, test results such as these demonstrate both the strengths and weaknesses of neuropsychological assessment methodologies. The strength concerns the sensitivity to cognitive impairment and the ability to powerfully describe cognition and behavior in functional descriptive terms, while the weakness concerns anatomic localization properties, particularly when the vertical organization of the brain is involved, so that etiology is frequently uncertain, arguable and open to question.

Case 4

The final case to be analyzed in this section features a complicated presentation. It is being reviewed in order to provide an example of how to organize historic and observational information and to integrate hypotheses drawn from this data with test results. This is a 10-year-old right-handed male. He has been diagnosed with Asperger's disorder, but he clearly demonstrates comorbid pathology that could just as well be diagnosed under the rubric of Tourette's syndrome. He has many symptoms of AD(H)D and OCD which are often observed within the spectrum of Tourette's. This is not the type of case that easily "fits" a single DSM label. As reviewed by Yaryura-Tobias, Rabinowitz, & Neziroglu (2003), many children with developmental disorders simultaneously fulfill diagnostic criteria for 1–5 DSM diagnoses. This is the type of challenge and ambiguity that a clinician often faces. The symptom picture demonstrates the value of descriptive diagnosis through an evaluation of brain–behavior relationships.

This was a very preterm baby who was born at 26 weeks gestation. This fact needs to be immediately interpreted as placing this child at risk for future cognitive difficulty (Bhutta, Cleves, Casey, Cradock, & Anand, 2002). Cerebellar and cerebral structural abnormalities often co-occur as a result of very pre-term birth (Limperopoulos et al., 2005b). The growth and development of the cerebellum are rapid during late gestation, but this growth is impeded by premature birth (Limperopoulos et al., 2005a). Very pre-term birth is associated with three possible patterns of abnormalities in cerebellar development. First, there can be volume reduction of the cerebellar hemispheres and a smaller vermis. Second, there can be volumetric cerebellar hemispheric reduction with an enlarged fourth ventricle and deformed vermis. Third, there can be normal cerebellar shape but with extensive reduction in its dimensions (Messerschmidt et al., 2005). These types of cerebellar abnormalities have been associated with a variety of cognitive, emotional, and non-motor difficulties (Allin et al., 2001, 2005; Herbert, Eckerman, Goldstein, & Stanton, 2004; Kessenich, 2003). There is also an association with white matter/

mylenation abnormalities and with ischemic hemorrhagic events (Back, Riddle, & McClure, 2007).

Therefore, these aspects of the history immediately establish the background for development of subcortical as well as possible cortical abnormalities that would predispose this child towards cognitive and general adaptive deficits. White matter abnormalities and tissue changes from hemorrhagic events increase the likelihood of lesions within prefrontal–subcortical circuitries, including the dorsolateral, orbitofrontal, and medial regions (see Chapter 3). In fact, there is also an intimate relationship between motor and cognitive development and the development of the cerebellum and prefrontal cortex (Diamond, 2000). Structural abnormalities within these cortical-subcortical brain regions could anticipate problems in motivation, affective regulation and social cognition and behavior, as well as attention/executive deficits. Therefore, he is at risk for developing the myriad problems often seen in the full-blown characteristic presentation of Attention Deficit Disorder.

Abnormalities in cerebellar development as a result of very pre-term birth have been associated with the types of deficits seen in the cerebellar cognitive affective syndrome (Schmahmann, 2004). These problems also include deficits in attention, executive function, language skills, visuospatial information processing, learning disabilities such as reading disorder, as well as in difficulties with affective regulation and personality functioning (Schmahmann, 2004; Kessenich, 2003). The point is that knowledge of developmental brain–behavior relationships should provide a background for guiding thinking towards establishing a framework within which to develop hypotheses about the patient's current presentation. This type of organizational framework is often the key to understanding the patient's presenting problems, rather than trying to establish a differential diagnosis based upon the observations of DSM-type criteria. In these ways, knowledge of the patient's history can be critical to conceptualizing the case, its brain-related descriptive diagnosis, its treatment, and prognosis. The patient in fact experienced "brain bleeds" in the perinatal period. Therefore, this case history presents a very fertile groundwork for establishing hypotheses about developing a variety of cognitive-emotional-social adaptive problems.

A variety of behavioral observations about this patient are informative. He exhibits oro-facial dyskinesias, involuntary choreo-athetoid types of movements involving the mouth and nose, sometimes referred to by parents as facial twitches. He sometimes feels compelled to "spin" during the process of walking. At school, he sometimes has to "spin" and kick the wall. Therefore, he also demonstrates complex motor tics. These are significant findings in terms of guiding the clinician's thinking. These types of behaviors, which can be considered to reflect diminished control over intention, are considered mediated by prefrontal–basal ganglia circuitry (Frey & Albin, 2006). As prefrontal–subcortical circuitries descend towards the basal forebrain, there is a geographic spatial constriction of these separate circuits, so that a "lesion" primarily impacting one individual circuit can easily impact upon another. As these circuits descend within the brain,

they begin to converge and become more closely packed. It becomes easy to imagine motor, cognitive, and emotional-social behavioral manifestations as a result of abnormal structure or chemistry of the basal ganglia, as the circuits begin to share the same geographic territory (Denckla & Reiss, 1997).

The patient also has a history of severe hypersensitivities. These sensitivities were evident with respect to sound, resulting in his attending to sounds that others would barely notice. Similarly, he was hypersensitive to clothing, such as the tags and labels on underwear. These types of behaviors imply two subcortical abnormalities. First, this suggests an abnormality in lower level basal ganglia-subcortical circuitries that gate orienting responses. He does not easily inhibit or "habituate" to these stimuli. These lower level stimuli compete for limited attentional resources and are disinhibited as a manifestation of abnormal basal ganglia selection mechanisms (see Chapter 2 for a review). Second, the intensity with which these stimuli are experienced reflects a disturbance in his modulation of the "force" of stimuli, so that not only is he distracted by these things, but he also experiences them as intense or excessive (Schmahmann, 2007). This implies abnormal cerebellar amplification. There are disturbances in both the selection and refinement of sensory stimuli or sensations.

Other behaviors are just as informative. He is unable to tie his shoes. It takes him a very long time to get dressed and to perform personal hygiene activities. He needs constant reminders to do simple things such as hang-up his coat. He typically forgets to take his lunch with him. He forgets to take his homework to school. He appears to become easily distracted in the performance of all of these routines. These observations are important because they imply difficulties in his acquiring basic routines. His engaging in these behaviors is slow and inefficient because they are likely under conscious, higher-order control, without adequate (or possibly any) assistance from subcortical participation. In other words, his behaviors suggest a disturbance of procedural learning systems. He cannot perform behaviors automatically or quickly, but instead, under conscious mediation. This necessarily requires effort and higher levels of concentration, and is easily disrupted by distracting influences. His slowness likely emerges because the basal ganglia and cerebellum are important for learning to perform tasks automatically and thus quickly. He is left to perform tasks in a deliberate fashion when they should ordinarily be executed by habit (Knowlton, 2002).

The patient was quite cooperative during the assessment. However, a number of behaviors were noteworthy. The patient's speech pragmatics were clearly impaired. He would interrupt while being given instructions. He would sometimes ask a question or make a statement that had nothing to do with the topic at hand. He would start tasks before directions were completed. His prosody of speech was atypical and excessive. He made odd statements, adding extraordinary aesthetic attachment to pedestrian aspects of the office, such as stating, "what a beautiful doorknob." He would also go off on

tangents. He was not motorically hyperactive, but he would immediately touch whatever was placed on the desk in front of him. He would start to turn pages on the easel test administration book in front of him and he was insistent that he be allowed to pursue this ambition. When given a break for a snack and taken to the reception area, he insisted that the door remain open so that he could keep the examiner in view. When the examiner used the rest room, he insisted on waiting outside the door. When he did eat a snack, he would stuff his mouth very full, to excess.

These are important observations because they can be interpreted as demonstrating both disturbances in intention programs and in adjusting the amplitude of behavior. For example, his behaviors reveal difficulties in knowing when to start a behavior, when not to start a behavior, when to persist with a behavior, and when to stop a behavior. These intention programs are presumably under the mediation of basal ganglia circuitries. Even his difficulties in separating from the examiner can be understood within the framework of a perseveration (see Chapter 3). It is important to realize that motor behaviors have cognitive and affective analogues, and this is very evident in his behavioral and affective predispositions. His excessive prosody and even his stuffing his mouth with food have the quality of disturbed behavioral amplification, with his "overshooting" the target or goal of the behavior. In these ways, observations of statements, emotional expression, and actual behavior can all be translated into motor equivalents, and can be formulated within the framework of subcortical contributions to the observable presentation. Again, in this regard, cognitive and affective functioning can be viewed as organized in parallel with the motor control system. Similarly, the interpretations of these observations can be weaved together with history and presenting symptoms, all of which implicate the same regional brain areas of involvement, specifically, prefrontal–basal ganglia and cerebro-cerebellar systems.

He obtained the following scores on a battery of neuropsychological tests:

SCORE SUMMARY SHEET

CASE 4 Age: 10 RH Male

INTELLECTUAL FUNCTIONG

Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV)

Verbal Comprehension		**Perceptual Reasoning**	
Similarities	10	Block Design	13
Vocabulary	6	Pic Concepts	7
Comprehen	1	Mat. Reason	11
(Information)	6	(Pic Complet.)	9

Verbal Comprehension	75 (5%ile)
Perceptual Reasoning	102 (55%ile)
Working Memory	86 (18%ile)
Processing Speed	59 (<1%ile)
Full Scale IQ	76 (5%ile)

Working Memory	**Processing Speed**
Digit Span 14	Coding 4
# fwd 8	Sym.Srch 1
# bkwd 5	
LN Sequen. 1	
(Arithmetic) 4	

ATTENTION/CONCENTRATION

Registration/Encoding

***WISC Digit Span forwards**	longest = 8	ss14
***WISC PI Spatial Span forwards**	longest = 3	ss 4
***CVLT Trial 1**	words 6	0 SD
***CVLT List B**	words 7	.5 SD
***NEPSY Narrative Memory**		ss 11
***NEPSY Sentences**		ss 11
***NEPSY Faces Short Delay** 16/16		ss 15
***NEPSY Mem. For Names** 1 6/8		
***CMS Story Recall, Immediate**		ss 3

Focus-Execute

***WISC Coding**		ss 4
***WISC Symbol Search**		ss 1
***NEPSY Visual Attention**		ss11
***NEPSY Auditory Attn/Rsps Set**		ss11
***Trails A**	27.9 seconds	SS 106

Shifting

***WCST PSV RSP**	SS99
***WCST PSV Errors**	SS98
***D-KEFS Color-Word Switching**	ss 11

Sustaining

***Gordon Diagnostic System**

GDS VIGILANCE SUBTEST

Summary Data		Selection Position		Tracking Data
Total Correct	40	1	0	19X
Block 1	15	2	1	XX9
Omissions	00	3	0	XX1
Commissions	03	4	2	X1X
Block 2	13	5	1	X9X
Omissions	02	6	0	XXX
Commissions	00	7	41	Block 1 Latency
Block 3	12	8	44	Block 2 Latency
Omissions	03	9	44	Block 3 Latency
Commissions	01	0	43	

Overall	Number	Classification	Percentile
Total Correct	40		14
Commissions	4		22
Omissions	05	–	

GDS DISTRACTIBILITY SUBTEST

Summary Data		Selection Position		Tracking Data
Total Correct	19	1	3	19X
Block 1	05	2	1	XX9
Omissions	10	3	1	XX1
Commissions	06	4	1	X1X
Block 2	07	5	0	X9X
Omissions	08	6	1	XXX
Commissions	00	7	47	Block 1 Latency
Block 3	07	8	44	Block 2 Latency
Omissions	08	9	42	Block 3 Latency
Commissions	01	0	44	

Overall	Number	Classification	Percentile
Total Correct	19		7
Commissions	07		23
Omissions	26		

***WCST** set losses	4	<1 percentile

EXECUTIVE FUNCTIONS

Planning

***Tower of London**	
Unscorable	
***WISC III Mazes**	ss 11

Inhibition

***Gordon Delay**	
Total Correct	36
Total Rspns	39
Total ER	.92

***Gordon Vigilance/Distractibility Commissions** 4/7	
***NEPSY Knock and Tap**	3–10 percentile
***NEPSY Statue**	3–10 percentile
***NEPSY Auditory Attn Commissions**	11–25 percentile
***NEPSY Rspns Set Commissions**	<2 percentile
***DKEFS Color Word Interference**	
Inhibition time	50 percentile
Inhibition errors	5 percentile

Shifting

***WCST**

128 Trials	90 Correct	
38 total errors	SS 96	39%
18 PSV RSP	SS 99	49%
17 PSV Err	SS 98	49%
21 Nonpsv	SS 92	45%
62% Concept.	SS 98	49%
4 cat. Completed	6–10%	
32 trials to first	2–5%	
4 set failure	<1%	

IDEA Generation

***NEPSY Verbal Fluency**	ss 12
Semantic	>75 percentile
Phonemic	11–25th percentile
***NEPSY Design Fluency**	ss 1

Working Memory

***WISC Digit Span** backward longest: 5		ss 16
*WISC PI Spatial Span backward longest: 4		ss 7
***WISC Arithmetic**		ss 4
***WISC LN Sequence**		ss 1
***Auditory Consonant Trigrams**		
0" delay 15 correct		
3" delay 7 correct	SS 81	
9" delay 4 correct	SS 84	
18" delay 7 correct	SS 107	

LEARNING AND MEMORY

***CVLT**		
List A Trial 1	6	0 SD
Trial 2	8	
Trial 3	5	
Trial 4	6	
Trial 5	13	1 SD
List B	7	5 SD
Total		T 40
Short Delay Free Recall	11	5
Short Delay Cued Recall	11	5 SD
Long Delay Free Recall	5	–2 SD
Long Delay Cued Recall	11	5 SD
Recognition	13/15	0 SD

***CMS**	
Immediate 1/15	ss3
Delayed 1/15	ss3
Recognition 22	ss1
***NEPSY Memory for Faces** Immediate 16/16	ss15
Delay 16/16	ss14
***NEPSY Memory for Names**	
Learning 22/24	ss14
Delayed 8/8	ss12
***NEPSY Narrative Memory**	ss11

LANGUAGE

Comprehension

***NEPSY Comprehension of Instructions**	ss10

Repetition

***NEPSY Sentences**	ss11
***NEPSY Repetition of Nonsense Words**	ss15

Phonological Awarenesss

***NEPSY Phonological Processing**	ss 11

Naming

***NEPSY Speeded Naming**	ss8

***D-KEFS Color Naming**	ss9
Word Reading	ss9
***NEPSY Verbal Fluency**	ss 12
Semantic	>75 percentile
Phonemic	11–25th percentile
***DKEFS Word Naming**	ss8
***DKEFS Color Naming**	ss5

VISUAL–PERCEPTUAL/ SPATIAL

***WISC Block Design**	ss13
***WISC Matrix Reasoning**	ss11
***NEPSY Design Copy**	ss10
***NEPSY Arrows**	ss1
***NEPSY Block Construction**	ss11

SENSORIMOTOR

***NEPSY Finger Discrimination**	
3 errors dom	3–10 percentile
4 errors non-dom	3–10 percentile
***NEPSY Oromotor Control**	26–75 percentile
***NEPSY Fingertip Tapping**	ss9
***NEPSY Imitating Hand Positions**	ss6
Preferred 9/12, Nonpreferred 10/12	
***NEPSY Visuomotor Precision**	ss4
***NEPSY Manual Motor Sequences**	26–75 percentile
***Grooved Pegboard**	
Right 113 seconds, 2 drops	SS 88
Left 107 seconds, 1 drop	SS 90

ACHIEVEMENT

***Gray Oral Reading Tests-Third Edition (Form A)**

	ss
Rate	7
Accuracy	9
Comprehension	5

*** Wide Range Achievement Test-Third Edition**

Spelling	Grade Equiv. HS	SS93
Reading	Grade Equiv. 5	96
Arithmetic	Grade Equiv. 4	76

He obtained a WISC-IV Full Scale IQ of 76. Although this technically falls within a "borderline" psychometric range, this finding is impossible to interpret with any sense of clinical confidence because the individual index scores which comprise the FSIQ value are characterized by such significant variability. He obtained a Verbal Comprehension Index of 75, a Perceptual Reasoning Index

of 102, a Working Memory Index of 86, and a Processing Speed Index of 59. Therefore, to the extent that the PRI serves as a very general problem-solving index, he performed like anyone else within that overarching domain, whatever it is that those multifactorial subtests measure. Verbal weaknesses are readily evident. The Similarities subtest items are highly structured and he performed as well as anyone else his age along that verbal concept formation dimension. However, difficulties were evident on those subtests that required the self-organization of language processes. He had difficulties in generating definitions to stimulus words and he found it even more difficult to generate solutions to questions requiring the application of age-appropriate common sense thinking. Performances on so-called working memory subtests were inconsistent, with solid scores in repeating digits forwards and backwards and great difficulties on Letter-Number sequencing. His very low level of performance actually implies he had difficulty understanding the idea behind the subtest. With respect to the so-called Processing Speed Index, he obviously performed very slowly when tasks required him to make perceptual discriminations while indicating his response with a simple motor reply.

With respect to the various elements of attention, the patient's initial encoding or registration of information seems to be intact. This inference can easily be made from his performances on immediate recall subtests. Most performances were extremely solid, with the exception of immediate story recall which was quite poor. Therefore, as material became longer or more extensive, he was unable to consistently self-direct attentional resources. This finding of difficulty with the registration of more lengthy information is important because it has implications for classroom behavior. For example, if this type of finding translates to the extra-test situation, one would predict that his being in a classroom listening to discussions would be problematic and that he would not initially register or "take in" the same range of information as his peers.

