FUNCTIONALLY RELEVANT BASAL GANGLIA SUBDIVISIONS IN FIRST-EPISODE SCHIZOPHRENIA

by

BABAK KHORRAM

B.Sc., The University of British Columbia, 2004

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

(Neuroscience)

THE UNIVERSITY OF BRITISH COLUMBIA

November 2007

© Babak Khorram, 2007
Schizophrenia is among the most debilitating mental disorders, yet the pathophysiology remains unclear. The basal ganglia, a region of the brain involved in motor, cognitive, and sensory processes, may be involved in the pathophysiology of schizophrenia. Some, but not all, neuroimaging studies suggest abnormalities of the basal ganglia in schizophrenia. However, previous studies have examined whole basal ganglia nuclei as opposed to using a unified basal ganglia complex that incorporates anterior-posterior divisions, dorsal-ventral divisions, and gray-white matter segmentation. The hypothesis for the present study was that basal ganglia sub-regions forming functionally relevant subdivisions might be different in schizophrenia. Magnetic resonance imaging scans were acquired from 25 first-episode schizophrenia subjects and 24 healthy subjects. Using manual and automated neuroimaging techniques, total and segmented (gray-white matter) volumes were obtained for the caudate, putamen, and globus pallidus. For the striatum (caudate and putamen), total and segmented volumes were obtained for their respective sub-regions. These sub-regions were restructured into associative, limbic, and sensorimotor subdivisions. Schizophrenia subjects had 6% smaller gray matter volumes for the caudate and 8% smaller gray matter volumes for the associative striatum relative to healthy subjects. Basal ganglia function was studied by examining performance on a neuropsychological test that assesses frontostriatal functioning. For male subjects there was a significant negative correlation between volume of the associative striatum and performance on the neuropsychological test ($r=-0.57$, $p=0.03$). Smaller volumes of the associative striatum were associated with more errors on the neuropsychological test. This test was specific to the associative striatum, as another neuropsychological test did not reveal any
correlation. In schizophrenia subjects, the relationship between basal ganglia volumes and motor symptoms severity was examined. For antipsychotic-naïve subjects there was a significant negative correlation between volume of the motor striatum and severity of Parkinsonism ($r=-0.65$, $p=0.03$). The present study suggests that total basal ganglia nuclei volumes are not different in schizophrenia, but gray matter volumes of total basal ganglia nuclei and subdivisions forming functional units may be different in schizophrenia. Structural abnormalities involving the basal ganglia may lead to disrupted functional circuits in schizophrenia.
# TABLE OF CONTENTS

Abstract ........................................................................................................................... ii

Table of Contents ........................................................................................................... iv

List of Tables .................................................................................................................. vi

List of Figures ................................................................................................................ vii

Acknowledgements ....................................................................................................... viii

CHAPTER I: Introduction .............................................................................................. 1

1.1 Basal Ganglia Anatomy and Functions ................................................................. 1
1.2 Functionally Relevant Basal Ganglia Subdivisions ............................................. 7
1.3 Basal Ganglia and Cognition ............................................................................... 11
1.4 Basal Ganglia Disorders ...................................................................................... 13
1.5 Schizophrenia ....................................................................................................... 15
1.6 Neuroimaging in Schizophrenia ......................................................................... 18
1.7 Basal Ganglia Pathology in Schizophrenia .......................................................... 20
1.8 Basal Ganglia and Cognition in Schizophrenia ................................................. 21
1.9 Basal Ganglia and Movement Disorders in Schizophrenia ................................ 22
1.10 Hypothesis ......................................................................................................... 24

CHAPTER II: Methods ................................................................................................. 26

2.1 Subjects ................................................................................................................. 26
2.2 Treatment and Clinical Measures ...................................................................... 28
2.3 MRI Acquisition and Measures ......................................................................... 31
2.4 Cognitive Measures ............................................................................................ 38
2.5 Statistical Analysis ............................................................................................... 40

CHAPTER III: Results ................................................................................................. 42

3.1 Demographics ....................................................................................................... 42
3.2 Reliability Studies ............................................................................................... 42
3.3 Basal Ganglia Volumes ....................................................................................... 43
3.4 ID / ED Shift, K-BIT, and NAART ................................................................. 48
3.5 Exploratory Analysis ............................................................................................ 50

CHAPTER IV: Discussion ............................................................................................. 53

4.1 Summary ............................................................................................................. 53
# Table of Contents

4.2 Comments ........................................................................................................... 54  
4.3 Caveats .............................................................................................................. 59  
4.4 Future Directions .............................................................................................. 64  
4.5 Conclusions ....................................................................................................... 65  

References .................................................................................................................. 66  

Appendix I: University of British Columbia Research Ethics Board Certificate of Approval  
........................................................................................................................................ 85
LIST OF TABLES

Table 1: Functional subdivisions, anatomic subdivisions, and primary function for the tripartite model of the striatum applied in human PET studies (adapted from Martinez et al., 2003) .................................................................10

Table 2: Demographic data for schizophrenia and healthy subjects .........................27

Table 3: Clinical data for schizophrenia subjects .....................................................30

Table 4: Total brain and basal ganglia volumes (mean with standard deviation reported in brackets) for schizophrenia and healthy subjects. Total volume equals gray matter volume plus white matter volume plus CSF volume (not provided) .........................45

Table 5: P-values for repeated measures ANCOVA (df=1,46)..................................46

Table 6: ID / ED shift, K-BIT, and NAART for schizophrenia and healthy subjects ......49

Table 7: Review of postmortem basal ganglia volumes from healthy subjects ..........62

Table 8: Review of MRI basal ganglia volumes from healthy subjects ....................63
LIST OF FIGURES

Figure 1: Location of basal ganglia nuclei within the coronal plane of the human brain (adapted from Nieuwenhuys et al., 1988) ...............................................................5

Figure 2: Main connections of basal ganglia circuitry (STN, subthalamic nucleus; GPe, external segment of the globus pallidus; GPI, internal segment of the globus pallidus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata) (adapted from Yin and Knowlton, 2006) ..........................................................6

Figure 3: Tracing of the caudate (slices 1 to 20), putamen (slices 1 to 14), and globus pallidus (slices 3 to 8) for one representative subject .........................................................35

Figure 4: Division of the striatum into anterior and posterior (A—axial, B—mid-sagittal), division of the putamen into dorsal and ventral (C—coronal), and division of the caudate into dorsal, medial, and ventral (D—coronal) .................................................................36

Figure 5: Schematic of the partition of the striatum into distinct sub-regions (anatomic subdivisions) and regrouping of the sub-regions into limbic, dorsal, and sensorimotor striatum (functional subdivisions) ........................................................................37

Figure 6: Caudate gray matter volume (A) and associative striatum gray matter volume (B) for schizophrenia and healthy subjects .........................................................47

Figure 7: Relationship between extra-dimensional shift errors and associative striatum volume in male schizophrenia subjects (A) and relationship between Parkinsonism scores and motor striatum volume in antipsychotic-naive schizophrenia subjects (B) ......................................................................................52
I am very grateful for the advice and support of my supervisor, Dr. William G. Honer. I sincerely thank him for his feedback and, in particular, his outstanding mentorship. His dedication and ingenuity, qualities that he inspires in all of his students, will always be remembered.

The recommendations and guidance provided by my supervisory committee, Dr. Anthony L. Traboulsee, Dr. Allen E. Thornton, Dr. Geoffrey N. Smith, and Dr. Elton T. Ngan have greatly enhanced my graduate education. Sincerest thank you to my readers, Dr. Donna J. Lang and Dr. Alasdair M. Barr, whose efforts have helped improve and clarify this work. Donna, in particular, has been excellent at keeping me focused on my research. Thank you to Mr. Wayne Su for his tireless technical assistance. I also owe abundances to my friends and colleagues, Dr. Fidel Vilas-Rodriguez, Ms. Vlte Barakauskas, and Dr. William J. Panenka. Our conversations and time together have greatly influenced my work.

The Michael Smith Foundation for Health Research has provided financial support for two years. Through his grants, Dr. Honer and the University of British Columbia Department of Psychiatry have provided additional financial support. The Institute of Neurosciences, Mental Health, and Addiction and the University of British Columbia Faculty of Graduate Studies have provided me with additional financial awards.
Chapter I: Introduction

1.1 Basal Ganglia Anatomy and Functions

The basal ganglia are a large subcortical motor system consisting of several interconnected nuclei that send output via the thalamus to the cortical motor system (Squire et al., 2003). In addition to its well-established role in the motor system there is increasing evidence that these subcortical structures play a role in non-motor behavior, including cognition (Yin and Knowlton, 2006). The basal ganglia consist of the striatum, subthalamic nucleus, globus pallidus, and substantia nigra (Squire et al., 2003). Location of basal ganglia nuclei within the human brain is provided in Figure 1.