He had obvious difficulties with stimulus selection, response selection and inhibition, and with sustaining attention over time. Errors of omission on continuous performance tests were always elevated between the 7th and 14th PR. Simply put, this means that he frequently failed to identify stimulus presentations. He "missed" information. Errors of commission were between the 22nd and 23rd PR on continuous performance tests, and he performed between the 3rd and 10th PR on a competing programs go–no-go task and on a subtest requiring him to maintain a posture while inhibiting extraneous movements and responses to orienting stimuli. Therefore, he was consistently unable to "not respond" to distracting influences and to prepotent, competing stimuli. Stimuli that should have evoked his response often did not, and stimuli that should not have elicited his response often did. He could not self-direct attentional resources by selecting appropriate stimuli and by inhibiting responding to distractions, so that attention was poorly focused and poorly controlled.

Shifting attentional focus from one thing to another was not a problem as manifest by an ordinary number of perseverative errors and responses on the WCST. He functioned at just about the same level as anyone else of his age

within the general population within these parameters. However, overall WCST performance was poor, as will be discussed below.

Within the focus/execute dimension of attention, his performances were variable. This type of variability is always difficult to interpret because the functional neuroanatomies of the subtests within this dimension have never been clearly identified. The focus/execute dimension as Mirsky (1996) has defined it in general terms cannot be a monolithic entity because it is composed of different tasks. The tasks that comprise the category likely rely on different anatomic networks. Therefore, in combining the tasks together to form a "unitary" dimension, the most accurate and conservative inference that can be made is that he does not focus upon and execute novel tasks efficiently. New tasks with seemingly similar yet somewhat different demands can evoke "cognitive control" episodes that are manifest by his concentrating very hard and working more slowly than his peers. Insofar as the extra-test environment changes and is difficult to predict, one would expect this youngster's functioning within the "real world" to be inconsistent and unpredictable. There is clear evidence for this conclusion on the basis of his "test taking" behavior during the course of the evaluation.

As might be predicted from such difficulty he experienced in the self-direction and control of attention, other aspects of executive functioning are affected. His Tower of London test performance could not be scored. This was because of his extremely numerous rule violations, which imply a disturbance in intention programs. His executive direction is characterized by a lack of self-control. When left to his own resources to determine the stimulus-based characteristics of novel situations, he cannot plan in order to solve problems. This implies he is quite dependent upon an external organization or structure, and this conclusion is supported by his performance on the WCST. He was initially slow to "catch-on" to what was required by discovering the initial category, with a performance that was between the 2nd and 5th PR. However, while he achieved 4 categories, only between the 6 and 10 PR, this occurred because of his significant failures to maintain set (since he achieved four of six categories, he discovered the three basic ideas, and it can be argued that if the test was longer, all six categories would have been achieved. His set failures influenced full category completion). He had obvious trouble in mentally tracking his performance. He would forget the principle he was applying as he was doing it, he would get distracted, lose his place, and make errors. Again, the data demonstrates he is unable to self-direct attention and concentration and he is easily distracted, so that he needs a very "tightly organized" structure in order to appropriately stay "on task."

While his WMI individual subtest performances imply inconsistent working memory, this was also evident in the great variability in his Auditory Consonant Trigrams performance. Similarly, his WCST set failures can be understood as working memory failures. Design fluency performance at less than the 1st PR reveals he was unable to be productive on a task requiring him to self-generate activity, again revealing his deficit in fundamental self-direction. Therefore,

executive functions are affected within dimensions of planning, working memory, and inhibition, all of which prevent him from appropriately initiating and maintaining self-directed activities. His intact "shifting" might actually be a manifestation of his distractibility. His ability to change the focus of or to shift attention actually reveals his inability to keep his mind on much of anything for very long.

Receptive language skills are intact. He performed at the expected mean level on a subtest requiring him to carry-out multiple step directions, so that basic language comprehension is unaffected. He has no difficulties in discriminating between or in reproducing novel speech sounds. Phonological processing was intact as inferred from his ability to delete sounds from words or to exchange sounds within words. However, rapid object naming was low, only at the 25 PR, and this is a potentially important finding that can predict problems with reading fluency. In contrast, he had no difficulties retrieving words on his own. Therefore, any language difficulty he experiences is subtle and would likely be practically evident in reading.

He has no visual–perceptual–spatial information processing deficits. Object identification functions are intact as inferred from his error-free performance on a facial recognition task. He had no difficulties with object location functions as manifest by his respectable performance on the NEPSY Route Finding subtest. Constructional skills were intact as inferred from Design Copy and Block Design performances. Therefore, given these good performances, his extremely weak performance on Arrows likely occurred for reasons other than visual–perceptual–spatial deficit. This poor Arrows subtest performance may be a manifestation of difficulties in self-directing eye movements as a manifestation of frontostriatal abnormalities (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Neggers, Raemaekers, Lampmann, Postma, & Ranset, 2005; Silk, Vance, Rinehart, Bradshaw, Cunnington, 2008), or perhaps an attempt at "solving" the task with a left-hemisphere information processing strategy, since a preponderance of his errors were from the left visual field. This does not appear to be a primary problem with analyzing left visual field input since he performed so well on most tasks requiring right-hemisphere information processing. These types of test score inconsistencies always need to be interpreted within the context of known brain–behavior relationships in order to make anatomic sense of inferences.

The mechanisms that support memory functions are intact. There is absolutely no evidence to demonstrate that he forgot anything he learned during the course of the evaluation. However, while the retention of new information is not an issue, his learning of new information represents an entirely different matter. The most obvious difficulty emerges from his performance on the CVLT-C. On a trial-by-trial basis, his learning was very inconsistent as indexed by free recall. He was able to recall information one time but then not the next time. The learning slope was, therefore, flat until trial 5, when he was able to suddenly recall at least as much information as his peers. However, after a 20-minute delay, free recall was again poor, and he needed a recognition paradigm to identify what he knew

because he could not remember it on his own. Therefore, he demonstrates a recall problem but not an information storage problem. He had difficulties with voluntary access, which is a finding that might be expected to correspond with complaints of forgetfulness or inconsistencies in learning. He never had difficulty in attempting to recall information on tasks that provided him with some sort of cueing or prompt. Once again, even his learning and memory test results demonstrate his reliance upon external structure. These aspects of the data also imply involvement of the frontostriatal system (see Chapter 9).

He did not perform well on any sensory–perceptual information processing task administered, on either hand. His poor finger discrimination scores are very difficult to interpret, since the findings are not lateralized and since there are no lateralizing cognitive deficits that would implicate brain regions surrounding somatosensory areas. Ability to perform imitation of hand positions follows a very skewed distribution, and he was continually inattentive to stimulus presentations. This inattention is the most likely reason for his poor performances on all sensory–perceptual tasks.

Motor speed on fingertip tapping tasks was unremarkable but this child demonstrated inconsistency in learning new motor sequences by touching one finger at a time in order. His performances on tasks of visuomotor precision were uniformly fast and inaccurate, demonstrating poor motor control. This again reveals his fundamental difficulties with self-directed processes. Against this background, it was surprising that he performed at the same level as his peers on a subtest requiring him to learn new motor programs. However, his acquisition in learning new programs was characterized by difficulties with movement refinement, characterized by changes in rate and rhythm, accompanied by pronounced force. Therefore, these motor findings might initially seem inconsistent, although qualitative observations imply subcortical involvement.

In terms of academic screening, his test data do reveal difficulties with reading rate, as might be predicted on the basis of his slowness in object naming. His difficulties with reading comprehension are consistent with his variability in the initial encoding of information and inconsistency in working memory functions. There is no evidence of fundamental academic skills disorder, but application problems would be expected on the basis of his "executive control" deficits.

This case is important for several reasons. It illustrates how to apply history to possible brain pathology. It also allows for linking presenting symptoms and behavioral observations to models of brain–behavior relationships while integrating cortical and subcortical systems. The test results were also interpreted within that framework of multiple systems. Once again, the data reveal the sensitivity of neuropsychological testing to brain-related pathology, while also demonstrating lack of specificity so that results are best described in cognitive and behavioral terms.

Summary

This chapter reviewed four cases. Subcortical, and specifically cerebellar, pathology was an issue in all of the cases. The cases were interpreted by applying the models of brain–behavior relationships that were presented earlier. Neuropsychological testing is sensitive to brain-related dysfunction, but by themselves, these tests are poor localizers of pathology. Certain aspects of qualitative observations were presented as possibly illuniating the contributions of subcortical regions, with an emphasis on how right hemisphere cerebellar pathology might have an impact on the quality of the patient's verbal responses. However, because of the lack of specificity of currently available neuropsychological tests and methodologies, results should be interpreted in behavioral instead of in anatomic terms.

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Chapter 12
The Integrated Brain: Implications for Neuropsychological Evaluation

"That is the story. Do you think there is any way of making them believe it?"
"Not in the first generation," he said, "but you might succeed with the second or later generations."

Plato

We put thirty spokes together and call it a wheel;
But it is on the space where there is nothing that the usefulness of the wheel depends.
Therefore just as we take advantage of what is, we should recognize the usefulness of what is not.

Tao Te Ching 11, trans. Waley

If you have come this far, dear reader, you have come a long way in modifying your knowledge about brain–behavior relationships. You have learned information about brain structures that have traditionally been considered mainly as co-processors of movement. You have learned about the vertical organization of brain–behavior relationships. You have learned how movement is organized within the brain, and you have learned how to apply these concepts of movement to cognition and emotion, because you have learned that cognition and emotion are organized in a way that is parallel to movement. You have learned that cognitive and emotional regulation should be understood as extensions of the motor control system. You have gone from "movement" to "thought" in your conceptualization of how these processes are organized within the brain.

The process of learning and applying these ideas may have challenged some of your beliefs about the brain, as most of us have been trained in the prevailing cortico-centric model. This may have made you feel very uncomfortable, and even resistant to accepting these "new" ideas. However, our intention was to provide you with a "behind the scenes" look at what goes on within the brain to support thinking and behavior, as much as is currently understood, anyway. We have challenged the cortico-centric view of cognition, but we do not negate or even minimize the role of cortex.

We wrote this book for the practicing clinician and for people in training, and we fully anticipated that much of this information might be interpreted

L.F. Koziol, D.E. Budding, *Subcortical Structures and Cognition*,
DOI 10.1007/978-0-387-84868-6_12, © Springer Science+Business Media, LLC 2009

as turning traditional neuropsychology "up-side down." We believe that if you were open to considering and applying these ideas, you have become a better clinician. We are not "maverick" or "rogue" neuropsychologists with an axe to grind. We are not trying to promote radical, idiosyncratic, or non-mainstream ideas. Our motivation is to keep the field of neuropsychology moving forward. In order to move forward, information from the various neurosciences needs to be better integrated, and accommodating this information results in abandoning the prevailing cortico-centric model of cognition. We are not questioning the assertion that cortex is extremely specialized, complex, daunting to understand, and quite obviously very significantly involved in cognitive processes. The evolutionary expansion of neocortex makes us uniquely human.

However, we have significant questions and reservations about traditional views that all but portray the cortex as operating in isolation. The cortex simply does not function alone or independently, at least not very well. We "need" all three brain regions operating in concert. For example, when the cortex and cerebellum function together (without appropriate basal ganglia input), the resultant behavior is characterized by a disturbance in intention. When the cortex and basal ganglia work together (without appropriate input from the cerebellum), the behavioral product is characterized by dysmetria. Cortex is part of a network that expresses its specialization through the mechanisms of subcortical structures, and it is dependent upon subcortical processes in order to execute many of its functions efficiently. Higher-level functions of the cortex are expressed through "lower level" systems, and these lower-level systems are critical in modulating cortical functions. Cortical and subcortical functions operate in concert in deciding upon behaviors that are in the best interest of the organism, which ensures survival. *This is because the basal ganglia and cerebellum play important roles in deciding what information is or is not "used" by cortex*.

The cortex, basal ganglia, and cerebellum therefore operate together in order to ensure adaptation. This is the heart of "executive" function. With these ideas in mind, we believe that this book is essentially organized around a few major themes. These themes can be briefly summarized as follows:

The brain's "default condition" is to learn. Our abilities to acquire information and to benefit from the experience of interacting with a complex environment provide the decisive advantage in adaptation. Posterior cortices are organized to allow perceptual experience to "persist," or to be remembered. Anterior cortices are organized to allow for storage of motor programs. However, there is a dual-system organization of behavioral control. First, higher-order control consists of determining the stimulus-based properties of problems in order to "survive" under conditions of novelty. Second, stimulus-based responding is based upon subcortical–cortical interactions. These automatic behaviors are actually elegant behavioral repertoires that ensure survival while simultaneously conserving biologic resources. Increasingly, unconscious "background processing," particularly that provided by the cerebellum, is being

understood to play important roles in creativity and giftedness as well as in pathological conditions (Ito, 2008, 2007; Vandervert, Schimpf, & Liu, 2007).

In order to benefit from the experience of adaptive activity, we automate new behavioral programs. This is accomplished through the cooperation of two vertically organized brain systems. A reinforcement-based system essentially learns by "carrot and stick." An additional system allows for efficient adaptation of behavioral programs to environmental perturbations. Therefore, the brain is "hard-wired" to select and implement the "best" response to the environment, which benefits the organism as a whole. It has been demonstrated that people not only learn and use complex patterns of information, but they also do so without necessarily intending to learn them. Thus, implicit learning is sensitive to the organism's non-conscious goals (Eitam, Hassin, & Schul, 2008). This essentially represents a central subcortical contribution to executive function.

It's Not "All Cortex"- It's the Flexibility of Interaction

The process of adaptation is not "all cortex." There appear to be two systems around which cognition and behavior are broadly organized. One of these systems rests upon stimulus-based processing. This system is composed of in ate behavior processes and behaviors that run on the basis of acquired associations. This allows for automatic responding when it is appropriate for the situation. These behaviors are adaptive because they allow for the exploitation of the predictable features of the environment, they conserve cognitive and higher-order resources in the process, and they act for the best interest of the organism as a whole. This system is part of the brain's "emotional/motivational" executive system (Ardila, 2008). This system includes aspects of cortical functioning in addition to subcortical systems. The second system is based upon higher-order control. This system allows for novel problem solving and provides flexibility in interacting with changing and unpredictable environments. Cognition and behavior do not appear to be organized around a verbal–nonverbal dichotomy. Instead, the nervous system is organized along a novelty–routinization gradient (Podell, Lovell, & Goldberg, 2001).

Interactions between the stimulus-based and higher-order control systems allow us to make that which was initially unfamiliar, familiar, or routine. The purpose of the brain is to allow the individual to survive through interaction with the environment. This is best accomplished by automating solutions to new problems, which is another way of saying that the brain is organized to benefit from experience. The brain is composed of multiple learning and memory systems in order to benefit from different types of perceptual and motor experiences. Most situations are composed of alternating episodes of automatic responding and higher-order control. As such, the two systems of behavior co-exist and continuously interact. We believe this dual-level organizational system drives most

adaptive functions, and we specifically demonstrated how these ideas can be applied to both social cognition and language, which have traditionally been largely viewed as under the mediation of cortical processes only.

Within this context of stimulus-based and higher-order control systems, three regions of the brain operate in parallel. These three regions are the neocortex, the basal ganglia, and the cerebellum. These regions do not operate in isolation. Instead, these three regions comprise a broad network underpinning cognition and behavior which also includes other important structures such as the thalamus. Very generally speaking, regions of the neocortex posterior to the central sulcus process and store sensory information. These brain regions are the occipital, parietal, and the temporal lobes. Anterior brain regions, or the frontal lobes, develop and retain motor or "interactive" programs. These anterior and posterior cortical regions operate according to principles of neuronal excitation.

The basal ganglia serve as an inhibitory region critical in the mediation of attention and action selections. Through a process of selective inhibition–disinhibition on the thalamus, the basal ganglia modulate activity within the cerebral cortex. Cortical–basal ganglia interactions "select" what the brain pays attention to and "release" the behavior considered appropriate for the situational context. Through a process of excitatory–inhibitory balance, the cerebellum regulates the duration and intensity of the neural signals that comprise the selected behaviors in order to make these behaviors "fit" the existing environmental perturbations. The cortex, which also functions as a storage mechanism, retains these adjustments so that with practice, these behaviors become more and more efficient. Therefore, the cortex is actually dependent upon the selections of the basal ganglia and is driven by the selected refinements of the cerebellum, while it learns through repetition or practise to perform behaviors faster and more accurately (Houk et al., 2007). The three brain regions, operating in concert, become a highly efficient, elegant learning mechanism.

Disturbances at these three different levels have their own characteristic impact upon cognition and behavior. Very broadly speaking, disturbances in posterior cortical regions result in sensory–perceptual deficits in object recognition and object location functions. Since these distributed functions provide critical support to a wide range of cognitive abilities, disturbances at this cortical level can take a variety of forms. The different types of agnosias and amnesias represent two large categories of the dysfunctions that can be manifest at this level. We assumed that the reader of this book is very familiar with manifestations of occipital, temporal, and parietal lobe impairment, so this topic was not directly covered in this book. Disturbances in anterior cortical regions result in deficits in motor programming and/or execution. When the motor, premotor, and supplementary motor cortices are involved, deficits in motor behavior, or apraxias, are readily evident but the specific symptoms are dependent upon the area of regional involvement.

When prefrontal regions are involved, behavioral disturbances can be observed in the programming of "action," in manifestations of the cognitive

dysexecutive syndrome, or in impulse control and motivational disorders. These programming deficits can be understood as dysfunction within higher-order control mechanisms, although similar presentations can be observed in disorders primarily featuring subcortical pathology. This is because these frontal regions project to basal ganglia and cerebellar structures. The basal ganglia are important for appropriate behavioral release and the cerebellum is important for appropriate behavioral amplification.