The striatum is located in the forebrain and includes the caudate and putamen (neostriatum) as well as the nucleus accumbens (ventral striatum) (Figure 1). In rodents, the caudate and putamen are a single structure with fibers of the internal capsule coursing through, whereas in primates the internal capsule separates the striatum into the caudate and putamen (Squire et al., 2003). Four different types of striatal neurons are thought to exist, but approximately 95% are medium spiny neurons (Parent and Hazrati, 1995b).

The striatum receives excitatory input from nearly the entire cortex (Squire et al., 2003). These inputs are topographically organized. For example, inputs from the motor cortex project to the posterior putamen and inputs from the prefrontal cortex project to the anterior striatum. The topographic relationship between the cortex and the stratum gives rise to the presence of parallel, but functionally different corticostriatal circuits (Alexander et al., 1986; Yin and Knowlton, 2006). In addition to excitatory input from the
cortex, the striatum receives input from dopamine-containing neurons in the substantia nigra pars compacta. Dopamine input to the striatum terminates primarily on dopamine D1 and D2 receptors, which are copiously found in the striatum (Cote and Crutcher, 1991). In primates, the nucleus accumbens is located where the striatum adjoins, just ventral to the anterior limb of the internal capsule and lateral to the septum pellucidum (Mai et al., 1997). Cellular composition of the nucleus accumbens is similar to the other parts of the striatum, with the majority of cells being medium spiny neurons (Squire et al., 2003).

Medial to the striatum and adjacent to the ventral internal capsule is the globus pallidus (Figure 1), a basal ganglia structure that is divided into two parts by the internal medullary lamina (Mai et al., 1997). The first part, named the internal segment is more medially located whereas the second part, named the external segment is more laterally located. The internal segment receives excitatory input from the subthalamic nucleus as well as inhibitory inputs from the striatum and external segment of the globus pallidus (Squire et al., 2003). Furthermore, the internal segment sends inhibitory output to the thalamus. The external segment receives inhibitory input from the striatum and it sends inhibitory outputs to the subthalamic nucleus and internal segment of the globus pallidus (Parent and Hazrati, 1995a).

The subthalamic nucleus is situated ventral to the thalamus, at the junction of the diencephalon and midbrain (Figure 1). It receives excitatory input from the cortex and inhibitory input from the external segment of the globus pallidus (Parent and Hazrati, 1995a). In addition, the subthalamic nucleus sends excitatory outputs to the external
segment of the globus pallidus as well as the internal segment of the globus pallidus and substantia nigra pars reticulata.

The substantia nigra is located in the midbrain, ventral to both the thalamus and subthalamic nucleus (Figure 1). Like the globus pallidus, the substantia nigra is divided into two parts. The first part, named the pars compacta, is densely populated with cells whereas the second part, named the pars reticulata, is more sparsely populated with cells (Haber and Fudge, 1997). The pars compacta is composed of dopamine-containing neurons, which send excitatory output to the striatum. Neuramelanin, a dark pigment found in these dopamine-containing neurons, gives the substantia nigra its appearance and gives rise to its name (Cote and Crutcher, 1991). Like the internal segment of the globus pallidus, the pars reticulata receives excitatory input from the subthalamic nucleus as well as inhibitory inputs from the striatum and external segment of the globus pallidus (Squire et al., 2003). Additionally, the pars reticulata sends inhibitory output to the thalamus.

The internal segment of the globus pallidus and substantia nigra pars reticulata send inhibitory output to the thalamus, with the downstream effect being inhibition of the cortex (Cote and Crutcher, 1991; Squire et al., 2003). This implies that basal ganglia output is inhibitory, as an increase in basal ganglia output leads to reduction in the activity of its cortical target. Although the basal ganglia participate in normal motor control, it was traditionally grouped as part of the extrapyramidal motor system because it was considered to be independent from the pyramidal (or corticospinal) motor system
(Squire et al., 2003). The main connections of basal ganglia circuitry are provided in Figure 2.

As well as an essential role in normal motor control, the basal ganglia play a role in non-motor behavior. Evidence suggests that the nucleus accumbens is an integral part of the attention, motivation, reward, and addiction pathways (Carelli, 2002; Sonuga-Barke, 2005; Di Chiara and Bassareo, 2007). Parallel but functionally different corticostriatal circuits exist based on their cortical targets (Alexander et al., 1986; Haber, 2003). Cortical targets include the motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate cortices.
Figure 1: Location of basal ganglia nuclei within the coronal plane of the human brain (adapted from Nieuwenhuys et al., 1988).
Figure 2: Main connections of basal ganglia circuitry (STN, subthalamic nucleus; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata) (adapted from Yin and Knowlton, 2006).
1.2 Functionally Relevant Basal Ganglia Subdivisions

The majority of inputs to the basal ganglia terminate at the striatum. Efferent inputs to the striatum are organized topographically and functionally into dorsal / ventral and anterior / posterior components (Alexander et al., 1986; Haber, 2003; Voorn et al., 2004). The major efferent inputs to the striatum arrive from the cortex, but also from the thalamus and brainstem (Haber, 2003). These cortical efferent inputs functionally subdivide the striatum (Joel and Weiner, 2000).

A tripartite model of the striatum into limbic, associative, and sensorimotor subdivisions has been delineated in both primates and rats (Parent, 1990; Joel and Weiner, 1994). In primates, the limbic striatum comprises the nucleus accumbens, ventral caudate, and ventral putamen (Joel and Weiner, 2000; Mawlawi et al., 2001). It receives inputs from limbic structures, such as the hippocampus and amygdala, as well as frontal cortical areas involved in limbic and autonomic functions, such as the orbitofrontal cortex (Lynd-Balta and Haber, 1994; Joel and Weiner, 2000). The associative striatum comprises the dorsal caudate and the dorsal putamen rostral to the anterior commissure (Joel and Weiner, 2000; Mawlawi et al., 2001). It receives inputs from the associative areas of the cortex, such as the dorsolateral prefrontal cortex (Haber, 2003). The sensorimotor striatum comprises the putamen rostral to the anterior commissure (Joel and Weiner, 2000; Mawlawi et al., 2001). It receives inputs from the primary motor cortex, premotor cortex, supplementary motor area, and postarcuate premotor area (Joel and Weiner, 2000).

Diffusion Tensor Imaging (DTI) is a noninvasive technique that allows demonstration of fiber tracts in humans (Poupon et al., 2000). In a DTI study, fiber
tracking was initiated from motor, premotor, prefrontal, and orbitofrontal cortical areas (Lehericy et al., 2004). Fiber tracts deriving from the motor and premotor cortices were directed to the posterior putamen (Lehericy et al., 2004; Leh et al., 2007). Fiber tracts deriving from the prefrontal cortex were directed to the anterior striatum and the head of the caudate (Lehericy et al., 2004). Fiber tracts deriving from the orbitofrontal cortex were directed to the ventral striatum (Lehericy et al., 2004; Croxson et al., 2005). DTI studies in humans are congruent with tracing studies in primates, which indicates that models of corticostriatal connectivity based on primate-human extrapolations are mainly accurate.

Most studies have examined some or all of the basal ganglia nuclei as opposed to using a unified basal ganglia complex that incorporates anterior-posterior divisions, dorsal-ventral divisions, and gray-white matter segmentation. Only a limited number of studies have implemented the tripartite model of functionality. Of importance are studies that have examined the ventral striatum in humans, which includes the nucleus accumbens, ventral caudate, and ventral putamen (Mawlawi et al., 2001). Interest in the ventral striatum was initiated by its role in the pathophysiology of the psychotic state and addiction to drugs of abuse (Mawlawi et al., 2001; Squire et al., 2003).

In previous Positron Emission Tomography (PET) studies, the human striatum was divided into functionally relevant limbic, associative, and sensorimotor subdivisions (Mawlawi et al., 2001; Martinez et al., 2003). The limbic subdivision corresponded to the ventral striatum (nucleus accumbens, ventral caudate, and ventral putamen), and related primarily to emotional function. The associative subdivision corresponded to the anterior dorsal caudate, anterior dorsal putamen, and posterior caudate, and related
primarily to cognitive function. The sensorimotor subdivision corresponded to the posterior putamen, and related primarily to motor function. PET researchers used the anterior commissure to divide the caudate and putamen into anterior (pre-commissural) / posterior (post-commissural) and dorsal / ventral components. An outline of the tripartite model applied in PET studies is provided in Table 1.
Table 1: Functional subdivisions, anatomic subdivisions, and primary function for the tripartite model of the striatum applied in human PET studies (adapted from Martinez et al., 2003).