In other words, sensory cortices allow the individual to determine what is in the environment and where these "objects" are located, which is an obvious and important underpinning for successful environmental interaction. Prefrontal cortices determine "what to do" and then program environmental interactions. The basal ganglia govern intention programs. These programs include knowing when to start a behavior, when not to start a behavior, when to persist with a behavior, and when to stop a behavior. These are behavioral "selections." The unique looped architecture of the basal ganglia allows for the serial processing necessary for these "when" to act programs. Disturbances in aspects of these intention programs are dramatically evident in Parkinson's and Huntington's diseases. However, these concepts of intentional control were also applied to functioning in cognitive and emotional domains in previous chapters. The cortico-basal ganglia system is highly compartmentalized, which is an underpinning of participation in various modular domains of behavior. Aspects of disturbances at this level are also exemplified in various psychopathologies and developmental disorders.

The brain's "how" to act programs are mediated by the cerebellum. Making the appropriate behavioral refinements is largely a matter of timing, or "online" behavioral adjustment for the current situation. This timing function appears to consist of adjusting the duration and intensity of the neuronal signals that are ultimately translated into behavioral expression. Involvement at this level is often observed as a disturbance within the parameters of the rate, rhythm, and force of behavior. The classic symptom at this level is dysmetria. Variations of this symptom were also translated to a variety of non-motor domains in previous chapters. The anatomic underpinning of the cerebellum's participation in cognitive and emotional functions was identified as the cerebro-cerebellar circuit, which allows the cerebellum to regulate neural signals within various regions of the brain.

These different cortical and subcortical regions, operating together, allow the brain to function as a highly specialized and efficient learning mechanism. The cortical, striatal and cerebro-cerebellar systems allow the brain to make that which is initially unfamiliar, familiar. While frontal systems devise new programs in novel circumstances, the serial processing of the basal ganglia and the refinement functions of the cerebellum allow for elegant representations of cognitive and behavioral skills to be retained cortically and to be expressed efficiently in subsequent circumstances. Operating together, these systems allow for behaviors that fulfill the "best interest" of the individual as a whole. In this way, all three brain regions are active participants, or equal partners, in broadly defined "executive functions."

The three brain regions nevertheless acquire different kinds of information in different ways. As implied by Squire and associates (Squire, Clark, Bayley, 2004), and as proposed by Doya (1999), the medial temporal lobe system of the cortex is part of an "unsupervised" learning and memory module. This system very quickly acquires information about the environment, such as the "what and where" of objects, declarative "facts," and personal "episodes" or experiences. In other words, this type of learning and memory is really an extension of sensory–perceptual experience. This memory system represents the state of the environment as well as experiential context. These representations are stored without "supervisory" guidance or intention. *These representations also are linked to the basal ganglia and to the cerebellum by way of the vertically organized cortico-striatal and cerebro-cerebellar systems respectively*, which have no "independent" sensory processing systems of their own. Therefore, *the neocortex and it's medial temporal lobe learning and memory system provides the entire organism with common representations*, and in this way, the cortical system "links" the basal ganglia with the cerebellum in terms of shared information or representations.

The basal ganglia, or cortico-striatal system, serve as a reinforcement learning module (Doya, 1999). As discussed in Chapter 4, learning within this system is critically dependent upon the positive and negative reinforcement characteristics of the environment. This system acquires information about perceptions and behavior on the basis of reward driven association learning. This system is sensitive to environmental context. It "evaluates" environmental contexts and guides behavior by selecting actions on the basis of that evaluation. It selects behaviors on the basis of the effectiveness of behaviors in past similar circumstances. In this way, it functions instrumentally. It knows "what" and "when" to do things because of previously experienced reward. Behaviors learned in response to interpersonal aspects of the social "environment" during development play a role in creating "unconscious" or intuitive templates for future interpersonal environments, setting the stage for "transference," or generalizing responses to later people and situations.

The cerebro-cerebellar system forms a "supervised" learning module (Doya, 1999). By this it is meant that this system actually establishes an "internal model" of the environment and the action to be taken. It stores that model, it detects errors, and corrects or "refines" behavior on the basis of those deviations that are detected. It returns that information to the neocortex. In this way, the cerebellum knows "how" to do things.

Clinical Applications

It is true that there is a prolific literature describing cortical participation in various neuropsychological and neurologic disorders. However, we also reviewed evidence that the basal ganglia and cerebellum are implicated in a

wide range of psychiatric conditions and developmental disorders. Most conditions appear to be characterized by disturbances in multiple systems, with abnormalities that can be demonstrated both cortically and subcortically. This fact has two immediate implications. First, while the DSM is organized around behavioral observations, it is very difficult to explain the frequent co-morbidities or symptom overlap between disorders on the basis of this diagnostic framework. We believe that a brain systems model that takes into account multiple levels of involvement provides a much better framework for understanding and evaluating pathological conditions, from Attention Deficit Disorder to learning disabilities to Schizophrenia. A multiple-system model based upon brain–behavior relationships has the distinct advantage of explaining symptom overlap and co-morbidities. Neuropsychology can be very informative in understanding diagnostic conditions as they are currently listed in the DSM because of neuropsychology's descriptive nomenclature in characterizing brain–behavior relationships.

Second, while most currently available neuropsychological tests are founded upon a cortico-centric model of cognition, this testing approach has significant limitations for the identification and elucidation of pathological conditions. One specific restriction concerns the lack of localization capability. Neuropsychological test results can generally demonstrate three possible sources of brain-related variability. Existing tests have limited sensitivity to deficits at different levels so that test results very frequently need to be described in cognitive and behavioral instead of in anatomic terms. Addressing this issue calls for the development of additional neuropsychological tests and methodologies. There are multiple brain areas involved in symptom presentations that are not currently directly measured in practical clinical evaluation, even though assessment techniques theoretically could be applied to evaluate these brain regions. To some degree, our current situation is akin to having to perform (neuro)surgery with a butter knife. In our view, there is a critical need for developing neuropsychological tests that can identify the functioning and contributions of specific cortico-striatal and cerebro-cerebellar circuitries.

Let's consider the symptom overlap or co-morbidity issue and the limitations of neuropsychological tests in a little more detail. We will use schizophrenia as a model to illustrate a few important concepts. This disorder is characterized by positive symptoms such as hallucinations, delusions, disordered thinking and affective dysregulation, as well as negative symptoms such as apathy, lack of motivation and interest, and withdrawal from other people. Cognitive and executive dysfunction is widespread. Executive deficits include difficulties with attention and inhibition, and these particular difficulties are similarly common to attention deficit disorder (Bradshaw, 2001). There are obviously no neuropsychological tests that identify the positive aspects of the symptom picture. Symptoms like hallucinations, delusions, and thought disorder are behaviorally defined and based upon observation in making the diagnosis.

Executive dysfunction, inattention, and disinhibition comprise features of the clinical presentation that can be identified through neuropsychological

assessment. However, this general executive dysfunction is certainly not differentiating or unique to schizophrenia. Metabolic hypofrontality has been reported in schizophrenia, and has been correlated with difficulties in shifting cognitive set as manifest by increased perseverative errors on the WCST (Goldsamt, 1994). However, hypofrontality has also been reported in depressed patient populations, and has been associated with deficits in attention and executive cognition (Mayberg, 2001a, b). Executive function deficits, including problems in shifting cognitive set, have been reported in obsessive-compulsive disorder (Fontenelle, Mendlowicz, Mattos, Versiani, 2006). Specific symptoms with symmetry and order have also been correlated with increased perseverative errors on the WCST (Lawrence et al., 2006). In these ways, executive function deficits are certainly not specific to schizophrenia. These findings nevertheless implicate frontostriatal, and specifically, dorsolateral–subcortical circuitry.

The symptoms of inattention and disinhibition seen in schizophrenia overlap with what is seen in ADHD, and this is very likely because both schizophrenia and attention deficit disorder share impairment in the same frontostriatal circuitry that mediates sustained attention and inhibitory focus or control. Therefore, from the point of view of brain–behavior relationships, the problems with attention and inhibition are seen in both disorders because impairment in that particular circuitry is involved, a co-morbidity which is not easily addressed or understood at the behaviorally defined level of observation. However, from a brain–behavior relationship standpoint, the meaning of the symptom overlap is clear. It points to involvement of the same circuitry. It is not a question of whether the patient has schizophrenia and attention deficit disorder, or whether deficits in attention are secondary to schizophrenia, etc. Instead, it means the same particular frontal-striatal-pallidal-thalamic circuit is involved in both conditions. Therefore, neuropsychology can be very informative in explaining aspects of symptom constellations when symptoms appear to be shared by different DSM diagnoses.

The negative symptoms are another matter because these are difficult to assess with traditional existing "tests." However, the apathy, lack of interest and diminished motivation, and withdrawal, all imply involvement of reward circuitry. This implicates involvement of the ventral striatum, suggesting that medial frontal–subcortical circuitry is involved in this disorder. This conclusion has been supported experimentally. For example, Foerde and her group of colleagues (Foerde et al., 2008) examined normal controls and schizophrenic subjects on the Serial Reaction Time task (SRT) and the Probabilistic Classification Task (PCT) Neither group demonstrated impaired motor learning on the SRT. However, schizophrenic patients were impaired at learning the PCT. Improvement in performance in control subjects actually peaked in the first evaluation session, while patients never reached the performance level of controls. These findings have several implications. First, schizophrenia may be associated with dysfunction within specific reward circuitry that includes the ventral striatum. Second, by comparing the performance on different neuropsychological tasks that are dependent upon different cortico-striatal regions,

motor skill and reward circuitries might be dissociated. Task performance comparison provides a powerful, synergistic methodology through generating an interpretation that neither test would suggest when considered in isolation. Third, because these tasks emphasize the "fast phase" of learning, developing and applying suitable clinical versions would be practical to administer during the course of a neuropsychological evaluation. Taking this approach to evaluating frontostriatal circuitry would enhance neuropsychology's role in the diagnostic and treatment process.

Schizophrenic and control subjects have also been compared on other procedural learning tasks. One such procedure consisted of a 5-minute sequence learning task administered in two separate random and sequence condition blocks, and in this regard, a 10-minute task would be practical to administer during a neuropsychological assessment. While schizophrenic patients demonstrated impaired procedural learning on this task, patterns of brain activation also differed between patients and normal control subjects. Healthy participants activated the striatum, thalamus, cerebellum, precuneus, medial frontal cortex, and cingulate gyrus. Degree of activation was associated with magnitude of procedural learning. The schizophrenic subjects demonstrated significantly less activation (Kumari et al., 2002). Zedkova and associates used a complicated version of the more basic SRT and found abnormal brain activation in procedural learning among schizophrenic subjects as compared to controls, consistent with pathology implicating frontal–subcortical circuitry (Zedkova, Woodward, Harding, Tibbo, & Purdon, 2006). The relative brevity of these tasks offers potential for application in the practical clinical setting.

Using these types of tasks clinically opens-up whole new avenues for neuropsychological evaluation. However, different procedural learning tasks activate different cognitive and motor networks, and differences in performance have been reported as task-dependent. Therefore, it is important to develop a clinically applicable variety of procedural learning tasks for the purpose of dissociating different cortico-striatal loops. This can likely be accomplished by comparing performances on two relevant but different tasks, as described above and in previous chapters.

The dissociation of different cortico-striatal loops is no small matter. For example, one study compared performance on an implicit learning mirror-reading task with performances on verbal and non-verbal social skills tasks in a structured role-playing paradigm (Kawakubo, Rogers, & Kasai, 2006). The authors report a significant correlation between mirror reading and non-verbal social skills, but not in relation to verbal communication skills. While this study was performed with schizophrenic subjects and not healthy controls, the data do establish a link between visually based implicit learning and non-verbal social skills, implicating the circuitry involved in implicit categorization learning. The same association was not established for verbal, presumably higher-order social communicative skills. Another study correlated slowed procedural learning and memory on a mirror reading task with the severity of negative symptoms in schizophrenia (Takano et al., 2002). Studies of these types will

assist neuropsychology in developing methodologies for evaluating the neural bases of social skills and motivation in clinical populations. By developing and implementing these types of clinical methodologies, neuropsychology will contribute to understanding and treating the different and overlapping symptom dimensions that comprise various behaviorally defined diagnoses.

Our discussion has so far focused upon the cortico-striatal learning system. As indicated in previous chapters, the cerebellum is typically recruited at least during the initial phases of most types of procedural learning tasks (with the exception of visually based category implicit learning as described in Chapter 5). This activation of the cerebellum probably occurs because learning based upon interaction with the environment always requires some sort of behavioral refinement. Others have argued a central role for the cerebellum in sequence learning (Leggio et al., 2008; Strangman, Heindel, Anderson, & Sutton, 2005). We have described this view in Chapter 5.

However, as implied above, procedural learning has been broken down into two general categories. One category comprises broadly defined instrumental learning which is "rule based," dependent upon participation of the basal ganglia. This system runs on the basis of acquired associations. The second category concerns behavior that compensates for environmental changes, which is dependent upon the participation of the cerebellum. It is known that this system is also affected in schizophrenia. For example, deficits in prism adaptation have been reported in that condition (Bigelow et al., 2006). However, while cerebellar abnormalities have been reported in schizophrenia (Picard, Amado, Mouchet-Mages, Olie, & Krebs, 2008), relationships have not been clearly established between poor prism adaptation and specific symptoms. Similarly, although abnormal cerebellar functioning has been implicated in a variety of clinical conditions (Schmahmann, Weilburg, & Sherman, 2007), these conditions have not been specifically correlated with the cerebellum's role in procedural learning. Therefore, this is an area that warrants further investigation.

Developmental disorders can also be used as models of brain–behavior relationships from which to develop clinical evaluation paradigms. This approach has been described in considerable detail by Nicolson and Fawcett (2007). The authors believe that our understanding of developmental disorders has been fragmented due to a focus on differences rather than commonalities of presentations. They propose that a neural systems model provides a more integrated and unified approach for identifying and understanding different conditions that have overlapping symptoms. This neural systems approach focuses upon the evaluation of brain networks that include cortical, cortico-striatal, and cerebro-cerebellar systems. Therefore, this approach is very similar to our above suggestions related to evaluating psychopathologies.

For example, as we discussed in Chapter 6, it has been argued that specific language impairment (SLI) can best be conceptualized as an impairment within cortico-striatal procedural learning systems (Ullman, 2004). Lexical, or "cortical" knowledge, is relatively well preserved in SLI. However, significant

impairment is observed in grammar, morphology and phonology. Associated deficits are noted in motor skills. The disorder is characterized by pronounced deficits in language output, but language comprehension is intact. Neuroanatomically, abnormalities are reported in those brain regions that are believed to subserve procedural learning (Ullman, 2001; Ullman et al., 2005; Ullman & Pierpont, 2005; Walenski, Mostofsky, Gidley-Larson, & Ullman, 2007). At the present time, SLI is conceptualized as primarily a disorder of the cortico-striatal procedural learning system. However, given that the cerebellum participates in cognitive function, including language (likely through the establishment of forward and inverse control models), the cerebellum probably plays a role in SLI as well. This promises to be a fruitful area of future investigation.

Although many children with SLI also demonstrate phonological processing impairments that contribute to reading problems, children with dyslexia without SLI primarily experience phonological processing deficits of very early onset (Nicolson & Fawcett, 2007). These authors also point out that if a child experiences maturational cerebellar difficulties during the course of early development, this often follows a characteristic pattern (Nicolson, 2000; Nicolson & Fawcett, 2006). This is manifest by mild motor difficulty, with the child being a little slower to sit-up and walk. There can be greater problems with muscle tone, leading to problems with fine muscular and motor control. Since speech production is a highly complex skill that requires fine motor sequencing and control for proper articulation, the child is slower to babble and talk. They believe that this developmental pattern is frequently associated with early onset phonological processing problems as an additional manifestation of this mild cerebellar impairment. Since more conscious effort is required to accomplish tasks due to subtle motor difficulties, cognitive resources are depleted for the performance of other tasks.

As a result, tasks are performed more slowly, less automaticity is acquired, and phonological "working memory" is less efficient due to diminished allocation of cognitive resources associated with more effortful processing for other tasks (Nicolson & Fawcett, 2005). Therefore, since there would appear to be multiple cortical–subcortical routes to the development of deficits in phonology that can generate dyslexia, they argue that neurocognitive tests that isolate the functioning of specific cortico-striatal and cerebro-cerebellar circuits are crucial for differentiating different subtypes of reading disorder (Nicolson & Fawcett, 2007).

A similar argument can be developed in relation to considering methodologies for evaluating Attention Deficit Hyperactivity Disorder. This condition is also characterized by multiple abnormalities and can be considered as a model for brain–behavior relationships. Maturational differences can be found in cortex (Rubia, 2007; Shaw et al., 2007). Abnormalities are noted within the frontostriatal system (Bradshaw, 2001). This includes deficits within reward circuitry (Scheres, Milham, Knutson, & Castellanos, 2007). A hypofunctioning mesolimbic branch generates altered responsiveness to reinforcement learning, which also affects behavioral extinction. These impairments give rise to inattention, distractibility, dininhibition, and impulsivity, while hypofunctioning

mesocortical circuitry generates executive functioning deficits (Sagvolden, Johansen, Aase, & Russell, 2005). Hypofunctioning within nigostriatal circuitry can lead to poor modulation of motor behavior and impairment in "habit formation" for certain types of procedural learning. Cerebellar abnormalities have also been reported and these have been related to executive function deficits and treatment outcome, as was discussed in Chapter 7 (Ashtari et al., 2005; Mackie et al., 2007).