<table>
<thead>
<tr>
<th>Functional Subdivisions</th>
<th>Anatomic Subdivisions</th>
<th>Primary Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbic striatum</td>
<td>Ventral striatum</td>
<td>Emotion</td>
</tr>
<tr>
<td>Associative striatum</td>
<td>Anterior dorsal caudate</td>
<td>Cognition</td>
</tr>
<tr>
<td></td>
<td>Anterior dorsal putamen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posterior caudate</td>
<td></td>
</tr>
<tr>
<td>Sensorimotor striatum</td>
<td>Posterior putamen</td>
<td>Motor</td>
</tr>
</tbody>
</table>
1.3 Basal Ganglia and Cognition

It has been established that the basal ganglia play a role in non-motor behavior, including cognition (Yin and Knowlton, 2006). Evidence emerges from circuit, lesion, and functional neuroimaging studies, as well as basal ganglia disorders. Through the striatum, the basal ganglia receive inputs from nearly the entire cortex, including areas involved in cognition (Squire et al., 2003). There are also inputs from cortical areas involved in sensory, autonomic, and limbic processes (Joel and Weiner, 2000; Yin and Knowlton, 2006).

It has been understood for some time that basal ganglia lesions cause sensory and cognitive disturbances, without gross motor impairments (Middleton and Strick, 2000). For example, posteroventral pallidotomy is an approach used to ameliorate tremor and rigidity in Parkinson's disease (Samii et al., 2004). However, this approach has been known to cause cognitive disturbances, especially when it is performed bilaterally with large lesions (Trepanier et al., 1998). Furthermore, lesions to the substantia nigra produce non-motor symptoms (Middleton and Strick, 2000). The best example being from a case report of a patient with bilateral infarctions of the substantia nigra pars reticulata (McKee et al., 1990). In addition to motor abnormalities, the patient demonstrated severe deficits in working memory as well as visual hallucinations.

Functional neuroimaging studies implicate the basal ganglia and, more specifically, the striatum in cognitive functioning (Lehericy and Gerardin, 2002). The striatum shows increased activity during neuropsychological tests that involve frontostriatal circuits, such as set-shifting tasks (Cools et al., 2004). In studies, dorsal /
ventral components of the striatum differed in level of activity depending on the specific phase of the task. Strong activation was noted in the ventral striatum during object switching (i.e., reversal learning) (Cools et al., 2002; Cools et al., 2004). Performance in reversal learning is sensitive to structural or neurochemical changes in the medial orbitofrontal cortex-ventral striatum circuit (Dias et al., 1996; Cools et al., 2004; Chudasama and Robbins, 2006). In contrast, performance at the critical set-shift (i.e., the extra-dimensional shift) is sensitive to structural or neurochemical changes in the dorsolateral prefrontal cortex-associative striatum circuit (Dias et al., 1996; Chudasama and Robbins, 2006).

Basal ganglia disorders, such as Parkinson's and Huntington's diseases feature cognitive symptoms as well as characteristic motor symptoms (Lange et al., 1995; Cools et al., 2001). However, there are interesting differences between basal ganglia disorders in relation to pathology and symptoms. For example, during the early stages of Parkinson's disease, the sensorimotor portions of the striatum are affected and at onset Parkinson's disease is coupled primarily with movement symptoms (Kish et al., 1988). In contrast, during the early stages of Huntington's disease the associative portions of the striatum are affected and at onset Huntington's disease is coupled primarily with cognitive decline (Middleton and Strick, 2000). Additionally, there are key differences between cognitive deficits in subcortical neurodegenerative disorders (e.g., Parkinson's and Huntington's disease) and cognitive deficits in cortical neurodegenerative disorders (e.g., Alzheimer's disease) (Salmon and Filoteo, 2007). For example, deficits in attention, working memory, and executive functions are more
prominent in subcortical than cortical neurodegenerative disorders (Caine et al., 1978; Huber et al., 1986). Whereas deficits in language and semantic knowledge (e.g., general knowledge of facts and concepts as well as the meaning of words) are a well-known feature of Alzheimer’s disease that are practically absent in Parkinson’s and Huntington’s diseases (Murray, 2000; Salmon and Filoteo, 2007).

1.4 Basal Ganglia Disorders

Numerous diseases have been linked with the basal ganglia including Parkinson’s disease, Huntington’s disease, and Tourette’s syndrome. Primary features of Parkinson’s disease are summarized by the acronym TRAP—tremor, rigidity, akinesia, and postural instability (Squire et al., 2003). The pathophysiology or mechanism of illness in Parkinson’s disease is injury to the dopamine-containing neurons that project from the substantia nigra pars compacta to the striatum, which results in a depletion of dopamine in the caudate and putamen (Samii et al., 2004). Clinical signs of Parkinson’s disease manifest when approximately 50% of dopamine-containing neurons are lost and 80% of dopamine has been depleted (Fearnley and Lees, 1991).

Aside from Parkinson’s disease caused by a known gene mutation or exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), the etiology of this disorder remains unclear. Most likely, there are several factors that act together, including aging, genetic susceptibility, and environmental exposures (Steece-Collier et al., 2002). Parkinson’s disease is treated with levodopa (or L-dopa), dopamine agonists, or, surgical approaches (e.g., posteroventral pallidotomy) (Samii et al., 2004). However, the
neurodegeneration is progressive and because there is no regenerative therapy, patients eventually become quite disabled (Squire et al., 2003). Although the primary features of Parkinson’s disease are motor-related symptoms, other symptoms are observed, such as cognitive and psychiatric changes as well as sensory symptoms and sleep disturbances (Squire et al., 2003; Samii et al., 2004).

Huntington’s disease is a rare autosomal dominant disorder characterized by chorea (involuntary movements), abnormal motor coordination, and dystonia, as well as cognitive decline and behavioral difficulties (Walker, 2007b). Clinically, it may manifest itself anytime between childhood and senescence, but it usually emerges in middle age after affected individuals have had children. With respect to the pathophysiology and etiology of the disorder, the causal HD gene gives rise to the mutant protein in Huntington’s disease—huntington (Htt) (Truant et al., 2006). Htt causes dysfunction and loss of neurons in the striatum (particularly, medium spiny neurons) (Squire et al., 2003). During the latter stages of the disorder, the neurotoxic effects of Htt extend beyond the striatum (Walker, 2007b). Although treatments may ameliorate symptoms, neurodegeneration is quite rapid, and Huntington’s disease is usually fatal within 15 to 20 years of onset (Walker, 2007a).

Individuals with Tourette’s syndrome experience motor and phonic tics (Leckman, 2002). In addition to tics, functional impairments in Tourette’s syndrome often result in comorbidity with other disorders, including obsessive-compulsive disorder. In terms of the pathophysiology, the corticostriatal circuitry seems to be aberrant in Tourette’s syndrome (Squire et al., 2003). Evidence from neuropathological
studies indicate increased neuronal packing in the striatum, and evidence from neuroimaging studies indicate reduced caudate volume (Swerdlow and Young, 2001). The etiology of Tourette's syndrome remains unclear but like Parkinson's disease genetic and environmental factors are thought to be involved (Leckman, 2002). Treatments for this disorder focus on direct tic suppression and amelioration of comorbid conditions (Squire et al., 2003). Typical antipsychotic medications, which are potent dopamine D2 antagonists, help suppress tics but have undesirable side effects (Leckman, 2002). Although these disorders represent clear examples of basal ganglia pathology, other disorders may also involve basal ganglia pathology, as part of a less parsimonious explanation of the disorder.

1.5 Schizophrenia

Schizophrenia is a complex and devastating mental disorder. It is among the world's top ten causes of long-term disability (Mueser and McGurk, 2004) and an economic burden in Canada (Goeree et al., 1999) and other developed countries (Rice, 1999). Schizophrenia usually develops in late adolescence or early adulthood (Mueser and McGurk, 2004). A diagnosis of schizophrenia is psychologically stressful and stigmatizing to individual patients as well as their families. The lifetime prevalence or risk of schizophrenia is about 1%, with an annual incidence of 0.2 to 0.4 per 1000 (Jablensky, 1997). The incidence of schizophrenia is the same in both genders, but females tend to have a later age of onset than males (Murray and Van Os, 1998), and a more benign course of illness (Angermeyer et al., 1990). The effects of estrogen on
reduced sensitivity of dopamine D2 receptors in the brain have been proposed as a possible mechanism to explain the later onset in females (Hafner et al., 1999).

The two major diagnostic systems for schizophrenia are the ICD-10 (World Health Organization: *International Classification of Diseases*, tenth edition, Geneva, Switzerland, 1992) and DSM-IV (American Psychiatry Association: *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, Washington, DC, 1994). Both systems objectively define the signs and symptoms of schizophrenia, and the reliability between the two systems is high (Peralta and Cuesta, 2003). According to the DSM-IV, the presence of two or more characteristic symptoms occurring in the context of a decline in function over a six-month period are sufficient to diagnose schizophrenia.

The three types of symptoms that characterize schizophrenia are psychotic symptoms, negative symptoms, and cognitive impairments (Mueser and McGurk, 2004). The most obvious of these are the psychotic or positive symptoms, which involve the loss of contact with reality (e.g., delusions, hallucinations, disorganized language, disorganized or catatonic behavior). Negative symptoms are thoughts, feelings, or behaviors normally present that are absent or diminished (e.g., blunted affect, anhedonia, avolition, and alogia). Cognitive impairments are typically present in schizophrenia, particularly impairments in attention and concentration, psychomotor speed, learning and memory, and executive functions (e.g., planning, abstract thinking, and problem solving). A less ubiquitous feature of the disorder is movement-related symptoms (e.g., Parkinsonism), which may appear at onset in both antipsychotic-naïve and antipsychotic-exposed patients (Chatterjee et al., 1995). Symptoms and the course
of the disorder often lead to comorbidity with other disorders as well as an increased suicide rate (approximately 5%) (Inskip et al., 1998).

Typically, both pharmacological and psychosocial treatments are used to manage schizophrenia (Mueser and McGurk, 2004). Pharmacotherapy for schizophrenia includes antipsychotic medications and/or mood stabilizers. Antipsychotic medications reduce psychotic symptoms and help prevent relapses, but have a more modest effect on negative symptoms and cognitive impairments (Kane and Marder, 1993). Conventional or typical antipsychotic medications are potent dopamine D2 antagonists that help suppress psychotic symptoms, but often produce problematic side effects such as tardive dyskinesia (Bezchlibnyk-Butler and Jeffries, 1999; Davis et al., 2003). These undesirable side effects often dissuade patient adherence (Kane and Marder, 1993). Atypical antipsychotic medications (developed more recently) target more receptors and are less likely to produce extrapyramidal symptoms (Kane and Marder, 1993; Bezchlibnyk-Butler and Jeffries, 1999). Psychosocial treatment focuses on helping patient individuals cope with schizophrenia, and enhance functioning in areas of their lives (Mueser and McGurk, 2004). Examples of psychosocial treatment include assertive community treatment, teaching schizophrenia management skills, and cognitive behavior therapy for psychosis.

Schizophrenia is a complex disorder, which entails that both genetic and environmental factors play a role in the etiology of the disorder. Unlike Huntington’s disease, schizophrenia does not follow a Mendelian inheritance pattern. Instead, at least several different genes have been associated with schizophrenia (Thaker and
Carpenter, 2001; Harrison and Owen, 2003). The genetic risk for schizophrenia increases with each affected relative, to nearly 50% when both parents are affected (McGuffin et al., 1995) and 60 to 84% when a monozygotic twin is affected (Cardno et al., 1999). Environmental factors thought to play a role in the emergence of schizophrenia are both biological and psychosocial. Biological factors include obstetric complications, viral infections, place and season of birth, and cannabis usage (van Os and Marcelis, 1998). Psychosocial factors include lower socioeconomic status, migration, and stressful life events.

Despite being among the most debilitating mental disorders, the pathophysiology of schizophrenia remains unclear. Neuroimaging and neuropathological evidence indicate that abnormal brain development may predispose to schizophrenia (Squire et al., 2003). Interest in neuroimaging in schizophrenia has expanded with the proliferation of magnetic resonance imaging (MRI).

1.6 Neuroimaging in Schizophrenia

MRI is a tool that permits *in vivo* visualization of tissue. It functions by manipulating the electromagnetic forces inherent in tissue and reconstructing images based on changes in these electromagnetic forces (Andreasen, 1989). MRI in medicine and health research is based on the excitation and relaxation of hydrogen atoms when exposed to electromagnetic radiofrequency pulses. Hydrogen atoms are prominent in water, but also in lipids, in human tissue. Excitation and relaxation of hydrogen atoms can then be measured and converted into an image (Keller, 1988). These images have densities of gray, white, and black corresponding to the strength of signal. MRI scanners
vary in strength but 1.5 to 3 Tesla are most commonly used in the clinical setting. MRI is a unique neuroimaging technique because it may be used to effectively study both structure and function. Functional MRI uses the blood oxygen-level dependent (BOLD) principle to detect blood flow to a particular region of the brain (Logothetis et al., 2001). Both structural and functional techniques have been used to investigate the pathophysiology of schizophrenia, although structural MRI studies have been performed for a longer period of time (Shenton et al., 2001).

Neuroimaging techniques have provided evidence for structural brain abnormalities in schizophrenia. Various studies have reported larger lateral and third ventricle, smaller temporal lobe and medial temporal lobe, and smaller frontal lobe volumes in schizophrenia patients (Shenton et al., 2001). Studies involving patients’ unaffected siblings indicate that there is at least some heritability associated with morphological changes (Goldman et al., 2007).

More recent structural MRI studies have utilized gray-white segmentation techniques (Fischl et al., 2002; Duncan et al., 2004). Whole brain or regions of interest are segmented into gray, white, and cerebrospinal (CSF) tissue classes. An increase or decrease in any these particular components may be indicative of various types of pathology. Decreases in white matter may be a sign of myelin abnormalities, decreases in gray matter a sign of neuronal abnormalities, and increases in CSF a sign of ventricular dilation. Structural MRI techniques have been used to provide evidence for white matter and CSF abnormalities in schizophrenia (Flynn et al., 2003; Nakamura et al., 2007). There is further evidence for gray matter abnormalities in schizophrenia,
including lower neocortical gray matter volumes in both the frontal and temporal lobes (Nakamura et al., 2007). Subcortical brain structures, such as the basal ganglia, have also been shown to be abnormal, but these findings are more complex and require further investigation (Shenton et al., 2001).

1.7 Basal Ganglia Pathology in Schizophrenia

The basal ganglia are a focal point of schizophrenia research for several reasons. First, the basal ganglia are involved in motor, cognitive, and sensory processes (Yin and Knowlton, 2006)—all of which are considered to be aberrant in schizophrenia (Chatterjee et al., 1995; Mueser and McGurk, 2004). Second, schizophrenia shares a number of similarities with more conventional basal ganglia disorders (Samii et al., 2004; Walker, 2007b). Third, the basal ganglia play an important role in the dopamine hypothesis of schizophrenia, which associates dopamine hyperactivity with psychosis (Squire et al., 2003). The striatum receives major input from dopamine-containing neurons, and dopamine D1 and D2 receptors are copiously found in the striatum (Cote and Crutcher, 1991). The therapeutic efficacy of antipsychotic medications is mediated, at least partially, by their action on dopamine receptors (Shenton et al., 2001). Furthermore, psychoactive substances that cause dopamine hyperactivity in the striatum (e.g., amphetamine), often lead to drug-induced psychosis in humans (Lieberman et al., 1990).

The first postmortem study of basal ganglia in schizophrenia showed no abnormalities except that globus pallidus internal segment volumes were smaller in schizophrenia relative to controls (Bogerts et al., 1985). A follow-up study showed
analogous results (Bogerts et al., 1990). Additional postmortem studies of basal ganglia structures in schizophrenia showed volume increases in both the striatum and globus pallidus (Heckers et al., 1991; Lauer and Beckmann, 1997).