While ADHD is clearly a multiple system disorder when considered from an anatomic point of view, disturbances are not evident at every level to the same degree in all patients. This fact underscores the critical need for developing neuropsychological tests that identify and isolate different levels of involvement. While tasks of executive function and inhibitory control are already employed in evaluating this condition, there is a need for developing tests that are sensitive to implicit learning while manipulating reinforcement characteristics, as in probabilistic learning tasks. Striatal and cerebellar procedural learning tasks would provide data on the acquisition of various domains of skill sets. In these ways, by implementing tasks that are sensitive to different vertically organized circuitries, neuropsychology can play an important role in identifying subtypes of this disorder and in developing specific treatment plans.

We have taken the model of Nicolson and Fawcett, developed as a proposal for assessing developmental disorders, and expanded this framework to include psychiatric conditions and behavioral disorders, which we consider to be neurodevelopmental in nature (Nicolson & Fawcett, 2007). Our model is summarized in Fig. 12.1. In our view, most neuropsychological testing focuses on cortical learning and memory systems. These systems can be significantly affected in many types of dementia, neoplasms, cerebro-vascular accident, and most types of traumatic brain injury. Involvement of this system is often manifest as generalized learning and memory difficulty, and dependent upon the region and scope of pathology, deficits can be observed in focal or diffuse sensory–perceptual information processing systems. These systems are frequently relatively unaffected in psychiatric and behavioral disturbances and in developmental disorders (dependent upon the condition in question), including learning disabilities. These latter conditions typically involve the vertically organized cortico-striatal and cerebro-cerebellar circuitries. The cortical aspects of these circuitries are frequently tapped in traditional neuropsychological assessment.

However, the "reinforcement based" and "supervised learning" aspects of these systems need to be systematically evaluated in order to diagnose and clarify problems with stimulus-based control, interaction of stimulus-based and higher-order control, motivational and emotional difficulties, and the domain-specific learning problems that are common to the presentations of these patients in clinical settings. We strongly believe that the "noise" of practice effect in data offers an important source of information that is neither random nor unimportant, and that our failure to make use of this aspect of patient

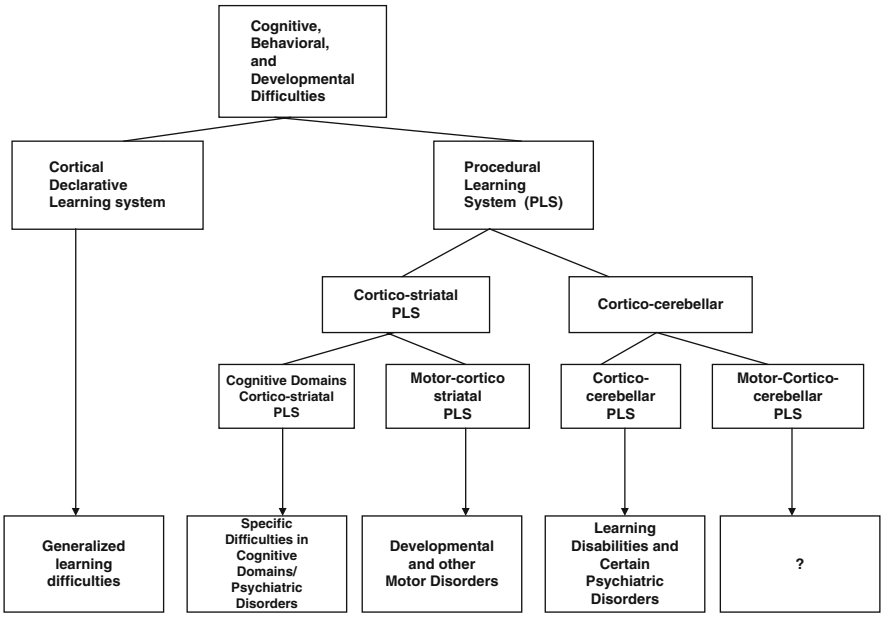

Fig. 12.1 A neural system typography for psychiatric conditions, developmental disorders, and learning disabilities. The top distinctions separate the declarative and procedural learning systems. Procedural learning systems are subdivided into the cortico-striatal and cortico-cerebellar systems.Each system can be divided further into cognitive and motor domains. It is not clear whether any specific disorder occurs in isolation, impacting the cortico-cerebellar motor system only. Affective domains would be evaluated through observation and self-report and are not included in this illustration. This figure is by permission, Nicolson and Fawcett, Trends in Neurosciences, 2007.

"communication" has significantly limited the ecological validity and applicability of our evaluations.

Experimental neuroscience has increasingly made use of nonlinear equations and the associated constructs of dynamical systems theory in order to model the complexities of brain function, often in concert with use of functional imaging techniques (Chen, Kiebel, & Friston, 2008; Frank, 2005, 2006; Heinke & Mavritsaki, 2009; Maddox & Filoteo, 2001; Marreiros, Kiebel, & Friston, 2008; Porrill & Dean, 2007; Yamazaki & Tanaka, 2007). This has allowed broader and deeper understanding of how complex brain systems actually function adaptively. Self-organization has become an important idea around which a number of unifying theories of brain evolution, development, and function have been developed (Mainzer, 2008). Quantifying and measuring these aspects of behavior clinically is a somewhat different matter and it will take creativity and ingenuity to develop appropriate methodologies. To some degree, we consider the subcortical contribution to cognition metaphorically akin to dark matter's role in the universe, and our failure to adequately

understand and measure this contribution clinically does not make it less necessary or important.

This book has emphasized that the brain's default condition essentially involves its learning functions. Inherent in the brain's learning functions—or our capacity to benefit from experience—is the ability to predict. For example, the basal ganglia system, a reinforcement-based learning mechanism, anticipates or predicts the reward-based value of events. It selects a behavior on the basis of what it expects, or predicts. In this way, learning is used for prediction of reward, which should ensure survival. The cerebellum operates as a supervised learning system that generates "models" for the control of behavior. These models allow for prediction of outcome, while the cerebellum adjusts behavioral output by detecting errors and correcting the difference between outcome and prediction. This similarly ensures adaptation.

Although sensory perception was not a topic of this book, the generation of sensory perceptions have also been described on the basis of prediction models. A sensory "prediction" model enables us to form visual perceptions on the basis of fragmentary sensory input, and it allows us to form accurate language-based, auditory perceptions on the basis of expectations calculated from fragmentary auditory input (Chen et al., 2008; Noppeney, Josephs, Hocking, Price, & Friston, 2008). These "predictions" of perceptions are computed on the basis of prior sensory–perceptual experience. These theories have been generated from the application of non-linear, computational, statistical models of brain function. In these ways, the organization of brain function can also be understood on the basis of prediction mechanisms that emerge from learning functions, which has obvious implications for adaptation and survival. We believe that we have laid a supportive yet fragmentary groundwork for understanding this variety of pioneering work on brain function which collectively promises to forever change the ways in which we approach, understand, and measure everything from pathology to prodigy.

A cortico-centric model of cognition is simply no longer tenable and is hampering our field's further development. Rapidly expanding information within the neurosciences contradicts a model that assumes cortex is the seat of cognition and that subcortical structures serve only as co-processors of movement. If clinical neuropsychology is to continue playing an active role in diagnosis and treatment, we must adapt to a (non-linear) dynamically changing neuroscientific landscape. We hope that this book contributes to initial conditions that will help determine the current stimulus characteristics of this changing landscape so that appropriate methodologies can be selected, developed and refined through experience. We hope also that it will therefore contribute to a creative and decidedly nonlinear "leap" toward a next level of function with further adaptation and change. We heartily encourage any and all movement in that direction. Perhaps, dear reader, the forward and inverse models of your cerebellum are working on this problem right now as you read this, and will help to create further avenues for exploration.

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Index

Note: The letters '*f*' and '*t*' following the locators refer to figures and tables respectively

A
Aarsland, D., 201
Aase, H., 114, 374
Abnormal basal ganglia selection mechanisms, 349
Aboitiz, F., 17, 18
Ackerman, S. L., 153, 170, 191
Ackermann, H., 170
Ackermann, R. F., 191
Acosta, M. T., 195
Action learning, 226
See also Brown-Peterson technique
ADHD, *see* Attention Deficit Hyperactivity Disorder (ADHD)
Adleman, N. E., 197, 246
Adler, C. M., 207
Adolphs, R., 174, 206
Affective information, 136
Afraimovich, V. S., 6
Agenesis of cerebellum, 153
Agid, Y., 2, 43
Aguilar, O., 201
Aharon-Peretz, J., 175
Ahearn, M. B., 71
Ahsgren, I., 154
Akinesia, 79
Akinetic mutism, 77
Akshoomoff, N. A., 139, 140
Albin, R. L., 55, 192, 348
Albouy, G., 98, 107
Alexander, G. E., 6, 31, 69
Alexander, M. P., 138
Alfonso-Reese, L. A., 45
Alivisatos, B., 47
Allen, G., 126, 136, 140, 154, 206
Allin, M., 347
Altered brain mechanisms, 195
Alvarez, J. A., 221
Alzheimer's disease, 207–208
Amado, I., 154, 176, 199, 372
Amaral, D. G., 154, 176
Ambridge, B., 173
Amodio, D. M., 175
A-motivational syndrome, 77
An, S. K., 61, 193
Anagnoson, R. T., 50, 201
Analogous memory systems, 16–17
frontostriatal system, 16
procedural learning, 17
Anand, K. J., 342
Anderson, J. A., 372
Anderson, S. W., 157
Andreasen, N. C., 6, 12, 135, 144, 202, 203, 205, 206, 321, 329, 345
Andreason, P. J., 200, 205
Andreou, G., 182
Anterior cingulate or medial frontal cortex (MFC), 70
Anthony, B. J., 71
Antiparkinsonian therapy, 112
Antonova, E., 199
Aparicio, P., 136
Apathy or irritability, 156
Arai, M., 198, 221, 322, 327
Arboix, A., 83
Archicerebellum, 21, 126
Ardila, A., 70, 71, 76, 78, 101, 102, 107, 365
Arslantas, A., 152
Ashby, F. G., 45, 51, 101, 102, 103, 104, 235
Ashe, J., 140
Ashley, D., 151
Ashtari, M., 154, 156, 195, 198, 374
Asperger syndrome, 206
Aston, J. A., 243, 260
Ataxic motor syndrome, 155

Attention, 71, 195
Attention/action, mechanism for selection of, 10, 20, 34, 39, 42, 43, 191, 197, 246, 366
Attention deficit disorder, 49, 61, 77, 83, 110, 114, 154, 188–190, 189, 190, 194–199, 197, 198, 231, 316, 348, 369, 370
  inattentive type, 231
  See also DSM-IV behaviorally defined conditions
Attention Deficit Hyperactivity Disorder (ADHD), 80, 108, 114, 189, 194–199, 247, 373
  altered brain mechanisms, 195
  functional imaging, 195
  Raven's Progressive Matrices test, 196
  thumb rules for understanding anatomical differences, 196–199
  See also Vertically organized brain in clinical psychiatric disorders
Attwell, P. J., 132
Auditory Consonant Trigrams (ACT), 72, 84, 220, 283, 287*t*, 291, 296, 296*t*, 334*t*, 344, 357
Auditory hallucinations, 145, 200
  See also Dysmetria
Autism, 83, 154, 156, 176, 180, 202, 205–207, 206, 322
  deficits in, 206
Autism spectrum disorder, 154, 156, 205–207
  ASD-including Asperger syndrome, 205–207
Automatic behaviors, 80–81
Automaticity, definition, 95
Automaticity and higher-order control in communication/ language/social cognition
  declarative-procedural model of language, 172–173
    concept of subcortical contribution to language function, 172
    patients with dementia/Parkinson's disease, 174
    specific language impairment (SLI), 174
    theory of language function and impairment, 172–173
  gesture/communication/speech, 169–171
  implications of dual-system models for social cognition and language, 180–182
    cerebellar deficits, 182
    Non-Verbal Learning Disorder (NVLD), 181
  reflexive and reflective systems
    attentional control, 178
    hippocampal paralimbic division, 178
    paleocortical evolutionary progression, 178
  social cognition-automatic and higher-order control systems, 174–177
    role of mirror neurons, 175
    social procedures, 177
  social intuition/skill and non-verbal communication, 178–180
    cortical control, traditional model of, 182
    isolation and loneliness, 179–180
    non-verbal learning disability, 180
Automatic processing and basal ganglia, 55–56
  dopaminergic instrumental conditioning, 56
  'first-responder' profession, 56
  instrumental learning and behavior, 56
Automatic *versus* higher-order control, 57–58
Automation, 226
  See also Action learning
Awh, E., 48, 53, 115, 197
Azizi, S. A., 21, 138

B

Back, S. A., 348
Backman, L., 113, 304
Baddeley, A., 47, 220
Baker, J. G., 242
Baker, S., 115
Baker, T. E., 114
Bakshi, R., 49
Baldo, J. V., 74, 337
'Ballpark' behavior, 61
Banich, M. T., 8, 10, 19, 134, 271, 272
Barbadillo, L., 199
Barbeau, A., 172
Barbour, B., 139
Barch, D. M., 248
Bares, M., 139
Bar-Gad, I., 34, 35
Barker, G. J., 202
Barker, R. A., 48, 49, 112, 116
Baron, I. S., 250
Baron-Cohen, S., 176
Barth, J., 169
Bartres-Faz, D., 83
Basal ganglia

anatomical structures and subdivisions, 28–33
anterolateral view, 29*f*
drawings of horizontal and coronal sections through, 30*f*
essential features of, 44–45
four structures, 28
input structures, 32*t*
intermediate structures, 32*t*
lateral view, 28*f*
mechanisms
basic mechanisms, 36
inhibitory, 20
learning, 59
selection, 51
and neuropsychological testing, *see* Neuropsychological testing and basal ganglia
output structures, 32*t*
pathology, 2
role in attention and action selection, 246
subdivisions, 31*t*
subthalamic nucleus (STN), 31
Basal ganglia, beyond motor system
anatomical structures and subdivisions of, 28–32
application of motor behavior to cognition, 42–44
surgical pallidotomy, 43
and automatic processing, 55–56
dopaminergic instrumental conditioning, 56
'first-responder' profession, 56
instrumental learning and behavior, 56
automatic *vs*. higher-order control, 57–58
circuitry, 32–33
basic cortico-basal ganglia circuitry, 33*f*
context and higher-order control in combination, 54–55
cortico-striatal system, function, 41–42
direct and indirect pathways, 36–37
essential features of, 44–45
five different pathologies, 27
frontostriatal system in operation, examples, 44–45
higher-order cognition and working memory, 46–49
integrated cortical–subcortical model of behavioral selection, 58
pathology/developmental disorders, 61–62
obsessive-compulsive disorder, 61
prefrontal cortex (PFC) decides upon behavior, 59–61
selection pathways (three), 42
sensitivity to context, basal ganglia in learning, 45–46
categorization, 46
WCST, 45
specific projections into striatum, 34–36
striatum, learning and mobilizing procedures, 58–59
learning, 59
striosomal pathway, 38
subcortical loops, 38–40
limbic circuit, 40
sensory integration disorder, 40
subthalamic pathway, 37–38
working memory, working of, 50–54
'central executive', 52
cerebellum, role of, 54
'error-detection' system, 54
serial order processing, 50
Basal ganglia and learning
declarative learning, 98
'habit system', 96
motor skill learning, 99
prism adaptation, task of, 99
sequence learning, 96
sequential reaction time task (SRT), 97
visuomotor learning tasks, 97
Basar, E., 6
Basso, M. A., 17, 27
Bastian, A. J., 132, 139, 273
Batson, C. D., 176
Baumgartner, T., 179
Baunez, C., 43
Baxter, L. R., 191, 192, 193
Bayley, P. J., 41, 103, 172, 368
Bearden, C. E., 207
Beauchamp, M. H., 242, 243, 260, 266, 267
Bedard, M. A., 2, 43
Beer, J. S., 174, 175
Behavioral processing and frontostriatal system, theories of types, 14–16
card sorting test, 14
dual-layered control system, 15
frontostriatal system, characteristics, 15–16
higher-order control, 14–15
instrumental behavioral system, 15
stimulus-based control, 14
See also Vertically organized brain/movement/cognition
Behavioral programming mechanisms, 158

Behavior Rating Inventory of Executive Function, 84
Beiser, D. G., 99
Bellebaum, C., 113
Bellodi, L., 61
Benasich, A. A., 154
Benedict, R. H., 49
Beninger, R. J., 104
Benton, A. L., 84, 86, 283, 308
Benton Finger Localization, 84, 283
Ben-Yehudah, G., 220
Bergman, H., 34
Berman, K. F., 47, 236
Berquin, P. C., 195
Bhutta, A. T., 347
Biederman, J., 52
Bigelow, N. O., 132, 202, 273, 372
Bilder, R. M., 245
Bipolar affective disorder, 284
Black, F. W., 245
Blair, C., 192
Blakemore, S. J., 46, 174
Blalock, G., 283
'Blind diagnosis', 188
Block Design subtest, 263, 267
Blumenfeld, H., 2, 13, 81, 129, 137, 138, 151
Bocconi, L., 117
Boecker, H., 57, 73, 242
Bohil, C. J., 104
Boks, M. P., 201
Bombois, S., 83
Bonci, A., 108
Bondi, M. W., 235
Book, G. A., 192
Borner, H., 195
Boschetto, C., 117
Boston Naming Test, 84, 283
Botez, M. I., 172
Bower, J. M., 125, 130
Bowirrat, A., 78
Bradshaw, J. L., 61, 77, 83, 97, 197, 199, 358, 369, 373
Bradyphrenia, 81
Brain
  in clinical psychiatric disorders, *see* Vertically organized brain in clinical psychiatric disorders
  regions of, 366
  systems, vertically organized, 6–9
    cerebro-cerebellar circuitry, 8
    cortico-striatal-pallidal-thalamic loop, 7
    'looped' architecture, 6
    simplified version of cerebro-cerebellar circuit, 8*f*
    simplified version of frontal–subcortical circuit, 7*f*
  systems in parallel
    illustration of cortico-basal ganglia and cortico-cerebellar interactions, 143*f*
    See also Vertically organized brain/movement/cognition
Brandt, J. P., 4
Bransome, E. D., Jr., 245
Brass, M., 172
Brass, S. D., 49
Brasted, P. J., 105
Braun, C. M., 76
Braus, D. F., 199
Brauth, S. E., 17
Braver, T. S., 248
Brent, M. M., 207
Brooks, D. J., 57, 73, 242
Broring, T., 196
Brown-Peterson technique, 72, 84, 220, 344
Bruhn, P., 195
Brunia, C. H., 132
Bruno, S. D., 207
Buchsbaum, B. R., 47
Buchsbaum, M. S., 247
Buckner, R. L., 231–232
Bunge, S. A., 195
Burgess, P. W., 73
Busatto, G. F., 200
Bushara, K. O., 140
Butler, R. W., 74