Since the proliferation of MRI, there have been numerous studies of basal ganglia structures in schizophrenia. Most of these studies have positive findings that report increased volumes (Shenton et al., 2001), but there are exceptions, with some studies reporting smaller caudate volumes in antipsychotic-naïve schizophrenia subjects relative to healthy subjects (Keshavan et al., 1998; Shihabuddin et al., 1998). Prior antipsychotic exposure is a factor in findings of increased volumes in basal ganglia structures (Chakos et al., 1994; Gur et al., 1998; Lang et al., 2001). Several studies suggest that this hypertrophic effect may be a function of typical antipsychotic medications, whereas atypical antipsychotic medications do not exert the same effects (Chakos et al., 1995; Gur et al., 1998; Lang et al., 2004). Animal studies have shown that typical antipsychotic medications increase striatum size in rodents, whereas atypical antipsychotic medications have the opposite effect (Chakos et al., 1998; Andersson et al., 2002). In one such study, larger increases were associated with more vacuous chewing movements (Chakos et al., 1998).

1.8 Basal Ganglia and Cognition in Schizophrenia

There is a modest amount known about the basal ganglia and cognition in schizophrenia. Structural MRI studies have been incongruent. In one study, there was no relationship between caudate volumes and cognitive functioning in schizophrenia subjects (Crespo-Facorro et al., 2007). However, another study noted a positive
relationship between striatum volumes and an attention/vigilance cognitive dimension in schizophrenia subjects (Mamah et al., 2007). This study also found a negative relationship between nucleus accumbens volumes and severity of delusions.

Much of the rationale for previous as well as prospective studies comes from neuropsychological testing, particularly tests that implicate frontostriatal circuitry. Lesions of the dorsolateral prefrontal cortex are linked with several deficits, including executive and other cognitive dysfunctions (Pantelis and Maruff, 2002). Lesions to this region of the brain also result in neuropsychological impairments—as in during set-shifting tasks (Pantelis and Maruff, 2002; Chudasama and Robbins, 2006). Although not exactly lesions, activation abnormalities of the dorsolateral prefrontal cortex are observed in schizophrenia (Cannon et al., 2005; Schlosser et al., 2007). Relatively high functioning schizophrenia patients show impairment in the extra-dimensional shift, whereas low functioning schizophrenia patients show impairment in reversal learning as well (Pantelis et al., 1999; Chudasama and Robbins, 2006). Of interest, Pantelis and colleagues observed more impairment during set-shifting tasks in chronic schizophrenia subjects than frontal lesion subjects (Pantelis et al., 1999). As stated, performance at the critical set-shift or extra-dimensional shift is sensitive to structural or neurochemical changes in the dorsolateral prefrontal cortex-associative striatum circuit (Dias et al., 1996; Chudasama and Robbins, 2006).

1.9 Basal Ganglia and Movement Disorders in Schizophrenia

Movement disorders may appear at onset in both antipsychotic-naïve and antipsychotic-exposed schizophrenia patients (Chatterjee et al., 1995). Many of the
signs indicate that movement disorders are extrapyramidal symptoms (Torrey, 2002). Extrapyramidal symptoms, which are an indicator of basal ganglia pathology, consist of Parkinsonism, dyskinesia, and dystonia (Chouinard and Margolese, 2005; Gharabawi et al., 2005). All these symptoms are present in at least a subset of antipsychotic-naïve schizophrenia patients (Honer et al., 2005).

Extrapyramidal symptoms become more frequent and severe after antipsychotic-exposure, particularly in chronically medicated patients (Lang et al., 2001; Honer et al., 2005). Of the two classes of antipsychotic medications, the typical class has a greater propensity to produce movement disorders (Blin et al., 1996; Glazer, 2000). Interestingly, the typical class is more intimately coupled with basal ganglia hypertrophy (Gur et al., 1998; Andersson et al., 2002; Lang et al., 2004). In one animal study antipsychotic-induced striatal hypertrophy was associated with more vacuous chewing movements (Chakos et al., 1998).

There are some functional neuroimaging studies that investigate the relationship between the basal ganglia and movement disorders in schizophrenia. One functional MRI study found subcortical over-activation in antipsychotic-naïve schizophrenia subjects during a self-paced unilateral finger-tapping task (Muller et al., 2002). More specifically, bilateral globus pallidus over-activation was observed in antipsychotic-naïve subjects relative to both healthy and antipsychotic-medicated subjects. A follow-up study indicated that there were remarkable similarities between schizophrenia and Parkinsonism subjects (Muller et al., 2003). Both groups showed motor-related changes in subcortical brain structures relative to healthy subjects. These results indicate that
movement disorders in schizophrenia are related to putative basal ganglia pathology in the disorder. However, previous structural studies have not been able to link basal ganglia morphology to extrapyramidal symptoms in schizophrenia subjects (Lang et al., 2001; Lang et al., 2004).

1.10 Hypothesis

To date, no studies have examined functionally relevant basal ganglia subdivisions in schizophrenia. Nor have any studies examined gray-white segmentation in basal ganglia nuclei in a first-episode schizophrenia sample. The model and rationale for the present study was partially based on previous approaches. For instance, previous studies that geometrically divided the thalamus into individual nuclei (Buchsbaum et al., 1996; Gilbert et al., 2001). In addition to global losses in thalamic volume, this approach observed more specific losses in thalamic nuclei volumes (Gilbert et al., 2001). The thalamus, like the basal ganglia, is a subcortical structure that is topographically and functionally organized (Jones, 1985). With respect to the present gray-white segmentation approach, a previous study noted altered gray-white proportions in the striatum despite no significant losses in overall caudate, putamen, and nucleus accumbens volumes (Tamagaki et al., 2005). Importantly, examining functionally relevant subdivisions provides a unique opportunity to link structural and functional measures.

For the present study, MRI scans were acquired from schizophrenia subjects and a cohort of healthy subjects. Using manual as well as automated neuroimaging techniques, total and segmented (gray-white matter) volumes were obtained for the caudate, putamen, and globus pallidus. For the striatum, total and segmented volumes
were obtained for the functionally relevant subdivisions (limbic, associative, and sensorimotor). The goal of the present study was to investigate whether basal ganglia abnormalities are present at the onset of schizophrenia. The primary hypothesis was that one or more of the functionally relevant basal ganglia subdivisions (limbic, associative, and sensorimotor) volumes would be different between schizophrenia and healthy subjects, in contrast to no expected differences in total basal ganglia nuclei (caudate, putamen, and globus pallidus) volumes between schizophrenia and healthy subjects. The secondary hypothesis was that gray matter but not white matter volumes would be different (in both total nuclei and functionally relevant subdivisions) between schizophrenia and healthy subjects. In addition to hypothesis testing, structural measures were compared with functional measures as part of a comprehensive exploratory analysis.
Chapter II: Methods

2.1 Subjects

Patients with first-episode psychosis were recruited as part of the South Fraser Early Psychosis Intervention (EPI) Program, which is based in a catchment-area population of approximately 603,300. Inclusion criteria were age 14-45 and presentation for treatment of first episode of psychosis. Exclusion criteria were psychosis primarily related to substance abuse and presence of neurological disorder or a developmental disability. All subjects provided written informed consent, and the Clinical Research Ethics Board of the University of British Columbia approved the protocol (Appendix I).

For the present study, 25 first-episode schizophrenia subjects were drawn from the EPI Program. Inclusion criteria were a final diagnosis of schizophrenia and scan date prior to January 2006 when there was a change made to the MRI scanning protocol. All patients meeting the inclusion criteria were incorporated into the present study. Patients with first-episode psychosis were followed for one-year and diagnoses were made following a review of all clinical data including a structured diagnostic interview (Structured Clinical Interview for DSM-III-R, SCID) (Spitzer et al., 1990), and used DSM-IV criteria. Healthy individuals were recruited from the local community as a comparison group. These healthy individuals and their first-degree relatives were free of major psychotic disorder. For the present study, 24 healthy subjects were drawn from the cohort of healthy individuals. Demographic data for schizophrenia and healthy subjects are provided in Table 2.
Table 2: Demographic data for schizophrenia and healthy subjects.

<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects</th>
<th>Schizophrenia subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>62.5</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>37.5</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>19</td>
<td>79.2</td>
</tr>
<tr>
<td>East Asian</td>
<td>4</td>
<td>16.6</td>
</tr>
<tr>
<td>South Asian</td>
<td>1</td>
<td>4.2</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Parental socioeconomic status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>19</td>
<td>79.2</td>
</tr>
<tr>
<td>Low</td>
<td>5</td>
<td>20.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>20.9</td>
<td>5.2</td>
<td>15.9-36.8</td>
<td>20.2</td>
<td>4.6</td>
<td>16.2-33.8</td>
</tr>
<tr>
<td><strong>Education (years)</strong></td>
<td>13.2</td>
<td>2.5</td>
<td>10-17</td>
<td>11.0</td>
<td>1.4</td>
<td>8-14</td>
</tr>
</tbody>
</table>

*Parental socioeconomic status was based on the Canadian National Occupational Classification system (HRDC, 1993), and reflects the higher-rated parent.