C

Cacioppo, J. T., 180
Cahir, M., 201
California Verbal Learning Tests (CVLT), 84, 230
  Test-II (CVLT-II), 85*t*
Caltagirone, C., 72, 133
Cambridge Gambling Task, 114
Cangelosi, A., 167
Cannon, T. D., 207
Caplan, D., 126, 134, 139
Carlesimo, G. A., 72
Carlin, D., 73
Carmona, S., 195
Carnahan, H., 201
Casale, M. B., 51
Casey, B. J., 196, 199

Casey, P. H., 347
Castellanos, F. X., 114, 154, 194, 195, 199, 373
Castelli, L., 112
Catani, M., 128, 154, 172, 176, 206, 323
Categorization and classification, 101–107
  category judgments, 102
  direction of dynamic anatomic change during category learning, 106*f*
  'emotional/motivational executive functions', 102
  'executive' ability, 104
  explicit category learning, 105
  hippocampal learning and memory system, 107
  information-integration learning tasks, 104
  'metacognitive executive functions', 102
  prefrontal lobe activity, 105
  probabilistic learning, 103
  social evaluations, 102
  timing, feature of, 107
  unstructured categories, 103
  visual discrimination learning, 102
  Wisconsin Card Sorting Test (WCST), 104–105
Category fluency, 87*t*
Category learning, 45, 55, 75, 96, 103, 106*f*, 136, 178, 239
  dynamic anatomic change, 106*f*
  information-integration, 107
  mechanisms of, *see* Category learning
  probabilistic, 104, 201, 273
  rule-based, tasks, 45, 73, 105, 107, 235
Cavedini, P., 61
Cell assemblies, 19
Cellular bridges, 18
Cerebellar cognitive affective syndrome
  feed forward/feedback, 151
  limbic cerebellum, 151
  plasticity, 151
  visuospatial deficits, 150
Cerebellar function, theories of
  detection and correction of errors in skill learning, 139
  learning machine, 140
  verbal working memory, 139
Cerebellar motor syndrome, 148
Cerebellar 'soft signs', 202
Cerebellum
  agenesis of, 153
  brain (three) systems in parallel
    illustration of cortico-basal ganglia and cortico-cerebellar interactions, 143*f*
cerebellar cognitive affective syndrome
  feed forward/feedback, 151
  limbic cerebellum, 151
  plasticity, 151
  visuospatial deficits, 150
cerebro-cerebellar circuit, 134–137, 135*f*
clinical presentations, 148–149
  cerebellar motor syndrome, 148
  cognitive deficits, 149
  limbic cerebellum, 149
  swaying of 'tremor', 149
  undershooting and overshooting, 148
cortex and cerebellum-superficial comparison of infrastructure, 128–129
DSM-IV behaviorally defined conditions, 154–155
dysmetria, significance, 143–145
  thinking, 144
dysmetria, undershooting and overshooting, 157
  affective disturbances, 157
  concrete thinking, 157
  paralyzing anxiety of panic attack, 157
functional regions, 21–22
  'fine-tuning', 21
  'online' adjustments, 21
hybrid model of, 140–142
infrastructure of cerebellum, 129–131
  interneurons, classes of, 129
as modulator, 155–157
  ataxic motor syndrome, 155
  sensory integration disorder, 157
and non-motor functions, 131–133
  cerebellar-hypothalamic connections, 132
  eye-blink conditioning, 132
olivo-cerebellar system, 137–138
  climbing fibers, 138
posterior fossa syndrome, 151–153
  behavioral syndrome, 152–153
  language deficits, 152
and principle of lateral crossed control, 137
in procedural learning, 133–134
  right cerebellum, role of, 133
  serial reaction time task (SRT), 133
subregions of, 127*f*
surface anatomy of, 126–128
  archicerebellum, 126
  subregions of cerebellum, 127*f*
theories of cerebellar function
  detection/correction of errors in skill learning, 139

Cerebellum (*cont.*)
'learning machine', 140
verbal working memory, 139
very pre-term infants, 153–154
working memory/expertise/creativity/giftedness, 145–148
'deliberate practice architecture', 147
forward and inverse models, 146
multiple inverse control models, 146
Cerebellum in neuropsycholocial testing
clinical case examples
case 1, high-functioning Autism *versus* Asperger's disorder, 322–330
case 2, known cerebellar pathology in left posterior hemisphere, 330–337
case 3, ADHD, OCD, and bipolar disorder, 337–347
case 4, Asperger's disorder/other complications, 347–359
Cerebro-cerebellar circuit, 134–137, 135*f*
simplified version of, 8*f*
Cervenka, S., 113, 304
Chabot, R. J., 194
Chan, A. S., 74, 232
Chan, Y. S., 128
Chang, C., 49, 302
Chavez-Eakle, R. A., 129, 147
Chelune, G. J., 14, 84, 235
Chen, H. M., 83, 298, 375, 376
Cheney, M. K., 142
Cheon, K. A., 195
Chitnis, X. A., 202
Chomsky, N., 167
Choudhury, N., 154
Chouinard, S., 2, 15, 43, 221, 223
Chow, T. W., 70, 76, 78, 82, 100, 277
Chui, H., 83
Ciaramidaro, A., 175
Cicchetti, D. V., 181
Cicchetti, F., 37
Cincotta, C. M., 45, 46, 55, 103, 105, 107, 267
Circuitry, basal ganglia, 33, 32*f*
Clark, E. C., 191
Clark, J., 103, 172, 368
Clark, L., 78, 104, 112
Clark, R. E., 16, 41, 228, 279
Classroom behavior, 189
Claus, E. D., 45, 104, 113
Clementz, B. A., 80
Cleves, M. A., 347
Clinical psychiatric disorders, 187–208
Coding/Digit Symbol test, 263
Cognitive and affective theory of mind (ToM) function, 175
Cognitive and neuropsychological tests, 248–250
Cognitive control episode, 223, 228
Cognitive deficits, 5, 43, 113, 148–150, 149, 152, 188, 199, 202–203, 207, 348, 361
'Cognitive', definition, 188
Cognitive dysmetria, 12, 145, 203, 205331
Cognitive sequence learning, 97, 133
Cohen, D., 139
Cohen, H., 172
Cohen, R. A., 246, 278
Cohen, R. M., 247
Coizet, V., 39
Concrete thinking, 157
Conscious declarative memory, 266
Content practice effects, 265, 268
Continuous performance and go–no-go tasks, 245–248
act of 'paying attention', 246
disinhibition syndromes, 248
inhibition, 247
Continuous performance test (CPT), 76
Controlled motor function, 280
Controlled practice effect, 268
Cools, R., 112
Cooper, K. L., 194
Coordination of movement, *see* Cerebellum
Corkin, S., 272
Cortese, L., 201
Cortex
and cerebellum-superficial comparison of infrastructure, 128–129
lesions of, 2
Cortical mechanisms, 48, 143
Cortical–subcortical projection system, 100
Cortico-basal ganglia
and basal ganglia–subcortical circuitry, Illustration of, 39*f*
circuitry, 33*f*
Cortico-basal ganglia and cortico-cerebellar interactions, illustration of, 143*f*
Cortico-centric bias, reason for, 5–6
Cortico-centric model of brain organization, 3
Cortico-cerebellar procedural learning systems, 17
Cortico-striatal learning mechanisms, 181
Cortico-striatal-pallidal-thalamic loop, 7
Cortico-striatal procedural learning systems, 17

Cortico-striatal system, function, 41–42
Courchesne, E., 136, 139, 140, 153, 154, 206
CPT, *see* Continuous performance test (CPT)
Cradock, M. M., 343
Craighero, L., 175
Crespo-Facorro, B., 23, 199
Criscimagna-Hemminger, S. E., 139
Crosson, B., 172
Crottaz-Herbette, S., 49, 302
Crowding effect, 206
Crowe, S. F., 12, 150
Cselenyi, Z., 113, 304
C-system, 177
Culbertson, C. W., 84
Culbertson, W., 235, 283
Cummings, J. L., 3, 70, 71, 74, 75, 76, 77, 78, 81, 82, 83, 100, 178, 191, 193, 207, 277
Cunningham, W. A., 178
Cunnington, R., 197, 358
Curran, T., 178
Curtis, G., 14, 84, 235, 283
Cusimano, M., 138
CVLT-II, *see* California Verbal Learning Tests (CVLT)

D

Dagher, A., 54, 57, 73, 236, 242, 243, 260, 309
Damasio, A. R., 157
Damasio, H., 157
Daum, I., 113, 153
Dawson, L., 79
Dayan, P., 50
Dean, P., 375
Decety, J., 176, 180
Declarative and lexical knowledge, 181
Declarative/episodic recall, 257
Declarative learning, 98
Declarative memory, mediation of, 172
Declarative-Procedural model, 172
Deco, G., 97
Deep brain stimulation (DBS), 43
Deep cerebellar nuclei, illustrating size and convolutions of dentate nucleus, 137*f*
Delbello, M. P., 207
Delgado, M. R., 35, 78, 104, 179
Delis, D. C., 74, 84, 230, 262, 283, 309, 337
Delis-Kaplan Executive Function System, 84, 283
Della, S. S., 241
DeLong, M. R., 6, 32, 69
Dementia, case of, 3–5, 4*t*
  neuropsychological testing, 4
Denckla, M. B., 37, 75, 194, 197, 246, 279, 325, 327, 345, 348
Dennis, M., 140, 152
Denys, D., 191
Deoni, S. C., 128
Derbyshire, S., 132
Deshmukh, A., 12
D'Esposito, M., 46, 48, 50, 220
Developmental disorders, 37, 61–62, 77, 79, 80, 113, 220, 247, 261, 317, 347, 367, 369, 372, 374
Devito, E. E., 114
Di, X., 97
Diagnostic and Statistical Manual (DSM), 187
Diamond, A., 151, 280, 348
Diedrichsen, J., 139
Dieudonne, S., 139
Diiaz, R., 273
Dillon, D. G., 104, 109
Di Martino, A., 33, 195
Di Michele, F., 194
Dimitrova, A., 153
Diseases
  degenerative cerebellar diseases, 151
  Huntington's diseases, 2, 27, 36, 37, 42, 48, 62, 72, 79, 97, 179, 201, 202, 272, 291, 316, 367
  Parkinson's diseases, 2, 3, 13, 27, 30, 35, 36, 42, 43, 44, 48, 62, 72, 73, 79, 97, 110, 111, 112, 115, 116, 135, 136, 174, 179, 201, 231, 242, 273, 293, 367
Disinhibition, 369
  syndromes, 248
Disordered thinking, 369
Disorders
  attention deficit disorder, 49, 61, 77, 83, 110, 114, 154, 188, 189, 190, 194–199, 197, 198, 231, 315, 316, 348, 369, 370
    inattentive type, 231
  attention deficit/ hyperactivity disorder, 80
  autism spectrum disorder, 154, 156, 205–207
  bipolar affective disorder, 284
  clinical psychiatric disorders, 187–208
  developmental disorders, 37, 61–62, 77, 79, 80, 113, 220, 247, 261, 317, 347, 367, 369, 372, 374

Disorders (*cont.*)
disordered thinking, 369
fundamental academic skills disorder, 359
hyperkinetic or hypokinetic movement, 2
impulse control and motivational disorders, 368
language disorder, 74, 152
mental disorders, 180
mood disorder, 156, 206, 207
of movement intention, 81
Non-Verbal Learning Disorder (NVLD), 181
obsessivecompulsive disorder, 61, 191–194
post-concussion disorder, 190
psychiatric disorders, 49, 81, 83, 126, 187–208
psychosis spectrum disorders, 156
schizophrenia, multiple systems disorder, 49, 61, 62, 83, 109, 154, 176, 180, 188–191, 199–204
sensory integration disorder, 40, 157
thought disorder, 12, 203–205, 369
Dissociable neuronal mechanisms, 194
Distractibility task, 87*t,* 88*t*
Divac, I., 7, 18
Division of labor, 50
Dixon, V., 224, 259
DLPFC, *see* Dorsolateral prefrontal cortex (DLPFC)
DLPF syndrome, 72
Dockstader, C., 196
Dolan, R. J., 49
Dominey, P. F., 96
Dopamine
activity, 111–115
-dependent tasks, 112
depletion, 110
inhibited neurotransmission, 110
-mediated reward systems, 175
Dopaminergic activity, 110
Dopaminergic 'bursts and dips', 115
Dopaminergic instrumental conditioning, 56
Dopaminergic instrumental learning mechanisms, 116
Dopaminergic mechanism, 116
Dopaminergic spike/burst, 111
Dorfler, A., 153
Dorsolateral prefrontal cortex (DLPFC), 70
Dove, A., 49
Doya, K., 9, 108, 142, 268, 368
Doyon, J., 17, 98, 99, 133, 242, 243, 259, 260, 267
D1 receptors, 110
D2 receptors, 110
Dronkers, N. F., 172
DSM, *see* Diagnostic and Statistical Manual (DSM)
DSM-IV behaviorally defined conditions, 154–155
Dudukovic, N. M., 195
Duff, K., 264, 316
Duffau, H., 172
Dujardin, K., 44
Duncan, C. C., 71, 278, 303, 313
Du Plessis, A. J., 154
Durston, S., 195, 196
Dysexecutive syndrome, 43, 71–72, 72, 73, 84, 367
Dyskinesia, 82
Dysmetria, 2, 12, 129, 132, 143–145, 148, 157, 203, 205, 329, 348, 364, 367
significance, 143–145
thinking, 144
undershooting and overshooting, 157
affective disturbances, 157
concrete thinking, 157
paralyzing anxiety of panic attack, 157
Dystonia, 27

E
Early, T. S., 201
Easton, N., 195
Eckerman, C. O., 347
'Ecological validity', problems with, 83
Edwards, C. R., 202
Edwards, J. D., 172
Eitam, B., 178, 365
Ekerot, C. F., 130
Ell, S. W., 51
Emily, C. B., 207
Emory, E., 221
'Emotional/motivational executive functions', 107
Emre, E., 152
Enkephalin (ENK), 36
Ennis, J. M., 101, 102, 104, 235
Environmental dependency syndrome, 76
Erhan, C., 152
Ernst, M., 206
Error detection mechanisms, 144
Esref, T., 152
Evans, A. C., 66, 242
Everett, B. J., 109
Excitation *versus* inhibition, 19–20
Excitatory mechanisms, 19

Executive functioning, 75, 83, 106, 150, 227, 228, 262, 287*t*, 290, 296*t*, 301*t*, 308*t*, 321, 333*t*, 357
deficit, 75, 78, 199, 303, 374
impaired, 42, 153
Explicit category learning, 105
Explicit/declarative knowledge, 267
Eye-blink conditioning, 132, 140

F
Fahn, S., 2, 43
Fallgatter, A. J., 193
Fan, J., 358
Faraone, S. V., 52, 195, 196
Farber, R. H., 80
Farde, L., 113, 304
'Faster' processing, 98
Faure, P., 265
Fawcett, A. J., 182, 327, 372, 373, 374
Fehr, E., 179
Feifel, D., 80
Fernandez-Ruiz, J., 273
Ferri, J., 47
Ffytche, D. H., 172
Fiez, J. A., 142, 220
Filipek, P. A., 195
Filoteo, J. V., 45, 107, 375
Finch, A. J., 182
Fineberg, N. A., 191
'Fine-tuning' behavioral output, 130
Finger localization test, 87*t*
'Finger sequencing', 283
Fink, G. R., 137, 175, 195
Fischbacher, U., 179
Fitch, W. T., 167
Fitzpatrick, L. E., 12, 150
Fletcher, J. M., 189
Fliessbach, K., 175
Flocculonodular lobe, 21, 126
Flombaum, J. I., 358
Foerde, K., 104, 201, 272, 372
Fogassi, L., 175
Fone, K., 195
Fontaine, D., 191
Fontenelle, L. F., 194, 370
Fossella, J., 358
Franceschi, M., 241
Frangou, S., 202
Frank, M. J., 35, 36, 37, 41, 43, 44, 45, 49, 50, 51, 60, 89, 103, 110, 111, 112, 113, 114, 115, 116, 143, 178, 197, 199, 220, 280, 292, 375
Frazier, J. A., 207
Freeman, W. J., 6
Frey, K. A., 192, 348
Friederici, A. D., 172
Friston, K. J., 375, 376
Frith, C. D., 46, 174, 175
Frith, U., 174
Frontal lobe syndrome, 82
Frontal–subcortical circuit, simplified version of, 7*f*
Frontal–subcortical real estate
divisions of frontal cortex and anterior circuits, 70–71
emotional/motivational executive functions, 71
metacognitive executive functions, 70
DLPFC, 71–75
attention, 71–72
deficits in programming new motor movements or behaviors, 74
language, 74
lesions, 71
neuropsychological tests, 74
performance on tests of learning and memory, 74
frontal system syndromes, 82–89
medial frontal circuit (MFC)/anterior cingulate circuit, 77–79
motor circuits, 79–80
hypokinetic movement disorders, 79
motor/cognitive/motivational/affective analogues, 80–82
orbitofrontal circuit (OFC), 75–77
prototypical cortico-striatal–pallidal–thalamic circuits, 70*f*
Frontal–subthalamic nucleus (STN), 196
Frontal system syndromes, 82–89
Frontostriatal/cognitive control episode, 228
Frontostriatal gating mechanisms, 327
Frontostriatal or cognitive control episode, 228
Frontostriatal system, evaluation
commonly used neuropsychological and cognitive tests, 249–251
continuous performance and go–no-go tasks, 245–248
act of 'paying attention', 246
disinhibition syndromes, 248
'inhibition', 247
dynamically changing locus of control, 225–226
frontostriatal system, 221–222