†Parental socioeconomic status and education data missing for one schizophrenia subject.
2.2 Treatment and Clinical Measures

Treatment for schizophrenia subjects included antipsychotic medications. However, 12 schizophrenia subjects were antipsychotic-naïve at the time of their MRI scan. All antipsychotic-treated subjects included in the present study received less than 90 days of antipsychotic medication treatment at the time of their MRI scan. Converging evidence indicates that antipsychotic medications alter the morphology of the basal ganglia (Chakos et al., 1994; Gur et al., 1998; Lang et al., 2001) as well as other brain regions (Khorram et al., 2006; Panenka et al., 2007). Antipsychotic medication treatment data for schizophrenia subjects are provided in Table 3. In addition to antipsychotic medications, 12 schizophrenia subjects were receiving one or more medications of a different class. Medications included lorazepam (six subjects), benztropine (three subjects), clonazepam, dextroamphetamine, valproate, fluvoxamine, levothyroxine, lithium, and sertraline (one subject for each of clonazepam to sertraline).

Symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The PANSS is divided into a seven-item positive subscale, a seven-item negative subscale, and a sixteen-item general psychopathology subscale. Each item assesses the severity of a particular symptom on a rating scale from 1 (absent) to 7 (extreme). In schizophrenia subjects, PANSS scores were obtained following the specified clinical interview, which was performed near the time of their MRI scan. Total PANSS scores as well as positive, negative, and general psychopathology subscale scores for schizophrenia subjects are provided in Table 3.
Movement disorder was assessed with the Extrapyramidal Symptom Rating Scale (Chouinard and Margolese, 2005; Gharabawi et al., 2005). The version of the ESRS used as part of the EPI Program included a questionnaire of extrapyramidal symptoms, an examination of Parkinsonism, an examination of dystonia, an examination of dyskinesia, and a clinical global impression of severity of the three types of movement disorders (Parkinsonism, dystonia, and dyskinesia). Parkinsonism, dystonia, and dyskinesia are scored on a scale from 0 (absent) to 6 (most severe). Parkinsonism consists of reduced facial expression / speech, bradykinesia (slowness of movements), rigidity, impaired gait / posture, tremor, akathisia (inner feeling of restlessness), and sialorrhea (excessive secretion of saliva). Dystonia, in which muscles are contracted and contorted, consists of acute dystonia and chronic or tardive dystonia. Dyskinesia is a movement disorder typified by movements that are repetitive, purposeless, and involuntary. For the present study, Parkinsonism scores, dystonia scores, dyskinesia scores, and total ESRS scores (Parkinsonism plus dystonia plus dyskinesia) were assessed at or just before the time of the MRI scan. Total ESRS scores as well as Parkinsonism, dystonia, and dyskinesia scores for schizophrenia subjects are provided in Table 3.
Table 3: Clinical data for schizophrenia subjects.

<table>
<thead>
<tr>
<th>Schizophrenia subjects</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipsychotic medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic-naïve</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>Risperidone</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antipsychotic medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (days)</td>
<td>51.2</td>
<td>24.9</td>
</tr>
<tr>
<td>Dose (mg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Positive and Negative Syndrome Scale scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>16.6</td>
<td>4.4</td>
</tr>
<tr>
<td>Negative</td>
<td>17.7</td>
<td>7.5</td>
</tr>
<tr>
<td>General</td>
<td>39.1</td>
<td>7.2</td>
</tr>
<tr>
<td>Total</td>
<td>73.4</td>
<td>14.3</td>
</tr>
<tr>
<td><strong>Extrapyramidal Symptom Rating Scale scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td></td>
<td>5.0</td>
</tr>
<tr>
<td>Dystonia</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>Total</td>
<td>6.6</td>
<td>5.7</td>
</tr>
</tbody>
</table>
2.3 MRI Acquisition and Measures

As part of the EPI Program, MRI scans were obtained from the UBC Hospital's Purdy Pavilion. Healthy and schizophrenia subjects were scanned on a General Electric Signa 1.5 Tesla MRI scanner. For the present study, a 3-Dimensional T1-weighted fast spoiled gradient-recalled (FSPGR) sequence was obtained. Each MRI scan sequence included 124 contiguous axial (horizontal) slices 1.5 mm thick, acquisition matrix 256 x 256, reconstruction matrix 256 x 256, field of view 260 mm, pixel spacing 1.0156 mm x 1.0156 mm, repetition time 11.2 ms, and echo time 2.1 ms.

Brain images from the T1-weighted sequences were loaded and the skull and scalp were automatically removed using the BET brain extraction tool from the FSL version 3.3 software library (www.fmrib.ox.ac.uk) (Smith et al., 2004). Each individual brain was segmented into gray, white, and CSF tissue using the FAST automated segmentation tool. With the FAST automated segmentation tool, each voxel is filtered and classified probabilistically as gray, white, or CSF on a voxel-by-voxel approach. Mixed voxels are classified probabilistically using two approaches. The first approach uses the nearest neighbors meaning if neighboring voxels are gray than the voxel being classified is likely to be mostly gray too. The second approach uses a priori probability mapping meaning that the likelihood of being classified as mostly gray, white, or CSF depends on the location of the voxel being classified. Total brain volumes (total gray plus total white plus total CSF) were obtained to serve as a covariate for region of interest volumes.
For the present study, a rater blind to subject identity obtained volumes of the caudate, putamen, and globus pallidus. For the caudate, caudate plus nucleus accumbens volumes were obtained as opposed to separate volumes because the nucleus accumbens could not be reliably separated from the caudate. Volumetric measurements were made following manual selection of regions of interest on a slice-by-slice basis using MultiTracer freeware (http://air.bmap.ucla.edu/MultiTracer/). All regions of interest were manually traced with reference to neuroanatomical atlases (Duvernoy, 1991; Mai et al., 1997). The final volumetric measurement for each subject was the mean of two independent trials.

For the caudate, measurements began on the most ventral (axial) slice where the nucleus accumbens was clearly visualized and continued to the most dorsal slice where the head and body of the caudate was clearly visualized. The tail of the caudate (the most posterior portion of the structure) was excluded because it could not be consistently measured. For the putamen, measurements began on the most ventral slice where the putamen was clearly visualized (usually the same slice as the nucleus accumbens) and continued to the most dorsal slice where the putamen was clearly visualized. In the most ventral region, the anterior limb of the internal capsule does not separate the nucleus accumbens–putamen striatal complex. At this level, the coronal and sagittal viewing planes allowed the usage of a stereotaxic approach to divide the striatal complex. The area under the most ventral portion of anterior limb of the internal capsule and medial to it was classified as nucleus accumbens (or ventral caudate) and the area lateral to the most ventral portion of the anterior limb of the internal capsule...
was classified as putamen. For the globus pallidus, measurements began on the most ventral slice where the globus pallidus was clearly visualized and continued to the most dorsal slice where the globus pallidus was clearly visualized. The putamen and the globus pallidus form the lentiform nucleus but were separated by the presence of the external medullary lamina of the globus pallidus (Mai et al., 1997). Manual tracing of the caudate, putamen, and globus pallidus for one representative subject is provided in Figure 3.

The striatum (caudate and putamen) was subdivided into distinct sub-regions to ascertain limbic, associative, and sensorimotor striatum volumes. Using an approach similar to those outlined in the introduction (Mawlawi et al., 2001; Martinez et al., 2003), the strategy was to define anatomical sub-regions then assemble these into functionally relevant basal ganglia subdivisions. The aligned brains were analyzed with FSLview and the anterior commissure was used as a landmark to divide the striatum into anterior-posterior and dorsal-ventral divisions. Previous studies have used the anterior commissure as a landmark for such anatomical divisions (Mawlawi et al., 2001; Martinez et al., 2003; Khorram et al., 2006; Lang et al., 2006). On the axial plane where the anterior commissure was most clearly visualized, the striatum was divided into anterior (pre-commissural) and posterior (post-comissural) caudate and putamen. The anterior putamen was divided into dorsal and ventral portions, using the peak of the anterior commissure bow on the coronal plane. The anterior caudate was divided into dorsal, medial, and ventral portions using a geometric approach; the most dorsal and
ventral slices were calculated, and the caudate was divided into equal one-third portions. A representation of the division of the striatum is provided in Figure 4.

Seven distinct sub-regions were yielded after division of the caudate and putamen: Posterior caudate, anterior ventral caudate, anterior medial caudate, anterior dorsal caudate, posterior putamen, anterior ventral putamen, and anterior dorsal putamen. Sub-region and globus pallidus volumes were placed on the whole previously segmented brain volumes to determine gray, white, and CSF content within each sub-region. Sub-regions were regrouped into limbic striatum (anterior ventral caudate and anterior ventral putamen), associative striatum (posterior caudate, anterior medial caudate, anterior dorsal caudate, and anterior dorsal putamen), and sensorimotor striatum (posterior putamen). A schematic of the striatal sub-regions regrouped into limbic, associative, and sensorimotor striatum is provided in Figure 5.

Reproducibility of MRI measures was assessed by means of intra- and inter-rater reliability studies. For intra-rater reliability, caudate, putamen, and globus pallidus volumes were compared between the two independent trials. For inter-rater reliability, caudate, putamen, globus pallidus, and sub-region volumes were compared between the original rater and an additional trained rater.
Figure 3: Tracing of the caudate (slices 1 to 20), putamen (slices 1 to 14), and globus pallidus (slices 3 to 8) for one representative subject.
Figure 4: Division of the striatum into anterior and posterior (A—axial, B—mid-sagittal), division of the putamen into dorsal and ventral (C—coronal), and division of the caudate into dorsal, medial, and ventral (D—coronal).
**Figure 5:** Schematic of the partition of the striatum into distinct sub-regions (anatomic subdivisions) and regrouping of the sub-regions into limbic, dorsal, and sensorimotor striatum (functional subdivisions).
2.4 Cognitive Measures

All subjects underwent the Cambridge Neuropsychological Test Automated Battery (CANTAB) at the time of their MRI scan. The CANTAB includes the intra-dimensional (ID) / extra-dimensional (ED) shift task, which is a test of frontostriatal function (Owen et al., 1991). The ID / ED shift is a computerized test with multiple stages of increasing difficulty. At each stage, the subject must discriminate between stimuli, one of which is correct. The computer provides feedback response and once it is apparent that the subject has understood the currently correct rule, the test moves to the next stage and the rule changes.

The ID / ED shift consists of nine stages of increasing difficulty (Jazbec et al., 2007). After six consecutive correct answers at each stage, the test automatically moves to the next stage. If six consecutive correct answers are not achieved after fifty trials, the test is discontinued. The subject is presented with series of images of colored shapes and lines, and must learn to discriminate between the stimuli. Initially, the subject learns that one dimension of the stimulus is relevant to correct responses (e.g., shapes as opposed to lines). One of the most difficult and critical stages of the test is the eighth stage—the extra-dimensional shift. During this stage of the test, previously relevant stimuli (e.g., shapes) become irrelevant and previously irrelevant stimuli (e.g., lines) become relevant. In addition to the extra-dimensional shift, the ID / ED shift consists of reversal learning stages (second, fifth, seventh, and ninth stages) where the subject must switch their response but within-dimension (e.g., different shape or line).

The dorsolateral prefrontal cortex mediates the extra-dimensional shift, whereas the
more ventral orbitofrontal cortex mediates the reversal stages (Chudasama and Robbins, 2006).

Performance measures for the ID / ED shift typically include the number of trials, number of errors, and latency. For the present study, the number of trials and errors was tabulated for subjects at the extra-dimensional shift and reversal learning stages. For the reversal learning stages, the ninth stage was excluded because not all subjects reached the final stage of the test and, instead, the second, fifth, and seventh stages were cumulatively examined.

All subjects underwent the Kaufman Brief Intelligence Test (K-BIT), which is designed to provide an estimate of cognitive ability (Kaufman and Kaufman, 1990). Benefits of the K-BIT include a brief administration time (approximately 15 to 30 minutes) as well as ease of administration and scoring. The K-BIT yields a vocabulary subtest score, a matrices subtest score, and a composite score. The vocabulary subtest is broken down into expressive vocabulary and definitions subsections. For the expressive vocabulary subsection the subject has to name objects shown in pictures (e.g., frog, bed) whereas for the definitions subsection, the subject has to determine a word based on a phrase describing the word and a partial spelling of the word (e.g. a dark color, br_w_). The matrices subtest consists of 45 items requiring the subject to solve multiple matrix analogies. Early matrix items include multiple-choice analogies that relate familiar objects (e.g., “This baseball goes with this baseball hat just as this football goes with which one of these?”) whereas more advanced items include multiple-choice analogies that require the subject to complete abstract patterns. In addition to
the K-BIT, all subjects underwent the North American Adult Reading Test (NAART) (Blair and Spreen, 1989). The NAART is designed to provide an estimate of premorbid or crystallized cognitive ability (Blair and Spreen, 1989; Griffin et al., 2002).

2.5 Statistical Analysis

Continuous demographic variables (age and education) between groups (schizophrenia and healthy) were analyzed by unpaired t-tests. Nominal demographic variables (gender, ethnicity, and parental socioeconomic status) between groups were analyzed by chi-square goodness-of-fit tests. For ethnicity, the test was performed between two groups—Caucasian and other (East Asian, South Asian, Hispanic, and Afro-Caribbean).

For the reliability studies, intra-class correlation coefficients (ICC) were used to determine the level of concordance between the two independent trials as well as the original and trained raters. For the inter-rater reliability study, separate ICC values were calculated for the right and left caudate, right and left putamen, and right and left globus pallidus. For the intra-rater reliability study, the trained rater measured right hemisphere volumes or left hemisphere volumes in ten different subjects. Separate ICC values were calculated for caudate, putamen, globus pallidus, and sub-region volumes.

Total brain volume between groups was analyzed by an unpaired t-test. To test the primary and secondary hypotheses, repeated measures analysis of covariance (ANCOVA) were performed with side (left and right) as a within-subject factor, group as a between subject factor, and total brain volume as a covariate. This model was used in order to investigate possible group differences in volumes as well as possible side by
group differences in volumes. To control for possible differences in total brain volumes a covariate, as opposed to normalization, approach was employed. Normalizing involves expressing a region of interest volume as proportion of total brain volume. Both approaches have strengths and weaknesses (Mathalon et al., 1993), but previous studies indicate that that the normalization approach does produce measures with lower reliability that are less sensitive to small changes (Arndt et al., 1991; Woods et al., 1991).

Cognitive measures (extra-dimensional shift errors, reversal learning errors, K-BIT composite scores, and NAART scores) between groups were analyzed by unpaired t-tests. For the extra-dimensional shift and reversal learning stages, the total number of errors was analyzed (not the total number of trials). Even though the two performance measures tightly correlate, several subjects reached the maximum number of trials for the extra-dimensional shift stage but no subjects reached the maximum number of errors for the same stage.

For the exploratory analysis, partial correlation matrices were used to compare cognitive or clinical measures to region of interest volumes, while controlling for total brain volume. The first goal was to compare PANSS scores to limbic striatum volumes in antipsychotic-naïve schizophrenia subjects. The second goal was to compare cognitive measures to associative striatum volumes in schizophrenia and healthy subjects. The third goal was to compare Parkinsonism scores to motor striatum volumes in antipsychotic-naïve schizophrenia subjects.
Chapter III: Results

3.1 Demographics

For the continuous demographic variables, age was not significantly different between groups (t=-0.45, df=47, p=0.65). However, education was significantly different between groups (t=-2.25, df=46, p=0.0004), with schizophrenia subjects having fewer years of formal education. For the nominal demographic variables, gender, ethnicity, and parental socioeconomic status were not significantly different between groups (gender: $\chi^2=0.01$, df=1, p=0.91; ethnicity: $\chi^2=0.01$, df=1, p=0.94; parental socioeconomic status: $\chi^2=1.61$, df=1, p=0.20).

3.2 Reliability Studies

Intra-rater reliability demonstrated that basal ganglia volumes were concordant between the two independent trials. ICC values for the right and left caudate, right and left putamen, and right and left globus pallidus were high (ICC right caudate=0.98, ICC left caudate=0.98, ICC right putamen=0.97, ICC left putamen=0.98, ICC right globus pallidus=0.95, and ICC left globus pallidus=0.95). Correlation analysis revealed that there was significant correlation between the two independent trials for all basal ganglia volumes, with the weakest correlation for the left globus pallidus ($r=0.93$, df=49, p<0.0001) and the strongest correlation for the right caudate ($r=0.96$, df=49, p<0.0001).