Frontostriatal system, evaluation (*cont.*)
ways of controlling cognitive processing, 222
frontostriatal system in operation, 222–223
interpretation paradigms, 224–225
neuropsychological testing and frontostriatal system, 226–228
Stroop Color Word Test, 233–235
task comparisons, 243–244
relationships between WCST and TOL, 244
test methodologies for identifying integrity of frontostriatal system, 228–232
traditional 'frontal lobe' problem-solving tests, 235–243
response decks, 238*t*, 240*t*
'rule violations' task, 243
Tower of London Test (TOL), 241–243
verbal fluency tasks, 232–233
working memory tests, 220
Frontostriatal system in operation, examples, 44–45
Fuentes, L. J., 197, 246
Fundamental academic skills disorder, 361
Funkenstein, H. H., 132, 273
Fusar-Poli, P., 199
Fuster, J. M., 11, 20, 43, 51, 71, 72, 76, 278

G
GABA, 36, 37
Gabrieli, J. D., 48, 97, 195, 261, 272
Gado-Garcia, J. M., 132
Galeno, R., 201
Gallese, V., 175
Garagnani, M., 19
Garavan, H., 52, 224, 259
Garvey, M. A., 280
Gaser, C., 12
Gasson, N., 79
Gautier, J. F., 132
Gauvreau, K., 154
Geday, J., 44
Geffen, G., 104
Geffen, L., 104
George, M. S., 78, 200, 201
Georgiadis, J. R., 132
Gerton, B. K., 49, 54, 302
Gesture, communication, and speech, 169–171
cerebellum, role of, 170
'non-verbal' communication, 171
social cognition and language, 171
Gesturing, 169
Gidley-Larson, J. C., 373
Giedd, J. N., 194, 195
Giese, M., 103
Giladi, N., 112
Gilhooly, K. J., 241
Gioia, G., 84, 89
Giorgi, C., 149, 151, 152
Gjedde, A., 44
Glass, B. D., 107
Glickstein, M., 127, 153
Globus pallidus (Gpi), 7, 17, 29, 31, 39, 42, 52, 77, 83, 97, 98, 192, 193, 200–202, 220, 277, 298, 309
Glover, G. H., 50, 197, 201, 246
Gluck, M. A., 96, 103
Goel, V., 73
Goetz, C. G., 261
Goldberg, E., 77, 168, 336, 365
Goldberg, T. E., 245
Golden, C., 84, 283
Goldman-Rakic, P. S., 47, 204
Goldsamt, L., 370
Goldstein, R. F., 347
Go-no-go tasks, 189, 195, 245–248
Gonzalez, A., 17
Goodglass, H., 84, 283
Goodman, W. K., 193
Goodyear, B. G., 172
Gordon, M. F., 84, 87, 283
Gordon, N., 149
Gordon Diagnostic System, 84, 87*t*, 283, 284
Gorini, A., 61
Gowen, E., 155, 202
Graceffa, A. M., 72
Graff-Radford, N. R., 4
Grafman, J., 12, 73, 139, 175
Grau-Olivares, M., 83
Graybiel, A. M., 33, 97, 202, 223, 224
Gray Oral Reading Tests, 283, 342, 355
Griffiths, D., 132
Groisser, D. B., 246
Grooved Pegboard, 84, 283
Grossberg, S., 140
Growdon, J. H., 272
Gruart, A., 132
Gruber, A. J., 50
Grupp, L. A., 207
Guediche, S., 220
'Guessing' or 'intuition', 103

Guirao, M., 201
Gunay Kilic, B., 196
Guntekin, B., 6
Gunturkun, O., 176
Guo, N. W., 83, 298
Gurney, K., 10, 20, 41
Gutbrod, K., 77
Gutkin, B. S., 50
Guttman, M., 201
Guy, S., 84
Guzzetta, F., 21, 126, 151

H
Habeck, C., 46
Habit formation, 114
Habit system, 96
Hager, F., 77, 247
Haidar, H., 153
Hale, T. S., 196
Hall, C., 273
Halldin, C., 113, 304
Hallett, M., 12, 132, 273
Hallucinations, auditory, 200
Hamburger, S. D., 194
Hamilton, J. M., 49
Hanisch, C., 195
Harada, M., 327
Harding, I., 371
Hargreaves, I. S., 172
Hariri, A. R., 196
Harris, J. G., 49
Harte, M. K., 201
Harvey, P. D., 201, 224, 259
Hassin, R. R., 178, 365
Hatta, T., 143, 322
Hauser, M. D., 167, 169
Haxby, J. V., 10, 47
Hayden, J., 115
Hayter, A. L., 54
Hazeltine, E., 97
Hazy, T. E., 50, 51, 220, 280
Heaton, R. K., 14, 73, 84, 87, 235, 283
Hebb, D. O., 19
Hebben, N., 265, 334
Heekeren, H. R., 54, 59, 60, 109, 175
Heiman, J. R., 133
Heimer, L., 17, 20, 40, 42, 77, 109
Heindel, W. C., 49, 67, 372
Heinke, D., 375
Hein-Kropp, C., 153
Heinrichs, M., 179
Henn, F. A., 199
Henriksen, L., 195
Henry, L. C., 172
Henson, R. N., 231
Herbert, J. S., 347
Hermsdorfer, J., 153
Herpertz-Dahlmann, B., 195
Herrmann, M. J., 193
Herzog-Krzywoszanska, R., 107
Heslenfeld, D. J., 195
Heuer, H., 97
Heuvel, O. A., 191
Higgens, E. S., 200
Higher-order control, 14–16, 22, 47, 52–55, 97, 101, 102, 104, 135, 222–227, 233–234, 280, 315, 335, 349, 365–367
  alternating episodes of automatic *versus,* 57–58
  automatic behavior and, 80
  and automaticity in communication, 167–183
  automatic responding and, 226
  context and, 54–55
  deficits in, 292
  interactions between automatic processing and, 101–102
  PFC supervisory, 60
  'precursor' of, 283
  prefrontal cortex and, 135
  problem-solving and, 15
  stimulus-based responding and, 225, 374
  working memory and, 145
Higuchi, S., 141
Hikosaka, O., 40, 268
Hill, D. E., 195
Hill, J., 74
Hippocampal learning and memory system, 107
Hirata, K., 198, 212, 322, 327
Hocking, J., 376
Hodges, J. R., 34, 100
Hodgetts, H. M., 241
Hodgins, S., 76
Hoffman, K. M., 207
Hogg-Johnson, S., 115
Hokkanen, L. S., 149, 150
Holroyd, C. B., 114
Holstege, G., 132
Horwitz, B., 134
Houk, J. C., 2, 8, 12, 21, 34, 36, 41, 44, 45, 99, 125, 128, 132, 136, 138, 140, 141, 143, 199, 202, 203, 366
Howieson, D., 72, 227, 245, 258

Hozumi, A., 198, 221, 322
Hu, D., 126, 129, 130, 148, 149
Huber, J. F., 152
Huber, W., 172
Hubert, V., 142, 266
Hull, E. M., 133
'Humaniqueness', 169
Huntington's disease, 13, 201
  See also Vertically organized brain/movement/cognition
Husted, D. S., 193
Hybrid model of cerebellar function, 140–142
Hynd, G. W., 195
Hyperdirect pathway, 37, 42
Hyperkinetic or hypokinetic movement, 2
Hyperphrenia, 81

I
Iacoboni, M., 175
'Imagined speech' task, 200
Imamizu, H., 141
Impulse control and motivational disorders, 367
Inattention, 369
Infants, very pre-term, 153–154
Inferotemporal and parietal loops, 99–101
Information-integration learning tasks, 104
Information processing, 98
Infrastructure of cerebellum, 129–131
  interneurons, classes of, 129
  summary of, 131*f*
Ing, A. D., 104
Inhibitory mechanisms, 20, 206
Inner speech, misidentification of, 200
Instrumental emotional responses, 118
Integrated brain, implications for neuropsychological evaluation
  clinical applications, 368–376
    cortico-centric model of cognition, 376
    cortico-striatal loops, dissociation of, 371
    developmental disorders, 372
    disinhibition, 369
    evaluating ADHD, 373
    executive dysfunction, 369
    experimental neuroscience, 375
    inattention, 369
    instrumental learning, 372
    negative symptoms, 370–371
    neuropsychological tests, 369
    reinforcement based/supervised learning, 373
    schizophrenia and ADHD, 370
    schizophrenia and procedural learning tasks, 371
    specific language impairment (SLI), 372
  flexibility of interaction, 365–368
    basal ganglia, or cortico-striatal system, 368
    brain, regions of, 366
    cerebro-cerebellar system, 368
    cognitive dysexecutive syndrome, 366–397
    dual-system organization of behavioral control, 364
Integrated cortical–subcortical model of behavioral selection, 58
Intention programs
  categories, 81
  when to do things
    'separation anxiety', 14
    'stimulus-based' responding, 13
Intention tremor, 12, 132, 148, 149, 329
  See also Cognitive dysmetria
Interactions, 'rule-based' aspects, 257
Intermediate zones, cerebellum, 126
Interpretation paradigms, 224–225
'Interrupts or intrudes upon others', 197
Intuitive grammar, 172–173
'In utero', behaviors, 117
Iowa Gambling Task, 104, 194
Iqbal, M., 191
Isaias, I. U., 112
Isles, R., 104
Isoardi, R., 201
Isope, P., 139
Isquith, P., 84
Ito, M., 139, 140, 141, 142, 145, 147, 365
Ivarsson, M., 132
Ivry, R. B., 97, 136, 321, 326
Izhikevich, E. M., 6
Izuma, K., 179

J
Jackson, M., 12, 150
Jacob, C., 193
Jaeger, J. J., 172, 245
Jagust, W. J., 115
Jansen, A., 137
Jantzen, K. J., 139
Jeannerod, M., 96
Jenkins, M. A., 246, 247, 278
Jimenez-Diaz, L., 132

Joel, D., 17, 35, 57, 59, 60
Johansen, E. B., 114, 374
John, E. R., 194
John, O. P., 175
Johns, L. C., 83
Johnsen, E., 44
Johnstone, S., 18
Jonas, B., 73
Jones, D. M., 241
Jones, S., 108
Jones-Gotman, M., 132
Jonides, J., 47, 48
Jorntell, H., 130
Josephs, O., 376
Joyal, C. C., 202
Joyce, E., 78
Junque, C., 83
Justus, T. C., 321, 326

K
Kalanithi, J., 96
Kalashnikova, L. A., 149, 198, 337
Kalivas, P. W., 78
Kaplan, E.F., 74, 80, 84, 230, 262, 265, 283, 334
Kaplan, J. T., 175
Kapur, N., 72
Karlsgodt, K. H., 154
Karni, A., 272
Kasai, K., 371
Kastrau, F., 172
Kates, W. R., 194
Katzir, T., 172
Kaufmann, R., 267, 317
Kaufmann, W. E., 194
Kauranen, V., 149
Kawagoe, R., 40
Kawakubo, Y., 371
Kawamura, M., 104
Kawato, M., 139, 141
Kay, G. G., 14, 84, 235, 283
Keele, S. W., 97
Kegl, J., 172
Kellam, S. G., 71, 93
Kelley, D., 52
Kelly, A. M., 199
Kelly, T. P., 245
Kelso, J. A., 139
Kemp, S., 247, 262, 283
Kennedy, S. H., 207
Kenworthy, S., 84
Keri, S., 49, 201, 236
Kerns, K. A., 114
Kerwin, R. W., 200
Kessenich, M., 347, 349
Ketteler, D., 172
Kiebel, S. J., 375, 377
Kiehl, K. A., 192
Kile, S. J., 199
Kim, J. J., 191, 192
Kim, S. H., 42
King, C., 72
King, M., 78
Kinoshita, T., 202
Kinsbourne, M., 16, 71, 234
Kirk, U., 247, 262, 283
Kirsch, J. A., 176
Kitt, C. A., 17
Klimkowicz-Mrowiec, A., 107
Klin, A., 181
Klingberg, T., 48, 49, 51, 53, 115, 205, 220
Knegtering, R., 201
Knight, J. A., 80
Knight, R. T., 47, 175
Knock and Tap subtests, 247, 312, 326, 327
Knowlton, B. J., 55, 57, 96, 99, 103, 349
Knutson, B., 114, 373
Knutson, K. M., 175
Kobayakawa, M., 104
Koch, B., 113
Koch, G., 133
Koch, P., 47
Koenigs, M., 175
Kolb, B., 6, 8, 19, 170
Konarski, J. Z., 207
Konishi, S., 236
Konrad, K., 195
Koob, G. F., 78
Korczyn, A., 2, 43
Korkman, M., 247, 262, 283
Korn, H., 265
Korsakova, N. K., 149, 198, 337
Kotila, M., 149
Kourtzi, Z., 103
Koyama, S., 104
Krain, A. L., 154
Kramer, J. H., 74, 84, 230, 262, 283, 337
Krebs, M. O., 154, 176, 199, 372
Kremer, J., 248
Krisky, C. M., 132
Krzywoszanski, L., 107
Kubler, A., 224, 259
Kujala, J., 172
Kumari, V., 371
Kustermann, A., 117

Kwan, A. L., 83, 298
Kwok-Chong, C. B., 128
Kyriakopoulos, M., 202

L
Lal, R., 115
Lamm, C., 176
Lampmann, E. E., 358
Landau, S. M., 115
Lang, C. E., 139
Langdon, D. W., 54
Language
  declarative-procedural model of, 172–173
    concept of subcortical contribution to language function, 172
    patients with dementia/Parkinson's disease, 174
    Specific Language Impairment (SLI), 174
    theory of language function and impairment, 172–173
  disorder, 74, 152
  and social cognition, dual-system models, implications of, 180–182
    cerebellar deficits, 182
    Non-Verbal Learning Disorder (NVLD), 181
    See also Automaticity and higher-order control in communication/language/social cognition
Lapierre, D., 76
Larsen, J. P., 201
Lateral crossed control, cerebellum and, 137
Lavond, D. G., 132
Lawrence, A. D., 34, 47, 48, 100
Lawrence, N. S., 193, 194, 370
Laywer, G., 199
Lazeron, R. H., 242
Le, M. M., 78
Learning
  and basal ganglia, action and reinforcement
    categorization and classification, 101–107
    cortical–subcortical projection system, 100
    diagram of temporal and parietal lobe prefrontal and basal ganglia circuitries, 101
    'emotional/motivational' executive functions, 100
    inferotemporal and parietal loops, 99–101
    positive and negative reinforcement learning, 108–118
    procedural and instrumental behaviors, 100
    Wisconsin Card Sorting Test (WCST), 104
    See also Basal ganglia and learning
  definition, 279
  mechanisms
    cortico-striatal, 181
    dopaminergic instrumental, 116
    instrumental and procedural, 219
Lee, A. Y., 83
Lee, K. H., 202
Lee, T. W., 197, 246
Leevers, H., 154
Leggio, M. G., 133, 372
Lehman, R. A., 73
Leng, N. R., 72
Leroi, I., 151
Letter fluency—FAS, 87*t*
Letter-Number sequencing, 220
Leung, H. C., 47
Levin, R. J., 132
Levy, F., 116
Lewis, S. J., 48, 49, 51, 112, 116
Lezak, M., 2, 72, 227, 232, 245, 249, 258, 264, 281, 289, 329, 337
Lhermitte, F., 76
Li, S., 103
Lichter, D. G., 3, 71, 72, 75, 76
Liddle, P. F., 201
Lieberman, M. D., 102, 177, 178
Lieberman, P., 167
Limbic cerebellum, 149, 151
Limbic/striosomal input mechanisms of basal ganglia, 59
Limperopoulos, C., 153, 154, 347
Lin, Y. H., 83, 298
Linden, D. E., 46
Little brain, 125
Liu, H., 365
Liu, T., 140
Logie, R. H., 241
Loh, M., 97
Lombardi, W. J., 43, 234
Loring, D., 72, 227, 245, 258
Lou, H. C., 195
Loughry, B., 35, 220
Love, B. C., 122

Lovell, M., 168, 336, 365
Luna, B., 206, 279
Luu, P., 259

M
McCaffrey, R. J., 263, 265, 266, 271
McCandliss, B. D., 358
McClure, M. M., 347
McCollough, A. W., 57
McCracken, J. T., 196
McDermott, K. B., 231
McDowall, J., 97
McHaffie, J. G., 39–40
Machizawa, M. G., 51, 57
McIntyre, R. S., 207
Mackie, S., 154, 155, 196, 198, 374
McNab, F., 48, 49, 51, 53, 115, 205, 220
Maddox, W. T., 104, 107, 136, 375
Mah, L., 175
Mainzer, K., 375
Maixner, W., 151
Makris, N., 127
Malhi, G. S., 207
Malla, A. K., 201
Malloy, P., 178, 193
Malloy, P. F., 71, 76, 80, 82, 204, 234, 246, 247, 278
Maltby, N., 192
Mamah, D., 200
Mamikonyan, E., 112
Manic/hypomanic patients, 81
Manipulating ideas, 145
Manly, C. F., 175
Mann, V., 182
Manner, H., 267
Marchant, N. L., 136
Margulies, D. S., 199
Marin, O., 17
Markowitsch, H. J., 175
Marois, R., 51
Marreiros, A. C., 375
Marrett, S., 54
Marsden, C., 195
Marsh, W. L., 194, 195
Marshall, F., 195
Martin, C. O., 157
Martinussen, R., 115
Massive inhibitory control mechanisms, 20
Mathiak, K., 170
Matsui, H., 73
Mattei, V., 191
Mattos, P., 194, 370
Mavritsaki, E., 375
Mayberg, H., 154, 207, 370
Mayr, U., 97
Mechanisms
  abnormal basal ganglia selection mechanisms, 349
  altered brain mechanisms, 195
  basal ganglia
    basic mechanisms, 36
    inhibitory mechanisms of, 20
    learning mechanisms, 59
    selection mechanisms, 51
  behavioral programming mechanisms, 158
  category learning, mechanisms of, *see* Category learning
  cortical mechanisms, 48, 143
  cortico-striatal learning mechanisms, 181
  dissociable neuronal mechanisms, 194
  dopaminergic instrumental learning mechanisms, 116
  dopaminergic mechanism, 116
  error detection mechanisms, 144
  excitatory mechanisms, 19
  frontostriatal gating mechanisms, 327
  inhibitory mechanisms, 20, 206
  learning mechanisms
    cortico-striatal, 181
    dopaminergic instrumental, 116
    instrumental and procedural, 219
  limbic/striosomal input mechanisms of basal ganglia, 59
  manipulating ideas, 145
  massive inhibitory control mechanisms, 20
  mechanisms of inhibitory control, 76
  multiple and flexible coding mechanisms of brain, 103
  noradrenergic mechanisms, 116
  PFC supervisory higher-order control mechanisms, 60
  prediction mechanisms, 376
  for selection of attention and action, 10, 20, 34, 39, 42, 43, 191, 197, 246, 366
  updating mechanisms, 53, 116
Mechanisms of inhibitory control, 76
Medial Frontal Circuit (MFC), 77–79
Medial-lateral gradient, layers, 126
  intermediate zones, 126
Medina, L., 18
Mega, M., 72, 74, 75, 76, 77, 81, 83, 100, 178, 191, 193
Mehta, M. A., 78
Mejia-Constain, B., 236

Melrose, R. J., 309, 344
Mendlowicz, M. V., 194, 372
Menon, V., 49, 50, 197, 201, 246, 302
Mental disorders, 180
Mental grammar, 172
Mental 'lexicon', 172–173
Mercuri, E., 21, 126
Merims, D., 112
Messerschmidt, A., 153, 347
Meston, C. M., 132–133
Mesulam, M. M., 128, 246
Meyer, E., 47
Meyers, J. E., 84, 283
Meyers, K. R., 84, 283
MFC, *see* Medial frontal circuit (MFC)
Miall, R. C., 155, 202
Michele, U., 194, 207
Mickel, S. F., 272
Middleton, F. A., 6, 7, 8, 19, 21, 28, 33, 34, 38, 45, 69, 73, 74, 83, 100, 136, 228
Milberg, W. P., 265, 334
Milham, M. P., 114, 373
Millar, L., 132
Miller, B. L., 75, 76, 83
Miller, E. K., 16
Miller, R., 19, 20, 36–40, 43, 55, 97, 100, 201
Mimura, M., 104
Mink, J. W., 18, 31, 32, 36, 37, 40, 41, 42, 55
Minnesota Multiphasic Personality Inventory, second edition, 283
Minshew, N. J., 206
Mirror-tracing task, 271
Mirsky, A. F., 71, 245, 278, 290, 303, 313, 334, 335, 343, 356–359
Mishkin, M., 10
Misra, M., 172
Molina, M., 133, 201
Molinari, M., 133
Molnar-Szakacs, I., 175
Monchi, O., 54, 57, 236, 239
Monkul, E. S., 207
Monteleone, G., 180
Montiel, J., 17
Mood disorders, 156, 206, 207
Morales, D., 17
Morey, L. C., 84
Morris, G., 34
Morris, J. P., 206
Morton, S. M., 132, 273
Mostofsky, S. H., 94, 373
Motor behavior to cognition, application of, 42–44
  surgical pallidotomy, 43
Motor skill learning, 55, 96, 99, 259, 268, 271–272
Mouchet-Mages, S., 154, 176, 199, 372
Moustafa, A. A., 43, 104, 115, 291
Movement intention disorder, 81
Mugnaini, E., 2, 8, 12, 125, 128, 132, 136, 138, 140
Mulder, M. J., 154
Muller, N. G., 47
Muller, U., 114
Multiple and flexible coding mechanisms of brain, 103
Munschauer, F., 49
Murray, K. E., 195
Myers, C. E., 96
Myers, D. C., 72

N
Nagano-Saito, A., 236, 290
Nagy, O., 97
Nakaaki, S., 78
Nakahara, H., 268
Nambu, A., 37
Navarro-Lopez, J. D., 132
Negative feedback effect, 110
Neggers, S. F., 358
NEPSY Neurodevelopmental Battery, 283
Nervous system, characteristics/ functions, 9–11
Neufang, S., 195
Neural system typography, psychiatric conditions/ developmental disorders/learning disabilities, 375*f*
Neuropsychological testing
  and frontostriatal system, 226–228
Neuropsychological testing and basal ganglia
  attention, domain of, 278
  body-side comparisons, 282–283
  clinical case examples, 283–317
    case 1, 283–293
    case 2, 293–298
    case 3, 298–304
    case 4, 304–309
    case 5, 310–316
  executive domain, 279
  interpretation paradigm, 280–281
  interpretive methodology, 278
  language domain, 278
  level of performance, 281
  pathognomonic signs, 282
  sensory and motor functioning, 279–280

tests, data interpretation, 283
test score comparisons/pattern analysis, 281–282
visual–perceptual–spatial domain data, 277
Neurosciences, 198
Neville, H. J., 172
Newman, A. J., 172
Neziroglu, F., 189, 347
Nicolini, U., 117
Nicolson, R. I., 182, 273, 327, 372–374
Nielsen, J. B., 195
Nigg, J. T., 199
Nissen, M. J., 267
Niv, Y., 110
Nllo-Vento, L., 80
Nobuhara, K., 202
Non-motor functions, cerebellum and, 131–133
cerebellar-hypothalamic connections, 132
eye-blink conditioning, 132
Non-verbal communication, *see* Gesturing
Non-verbal communication and social intuition/skill, 178–180
cortical control, traditional model of, 182
non-verbal learning disability, 180
social isolation and loneliness, 179–180
Non-Verbal Learning Disorder (NVLD), 181
Noppeney, U., 376
Noradrenergic mechanisms, 116
Nordahl, C. W., 154, 176
Norman, R. M., 201
Norris, C. J., 180
Nosarti, C., 154
Novelty-routinization hypothesis of hemispheric specialization, 168
Nowak, D. A., 153
Nudmamud-Thanoi, S., 201
Nusbaum, H., 180
NVLD, *see* Non-Verbal Learning Disorder (NVLD)

O

Ober, B. A., 84, 230, 283
Oberg, R., 7, 18
Object identification/recognition, 9, 10, 19, 34, 136, 280, 288, 293, 297, 303, 345, 358
Object location, 9, 10, 19, 34, 47, 100, 277, 280, 291, 314, 348, 358, 366
O'Brien, J. B., 103
Obsessive-compulsive disorder (OCD), 27, 191–194
auditory obsessions, 193
Globus Pallidus (Gpi), 192
hyperactive neural activity, 191
orbitofrontal circuit, 193
'rule-governed' behavior, 193
Tourette's syndrome, 192
Obwegeser, A. A., 43
OCD, *see* Obsessive-compulsive disorder (OCD)
Ochsner, K. N., 174
Odhuba, R. A., 83
OFC, *see* Orbitofrontal cortex (OFC)
'Off-task', 197
Oh, H., 47
Okamoto-Barth, S., 169
Okugawa, G., 154, 202
O'Leary, D. S., 12, 144, 205, 329
Olie, J. P., 154, 176, 199, 372
Olincy, A., 49
Oliveri, M., 133
Olivo-cerebellar system, 137–138, 142
climbing fibers, 138
Olsen, R. K., 47
O'Neil, J. P., 115
On-line error correction (mediated by cerebro-cerebellar circuitry), 203
Oosterlaan, J., 195
Orbitofrontal cortex (OFC), 70, 75–77
O'Reilly, R. C., 35, 41, 50, 89, 103, 111, 114, 178, 220, 280
Ortiz-Mantilla, S., 154
Oscar-Berman, M., 78
Ostergaard, K., 44
Ostwald, D., 103
Otten, L. J., 231
Ouellet, M. C., 242, 267
Overmeyer, S., 195
'Overshooting'/'undershooting', cognitive, 12
Owen, A. M., 48, 49, 57, 73, 116, 228, 242, 267

P

Paleocerebellum, 21, 126
Pallidum, 29
Pally, R., 118
Pancheva, R., 172
Pandya, D. N., 8, 125, 126, 134, 136, 137, 138, 321
Panic attack, paralyzing anxiety of, 157

Papathanasiou, I., 182
Paradiso, S., 12, 144, 205, 329
Parent, A., 17, 37
Pari, G., 104
Parisi, D., 167
Parkin, A. J., 72
Parkinsonian syndromes
  akinesia/bradykinesia, 79
Parkinson's disease, 2, 3, 13, 27, 30, 35, 36, 42–44, 48, 73, 81, 97, 110, 111, 112, 116, 136, 179, 201, 231, 242, 273
  See also Vertically organized brain/movement/cognition
Parsons, L. M., 125
Parvizi, J., 157
Passetti, F., 78
Pasupathy, A., 97
Pathologies (five different), 27
Pathology/developmental disorders, 61–62
PCT, *see* Probabilistic Classification Task (PCT)
Pelayo-Teran, J. M., 199
Pelphrey, K., 206
Penhune, V., 99, 133, 259
Pennington, B., 189
Peppe, A., 72
Perceptual Organization Index (POI), 334
Perceptual Reasoning Index, 250, 325, 355
Perretta, J. G., 104
Perry, W., 80, 199
Perseveration, 13, 14, 82, 229, 239, 290, 350
Personality assessment inventory (PAI), 84, 88*t*–89*t*
Pessoa, L., 193
Peter, H. S., 207
Petersen, S. E., 142, 247
Peterson, B. S., 192
Petre, V., 54, 236
Petrides, M., 47, 54, 236
Petrosini, L., 133, 141
Pexman, P. M., 172
PFC supervisory higher-order control mechanisms, 60
Pfefferbaum, A., 12, 50, 201
'Phasic' changes in dopamine levels, 110
Phillip, H. W., 207
Phillips, J. G., 80, 95, 96, 98, 143, 223, 259, 262
Phillips, L. H., 241
Phillips, M. L., 193
'Phineas Gage'syndrome, 76
Phobic social anxiety, 180
Picard, H., 154, 176, 199, 203, 372
Pickering, A. D., 104
Piefke, M., 175
Piek, J. P., 79
Pierpont, E. I., 172, 373
Pierson, R., 6, 135, 144, 200, 202, 205, 206, 321, 345
Pillon, B., 76
Piontelli, A., 117
Piyabhan, P., 201
Pizzagalli, D. A., 78, 111, 113
Plasticity, 151
Podell, K., 168, 245, 336, 365
Poldrack, R. A., 52, 80, 96, 97, 104, 172, 268
Ponzi, A., 51, 115
Porrill, J., 375
Positive feedback effect within striatum, 110, 111
Posner, M. I., 247, 358
Post-concussion disorder, 190
Posterior fossa syndrome, 151–153
  behavioral syndrome, 152–153
  language deficits, 152
Postma, A., 358
Poulin, R. M., 309, 344
Powell, S., 141
Practice effect, definition, 265
Prediction mechanisms, 376
Preece, M., 104
Prefrontal cortex (PFC) decides upon behavior, 59–61
Prefrontal lobe activity, 105
Prescott, T. J., 10, 20, 41
Price, G., 128, 199
Prichep, L., 194
Primary motor cortex, 136, 283
Prism adaptation, 202
Probabilistic Classification Task (PCT), 272, 370
Probabilistic learning, 103
Procedural learning
  cerebellum in, 133–134
    right cerebellum, role of, 133
    serial reaction time task (SRT), 133
  in neuropsychological evaluation, 268–271
    cortico-striatal loops, illutrations of, 269*f*
    trailmaking tests, 270–271
    Wechsler mazes, 269–270
    See also Thought in action
Procedural memory system, 172
Processing speed, 259–260

by-product of cognitive/executive control, 262–263
Coding/Digit Symbol subtest, 260
decisive advantage for adaptation, 264
definition, 224, 259
memory, types of, 265
Processing Speed Index, 260
Symbol Search subtest, 260, 261
types of processing speed, 263
WAIS III Symbol Search task, 261
See also Thought in action
Processing Speed Index, 249, 260, 261, 262, 325, 355, 356
Prototypical cortico-striatal/pallidal/thalamic circuits, diagram of, 70*f*
Prototypical syndrome, 181
Psychiatric disorders, 49, 81, 83, 126, 187–208
Psychosis spectrum disorders, 156
Pugacheva, O. V., 149, 198, 337
Pujol, J., 192
Pulvermuller, F., 19
Purdon, S. E., 372
Purkinje cell, 120–131, 142, 206

Q
Quay, H. C., 108

R
Rabbitt, P., 262
Rabinovich, M. I., 6
Rabinowitz, D. C., 189, 347
Radant, A., 49
Raemaekers, M. A., 358
Raichle, M. E., 142, 201
Ramnani, N., 54, 127, 136
Randolph, C., 283
Ranganath, C., 47
Rao, H., 97, 112, 236
Rao, S. M., 45, 52
Rapid naming tests, 262
Rapoport, J. L., 194, 199, 206
Rapoport, M., 154
Raven's Progressive Matrices test, 196
Ravizza, S. M., 54, 139, 198, 220
Ray Li, C. S., 197, 246
RCFT, *see* Rey Complex Figure Test (RCFT)
RCFT and Recognition Trial, 84
Rebok, G. W., 245
Recognition Trial, 84, 283
Redfern, B. B., 172
Redgrave, P., 10, 20, 39, 41, 44
Re-entrant systems, 6
Reflexive and reflective systems
attentional control, 178
hippocampal paralimbic division, 178
paleocortical evolutionary progression, 178
Reichenberg, A., 201, 224, 259
Reiman, E. M., 201
Reiner, A., 18
Reinforcement learning, positive and negative, 108–118
Cambridge Gambling Task, 114
dopamine depletion, 110
dopamine reward system, 108
habit formation, 114
instrumental emotional responses, 118
'in utero', behaviors, 117
reversal learning, 112
separation anxiety, 118
working memory problem, treatment of, 116
Reiss, A. L., 37, 75, 197, 246, 327, 348
Reitan, R. M., 274, 280, 282, 289
Remijnse, P. L., 191
Repeatable Battery for Assessment of Neuropsychological Status, 283
Repeating digits forward/backward, *see* Working memory
Resnick, N., 132–133
Reversal learning, 112
Reward-driven association learning, 17, 35, 38, 111
Rey Auditory Verbal Learning Test (RAVLT), 230, 284
Rey Complex Figure Test (RCFT), 84, 85*t*, 283
Reynolds, G. P., 201
'Rhythm' functions of cerebellum, 197
Ricciardi, E., 47
Richardson, E. D., 71, 76, 80, 82, 204, 234
Richardson, J. T. E., 47
Richer, F., 15, 221, 223
Richter, S., 153
Riddle, A., 347
Riecker, A., 170
Rinehart, N., 197, 358
Riva, D., 149, 151, 152
Rizzolatti, G., 175
Robbins, T. W., 34, 43, 48, 49, 100, 109, 112–113, 116
Robert, P. H., 191

Robertson, G. R., 283
Robertson, I. H., 246
Robinson, A. L., 73
Robinson, R. G., 248
Rodriguez-Sanchez, J. M., 199
Rogers, M. A., 371
Roine, R. O., 149
Rolls, E. T., 18
Rombouts, S. A., 49
Rommelse, N. N., 196
Rorsman, I., 74
Rose, J., 105, 176, 200
Rose, S. E., 176, 200
Rosen, A., 52
Rosenbloom, M. J., 12
Rosenfeld, J. V., 151
Ross, R. G., 49
Rosvold, H. E., 245
Rouby, C., 132
Rourke, B. P., 181
Rubia, K., 194, 326–327
Rugg, M. D., 231
Rule-based category/information-integration learning, differences, 107
Rumsey, J. M., 206
Rusch, N., 199
Ruschemeyer, S. A., 172
Rush, B. K., 248
Russell, V. A., 114, 374
Russo, S., 201

S

Sadato, N., 179
Sadikot, A., 242
Sagvolden, T., 114, 374
Sahakian, B. J., 34, 100, 112–113
Saint-Cyr, J. A., 34, 43, 44, 45, 73
Saito, D. N., 179, 236, 290
Salazar, A., 73
Saling, L. L., 80, 95, 96, 98, 123, 143, 259, 262
Salloway, S., 178, 193
Salmelin, R., 172
Salmon, D. P., 49, 74, 232
Salonen, O., 149
Salthouse, T. A., 262, 342
Salvucci, D. D., 53, 95–96
Samanta, J., 43, 44, 104
Santamaria, A., 41–42, 44, 89, 114, 115, 116
Sarason, I., 245
Satterlee-Cartmell, T., 241
Sauer, H., 12, 49
Savic-Berglund, I., 133
Sax, K. W., 207
Sbordone, R. J., 83
Scabini, D., 175
Schall, U., 242
Scherder, E. J., 196
Scheres, A., 61, 111, 113, 114, 143, 197, 373
Schiffer, R., 157
Schimpf, P. H., 140, 365
Schizophrenia, 201
  anti-psychotic medications, 201
  basal ganglia in, 200–202
  'bouncer in brain', 204
  cerebellar 'soft signs', 202
  cerebellum in schizophrenia, 202–203
  cognitive dysmetria, 203, 205
  delusions, 203–205
  hallucinations, 199
  'imagined speech' task, 200
  mapping anatomy and symptomology, 203–205
  multiple systems disorder, 49, 61, 62, 83, 109, 154, 176, 180, 188–191, 199–204
  PET and SPECT imaging studies, 200
  thought disorder, second type of, 204, 205
  See also Vertically organized brain in clinical psychiatric disorders
Schlosser, R. G., 49
Schmahmann, J. D., 2–3, 8, 12, 21, 125, 126, 129, 134, 136, 137, 138, 139, 149, 154, 155–157, 176, 198, 203, 321, 336, 337, 346, 348, 349, 372
Schmidt, M., 230, 283
Schmidtke, K., 267, 317
Schmolck, H., 267, 317
Schnider, A., 77
Schore, A. N., 175
Schul, Y., 178, 365
Schulte-Ruther, M., 175
Schulz, K. P., 247
Schumann, C. M., 154, 176
Schutter, D. J., 176
Schwarz, M., 113
Schweighofer, N., 265
Schweizer, T. A., 138
Seeberger, L. C., 103
Seger, C. A., 35, 41, 45, 46, 55, 96, 100, 102–107, 112, 236, 267, 268, 269, 344
Seidman, D., 140
Seidman, L. J., 52, 195
Sensory information-processing systems, 167

Sensory integration
disorder, 40, 157
problems, 196
Sensory-lobe, pathology, 204
Seok, J. H., 200
Separation anxiety, 118
Sequence learning, 96
Sequential reaction time task (SRT), 97
Serdaru, M., 76
Sergeant, J., 196
Sergeant, J. A., 195
Serial ordering (mediated by striatum/basal ganglia gating), 203
Serial order processing, 50, 99, 146, 170, 223, 224, 261, 279
Serial reaction time task (SRT), 133, 272, 370
Shadmehr, R., 139
Shaham, Y., 78
Shallice, T., 73
Shamay-Tsoory, S. G., 175
Shapira, N. A., 193
Shaw, P., 194, 199, 373
Shaywitz, B. A., 189
Shaywitz, S. E., 189
Shen, H., 126
Shergill, S. S., 200
Sherman, E., 84, 220, 283
Sherman, J., 337
Sherman, J. C., 12, 155, 156, 198, 372
Sherman, S. J., 43, 61, 103, 111, 143, 197, 291
Shimamura, A. P., 74, 257, 279, 337
Shinn-Cunningham, B. G., 245
Shohamy, D., 96, 105
Siegel, D. J., 175
Silk, T., 197, 358
Sil'kis, I. G., 110
Sillitoe, R. V., 79, 109
Silver, C. H., 83
Simo, L. S., 132
Singh, J., 261
Sinha, R., 197, 246
Sipski, M. L., 132–133
Skelly, L. R., 199
Slabosz, A., 48, 116
Slattery, M. J., 280
SLI, *see* Specific Language Impairment (SLI)
Slowik, A., 107
Smeets, W. J., 17, 19
Smith, E. E., 46, 47, 48
Smith, J. F., 134
Smith, J. G., 97
Smith, L. M., 79
Soares, J. C., 207
Sobel, N., 132
Social avoidance, 180
Social awkwardness, 180
'Social butterfly', behavior of, 81
Social cognition-automatic and higher-order control systems, 174–177
role of mirror neurons, 175
'social procedures', 177
Social isolation and loneliness, 179
Solla, S. A., 50
Soul, J. S., 153–154
Spano, M., 21, 126
Sparrow, S. S., 181
Specific Language Impairment (SLI), 174, 181, 372
Speech, emotional prosody/melody of, 179
Spiering, B. J., 51, 102
Spinks, R., 62
Spinocerebellum, 21
Spitznagel, E. L., 201
Spreen, O., 84, 220, 229, 283
Squire, L. R., 16, 41, 98, 103, 172, 228, 257, 279, 368
SRT, *see* Serial reaction time task (SRT)
Standard flexible battery of tests, 84
Stanfield, A. C., 154
Stanford, T. R., 39
Stanton, M. E., 347
Stargatt, R., 151, 152
Stark, C. E., 16, 41, 98, 228, 279
Starkstein, S. E., 248
Statue, 249, 326–327
Stebbins, G. T., 261
Stein, E. A., 52
Steinberg, F. L., 139
Steinlin, M., 150, 152
Stenger, A., 132–133
Stereotyping and prejudice, 175
Stern, C. E., 309, 344
Stern, E. R., 192
Stewart, J. T., 71, 72, 74, 277
Stilson, D. W., 73
Stine, M., 241
Strafella, A. P., 236
Strakowski, S. M., 207
Strangman, G., 372
Strategy
systematic interpretation, 280
'win-stay', 113
Strauss, E., 84, 220, 229, 283
Striatal matrix, 33

Striatum, 29
learns and mobilizes procedures, 58–59
specific projections, 34–36
Strick, P. L., 6, 7, 8, 19, 21, 32, 34, 69, 100, 136
Striedter, G. F., 17
Striosomes, 38
Stripling, R., 259
Stroop Color Word Test, 84, 85*t*, 86*t*, 233–235, 248, 249, 262, 283
Strub, R. L., 245
Stuss, D. T., 45, 74, 75, 138
Su, C. Y., 83, 298
Subcortical loops, basal ganglia, 38–40
limbic circuit, 40
'sensory integration disorder', 40
Subiaul, F., 169
Subregions of cerebellum, 127*f*
Substantia nigra pars reticulata (SNpr), 30–31
Subthalamic pathway, 37–38
Sugihara, I., 130
Sugimoto, T., 202
Sullivan, E. V., 12
Sultan, F., 127
Surface anatomy of cerebellum, 126–128
archicerebellum, 126
subregions, 127*f*
Sutton, J. P., 372
Swaying of 'tremor', 149
Swedo, S. E., 280
Sweeney, J. A., 132, 206, 279
Sweet, L. H., 261, 262
Symbolism and language, 168
Symbol Search subtests, 263, 313
Symptoms
of ADHD, 156, 190
of dementia, 42, 188
of disinhibition, 197
of DSM, 197
expressive aphasic symptoms, 74
inattention and disinhibition, 370
motor symptoms in Parkinson's disease, 43
of OCD, 191
of psychosis, 201
of schizophrenia, 199
Syndromes
akinesia and bradykinesia of Parkinsonian syndromes, 79
a-motivational syndrome, 77, 81
Asperger's syndrome, 154, 205
ataxic, 2, 131, 155
cerebellar cognitive affective syndrome, 149–151, 336, 348
cerebellar motor syndrome, 148, 149
disinhibition syndromes, 248
DLPF syndrome, 72, 74
dorsolateral syndrome, 77
dysexecutive syndrome, 43, 71, 73, 84, 367
environmental dependency syndrome, 76
frontal lobe syndrome, 43, 82, 83
frontal system syndromes, 82–89
hyperkinetic syndrome of Huntington's disease, 79
orbitofrontal syndrome, 77
'Phineas Gage' syndrome, 76
posterior fossa syndrome, 151–153
prototypical syndrome, 188
syndrome of Non-Verbal Learning Disorder (NVLD), 181
Tourette Syndrome, 27, 49, 83, 347
utilization behavior, 76
Szczudlik, A., 107

T

Taatgen, N. A., 53, 95–96
Takano, K., 371–372
Takarae, Y., 206
Takikawa, Y., 40
Talley, J. L., 14, 84, 235, 283
Tanabe, J., 78
Tanaka, H., 198, 221, 322, 327
Tanaka, S., 141, 142, 143, 376
Tannock, R., 115
Taylor, A. E., 45, 73
Taylor, E., 195
Temper
outburst, 12
tantrums, 198
Temporal and parietal lobe prefrontal and basal ganglia circuitries, diagram of, 101*f*
Theobald, D. E., 43
Theories of cerebellar function
detection and correction of errors in skill learning, 139
learning machine, 140
verbal working memory, 139
Thielscher, A., 193
Thinking, 144, 226
Thomann, P. A., 151, 208
Thomas, M. J., 78
Thomason, M. E., 195
Thought broadcasting, 145
See also Dysmetria
Thought disorder, 12, 203–205, 369

Thought in action
motor adaptation, 273–274
perceptual–motor skill learning, 271–272
practice effect, 263–265
procedural learning in neuropsychological evaluation, 268–271
cortico-striatal loops, illustrations of, 269*f*
processing speed, 259–260
by-product of cognitive/executive control, 262–263
subcircuit differentiation, 272–273
types of practice effect, 265–268
Thought insertion, 145
See also Dysmetria
'Threaded cognition', 95
Thumb rules for understanding anatomical differences, 196–199
behavioral regulation, problems with, 197–199
impulsivity and cognitive disinhibition, 197
sensory inattention and certain cognitive processing deficits, 196–197
Tibbo, P. G., 371
Timmann, D., 153
Toates, F., 11, 14–16, 55, 221, 223
Toda, A., 141
Todd, J. J., 51
Tolin, D. F., 192
'Tonic' dopamine level, 110
Tonic pallidal inhibition, 52
Torriero, S., 133, 142
Torta, D. M., 112
Tourette syndrome, 27
Tower of Hanoi, 73, 267
Tower of London Test (TOL), 38, 73, 84, 221, 235, 241–243, 244, 266, 267, 283, 327, 335, 357
Townsend, J., 139
Tracy, D. K., 200
Traditional 'frontal lobe' problem-solving tests, 235–243
response decks, 238*t*, 240*t*
'rule violations' task, 243
Tower of London Test (TOL), 241–243
Trail Making Tests, 84, 87*t*, 221, 262, 283
Tranel, D., 4
Trimble, M., 17, 40, 77, 109
Trites, R., 84, 283
Tsatsanis, K. D., 181
Tucker, D. M., 259
Tuma, R., 74
Turken, A. U., 45
Turner, A., 72

U
Uddin, L. Q., 175
Uhlikova, P., 195
Ullman, M. T., 169, 172, 174, 181, 372–373
'Undershooting and overshooting', 148
Ungerleider, L. G., 10, 17, 47, 54, 98, 99, 133
'Universal Cerebellar Transform', 155
Unterecker, S., 193
Updating mechanisms, 53, 116
Utter, A. A., 17, 27

V
Vaidya, C. J., 195, 197
Valentin, V. V., 51
Valera, E. M., 52, 54, 195
van, d. B., 83, 154
van, H. J., 176
van Boxtel, G. J., 132
Vance, A., 197, 358
van den Bosch, R. J., 201
van Erp, T. G., 161
Van Hoesen, G. W., 17, 40, 77, 109
van Meel, C. S., 195
Varambally, S., 202
Veltman, D. J., 49, 191
Ventral pallidum, 29
Verbal Comprehension Index (VCI), 249, 334, 355
Verbal fluency tasks, 230–231
Vergara, P., 273
Vernacular 'motor strip', *see* Primary motor cortex
Versiani, M., 194, 370
Vertically organized brain in clinical psychiatric disorders
attention deficit hyperactivity disorder, 194–199
Obsessive-compulsive disorder (OCD), 191–194
organizational difficulty, 194–199
other clinical disorders
Alzheimer's disease, 207–208
Autism Spectrum Disorder (ASD-Including Asperger Syndrome), 205–207
mood disorders, 207
schizophrenia

Vertically organized brain in clinical psychiatric disorders (*cont.*)
basal ganglia in schizophrenia, 200–202
cerebellum in schizophrenia, 202–203
mapping anatomy and symptomology, 203–205
Vertically organized brain/movement/cognition
adjustment of motor 'how', changing characteristics of excitation and inhibition, 20–22
functional regions of cerebellum, 21–22
analogous memory systems, 16–17
frontostriatal system, 16
procedural learning, 17
basal ganglia pathology, 2
behavioral processing and frontostriatal system, 14–16
See also Behavioral processing and frontostriatal system, theories of types
case of dementia, 3–5, 4*t*
neuropsychological testing, 4
cognition, 1
cortico-centric bias, reason for, 5–6
doing things in changing environment
cardinal symptom of thought disorder, 11–12
excitation *versus* inhibition, 19–20
lesions of cortex, 2
phylogenetic perspective, 17–19, 19–20
basal ganglia, re-entrant system, 19
caudoputamen, 18
motivation, 17
neurotransmitter organization, 18
systems, 6–9
cerebro-cerebellar circuitry, 8
cortico-striatal-pallidal-thalamic loop, 7
'looped' architecture, 6
simplified version of cerebro-cerebellar circuit, 8*f*
simplified version of frontal–subcortical circuit, 7*f*
theoretical and historic context, 9–11
nervous system, minimal characteristics, 9
'when to do things'-intention programs 'separation anxiety', 14
when to do things-intention programs 'stimulus-based' responding, 13
Very pre-term infants, 153–154
Video-based gambling tasks, 104
Visual discrimination learning, 102
Visuomotor learning tasks, 97
Vlachos, F., 182
Vocalization, 170
Voeller, K. K., 194
Vogel, E. K., 48, 51, 53
Vohn, R., 172
Volkmar, F. R., 181
Volpe, U., 199
Volz, H., 12
Von Hofsten, C., 79
Vonk, J., 169
Vonlanthen, A., 179
Vyas, N. S., 202

W
Wager, T. D., 46, 48
Wagner, A. D., 231
Wagner, G., 49
Waldron, E. M., 45
Walenski, M., 174, 373
Waligura, D. L., 172
Wallis, J. D., 16
Wang, J. J., 128, 133, 140
WASI, *see* Wechsler Abbreviated Scale of Intelligence (WASI)
Watkins, L. H., 34, 73, 100
Watson, P. J., 132
WCST, *see* Wisconsin Card Sorting Test (WCST)
WCST and TOL, relationships between, 244
Weaver, A. H., 126
Wechsler, D., 84, 205, 260, 283, 289, 309, 310, 312, 329, 342
Wechsler Abbreviated Scale of Intelligence (WASI), 84*t*–85*t*
Wechsler Adult Intelligence Scale series, 269
Wechsler Block Design subtest, 267
Wechsler Intelligence, Memory and Academic measures, 84, 260, 283, 312
Wechsler Intelligence and Memory Tests, 84
Wechsler Memory Scale-III Abbreviated (WMS-III), 85*t*
Weeks, A. C., 132
Weickert, T. W., 201
Weidenheim, K. M., 206
Weilburg, J. B., 12, 156, 198, 372
Weiler, M. D., 196
Weiner, I., 17, 35, 57, 59, 60
Weiner, M. J., 132, 273

Weinstock-Guttman, B., 49
Weintraub, S., 84, 283
Welling, H., 140, 147
Welsh, M. C., 241, 246
Wennekers, T., 19
Westenberg, H. G., 191
Westervelt, H. J., 264
Whalley, H. C., 202
Whishaw, I. Q., 6, 19, 170
White, C. D., 197, 246
Wide Range Achievement Test, 283
Wiederholt, J. L., 283
Wilhelm, H., 283
Wilkins, D. P., 172
Wilkinson, G. S., 283
Willcutt, E., 41, 89, 114
Willingham, D. B., 261, 272
Willis, W. G., 196
Winstanley, C. A., 43
'Win-stay' strategy, 113
Winston, J., 174
Wisconsin Card Sorting Technique, 84, 86*t*, 194, 221, 283
Wisconsin Card Sorting Test (WCST), 37, 45, 104
Wise, S. P., 45, 105
WMS-III, *see* Wechsler Memory Scale-III Abbreviated (WMS-III)
Wolfson, D., 274, 282, 289
Wolpert, D. M., 46, 139
Woodruff, P. W., 200
Woodward, N. D., 371
Worhunsky, P., 192
Working memory
  deficient working memory capacity, 48
  definition, 46
  expertise/creativity/giftedness, 145–148
    'deliberate practice architecture', 147
    forward and inverse models, 146
    multiple inverse control models, 146
  higher-order cognition and, 46–49
  neuroanatomy, aspects of, 47–48
  neuropsychiatric disorders, 49
  problem, treatment of, 116
  subtests, 356
  tests, 220–221
  types, 47
  working of, 50–54
    'central executive', 52
    cerebellum, role of, 54
    error-detection system, 54
    serial order processing, 50
Worsley, K., 54, 55, 234
Wu, J. C., 247
Wurtz, R. H., 40
Wynn, V., 241

X
X-system, 177–178
Xu, D., 140

Y
Yamazaki, T., 141, 142, 376
Yan, P., 197, 246
Yarom, Y., 139
Yaryura-Tobias, J. A., 189, 347
Yener, G. G., 74, 77, 172, 228, 279
Yeo, C. H., 132
Yi, Y., 47
Yokochi, F., 43
Yung, W. H., 128

Z
Zaffos, A., 74, 77, 172, 228, 279
Zahm, D. S., 17, 40, 77, 109
Zaidel, E., 175
Zald, D. H., 191
Zametkin, A. J., 195
Zand, R., 112
Zatorre, R. J., 132
Zedkova, L., 371
Zelazo, P. D., 174
Zeng, X. H., 198, 221, 322
Zhigulin, V. P., 6
Zhou, Z., 126
Zhu, J. N., 128, 132, 133, 140
Zillmer, E., 84, 235, 283
Zueva, Y. V., 149, 198, 337