Inter-rater rater reliability demonstrated that basal ganglia volumes were reproducible between the original and trained raters. ICC values for both the caudate and putamen were high (ICC caudate=0.95; ICC putamen=0.95). Correlation analysis revealed that there were significant correlations between the original and trained raters
for both the caudate ($r=0.93$, $df=9$, $p<0.0001$) and putamen ($r=0.92$, $df=9$, $p=0.0002$).

ICC for the globus pallidus was lower than the ICC for the striatal structures (ICC=0.81).

In addition, correlation analysis revealed that there was a significant correlation between the original and trained raters for the globus pallidus ($r=0.77$, $df=9$, $p=0.01$).

The components of the limbic striatum had ICC values of 0.87 (anterior ventral caudate) and 0.73 (anterior ventral putamen). The components of the associative striatum had ICC values of 0.86 (posterior caudate), 0.90 (anterior medial caudate), 0.81 (anterior dorsal caudate), and 0.99 (anterior dorsal putamen). The posterior putamen, the only component of the sensorimotor striatum, had an ICC value of 0.91.

Correlation analysis revealed that there was significant correlation between the original and trained raters for all sub-regions, with the weakest correlation for the anterior dorsal caudate ($r=0.68$, $df=9$, $p=0.03$) and the strongest correlation for the anterior dorsal putamen ($r=0.99$, $df=9$, $p<0.0001$).

### 3.3 Basal Ganglia Volumes

Volumes of total brain and basal ganglia are provided in Table 4. Total brain volume was not significantly different between groups ($t=-0.76$, $df=47$, $p=0.45$). Total brain volume was used as a covariate in subsequent analyses because it correlated with regions of interest volumes. The correlations between total brain volume and regions of interest were similar in both schizophrenia and healthy subjects. Results for the statistical analyses of the primary and secondary hypotheses are provided in Table 5. Basal ganglia nuclei (caudate, putamen, or globus pallidus) were not significantly different between groups. Statistical analysis of the segmented volumes revealed a
significant result only for the caudate, with schizophrenia subjects having 6% smaller gray matter volumes of the caudate relative to healthy subjects (Figure 6A). White matter volumes for the basal ganglia nuclei were not significantly different between groups.

Functionally relevant basal ganglia subdivisions (limbic, associative, or sensorimotor striatum) were not significantly different between groups. For the associative striatum there was a 6% difference approaching statistical significance, with schizophrenia subjects having smaller associative striatum volumes relative to healthy subjects. Statistical analysis of the segmented volumes revealed a significant result only for the associative striatum, with schizophrenia subjects having 8% smaller gray matter volumes for the associative striatum relative to healthy subjects (Figure 6B). As with the basal ganglia nuclei, white matter volumes for the functionally relevant basal ganglia subdivisions were not significantly different between groups.
Table 4: Total brain and basal ganglia volumes (mean with standard deviation reported in brackets) for schizophrenia and healthy subjects. Total volume equals gray matter volume plus white matter volume plus CSF volume (not provided).

<table>
<thead>
<tr>
<th>Structure</th>
<th>Healthy subjects (N=24)</th>
<th>Schizophrenia subjects (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (cm³)</td>
<td>Total (cm³)</td>
</tr>
<tr>
<td></td>
<td>Total (cm³)</td>
<td>Gray matter (cm³)</td>
</tr>
<tr>
<td>Total Brain Volume</td>
<td>1501 (141)</td>
<td>1469 (150)</td>
</tr>
<tr>
<td>Nuclei subdivisions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left caudate</td>
<td>5.6 (0.5)</td>
<td>5.4 (0.5)</td>
</tr>
<tr>
<td>Right caudate</td>
<td>5.6 (0.6)</td>
<td>5.4 (0.5)</td>
</tr>
<tr>
<td>Left putamen</td>
<td>5.6 (0.6)</td>
<td>5.5 (0.5)</td>
</tr>
<tr>
<td>Right putamen</td>
<td>5.6 (0.6)</td>
<td>5.5 (0.5)</td>
</tr>
<tr>
<td>Left globus pallidus</td>
<td>1.5 (0.2)</td>
<td>1.5 (0.2)</td>
</tr>
<tr>
<td>Right globus pallidus</td>
<td>1.5 (0.2)</td>
<td>1.5 (0.2)</td>
</tr>
<tr>
<td>Functional subdivisions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left associative</td>
<td>6.4 (0.7)</td>
<td>6.0 (0.6)</td>
</tr>
<tr>
<td>Right associative</td>
<td>6.6 (0.9)</td>
<td>6.1 (0.6)</td>
</tr>
<tr>
<td>Left limbic</td>
<td>2.3 (0.3)</td>
<td>2.3 (0.3)</td>
</tr>
<tr>
<td>Right limbic</td>
<td>2.4 (0.3)</td>
<td>2.4 (0.4)</td>
</tr>
<tr>
<td>Left sensorimotor</td>
<td>2.6 (0.3)</td>
<td>2.5 (0.4)</td>
</tr>
<tr>
<td>Right sensorimotor</td>
<td>2.3 (0.2)</td>
<td>2.3 (0.3)</td>
</tr>
</tbody>
</table>
Table 5: P-values for repeated measures ANCOVA (df=1,46).

<table>
<thead>
<tr>
<th>Structure</th>
<th>Total volume</th>
<th>Gray matter volume</th>
<th>White matter volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F-Value</td>
<td>P-Value</td>
<td>F-Value</td>
</tr>
<tr>
<td>Nuclei subdivisions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate</td>
<td>2.786</td>
<td>0.102</td>
<td>4.182</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.183</td>
<td>0.671</td>
<td>0.888</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>0.118</td>
<td>0.733</td>
<td>0.002</td>
</tr>
<tr>
<td>Functional subdivisions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limbic striatum</td>
<td>0.240</td>
<td>0.627</td>
<td>0.272</td>
</tr>
<tr>
<td>Associative striatum</td>
<td>3.805</td>
<td>0.057</td>
<td>5.389</td>
</tr>
<tr>
<td>Sensorimotor striatum</td>
<td>0.022</td>
<td>0.882</td>
<td>0.410</td>
</tr>
</tbody>
</table>
Figure 6: Caudate gray matter volume (A) and associative striatum gray matter volume (B) for healthy and schizophrenia subjects.
3.4 ID / ED Shift, K-BIT, and NAART

For the ID / ED shift, extra-dimensional shift trials and errors as well as reversal learning trials and errors are provided in Table 6. Extra-dimensional shift errors were not significantly different between groups \((t=1.97, df=46, p=0.055)\), although schizophrenia subjects made, on average, twice the number of errors relative to healthy subjects. Reversal learning errors were not significantly different between groups \((t=1.06, df=46, p=0.29)\). NAART as well as K-BIT vocabulary, matrices, and composite scores are provided in Table 6. K-BIT composite and NAART scores were significantly different between groups (K-BIT composite: \(t=-5.22, df=46, p<0.0001\); NAART: \(t=-5.16, df=45, p<0.0001\)), with schizophrenia subjects having lower scores than healthy subjects.
<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects</th>
<th>Schizophrenia subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td><strong>Extra-dimensional shift stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials</td>
<td>16.3</td>
<td>13.3</td>
</tr>
<tr>
<td>Errors</td>
<td>5.8</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Reversal learning stages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials</td>
<td>23.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Errors</td>
<td>3.8</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>K-BIT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocabulary</td>
<td>105.0</td>
<td>9.4</td>
</tr>
<tr>
<td>Matrices</td>
<td>109.0</td>
<td>8.5</td>
</tr>
<tr>
<td>Composite</td>
<td>107.7</td>
<td>8.6</td>
</tr>
<tr>
<td><strong>NAART</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>103.4</td>
<td>7.3</td>
</tr>
</tbody>
</table>

*ID / ED shift and K-BIT data missing for one schizophrenia subject.

tNAART data missing for one healthy subject and one schizophrenia subject.
3.5 Exploratory Analysis

There was a significant negative correlation between extra-dimensional shift errors and associative striatum volume in schizophrenia subjects \((r=-0.47, \text{ df}=23, p=0.02)\), but not healthy subjects. However, this finding was not retained after total brain volume was used as a covariate in a partial correlation matrix model. After examining associative striatum volumes between schizophrenia and healthy subjects, a subsequent analysis was performed using male subjects. For this subset, there was a significant result for the associative striatum \((F=6.55, \text{ df}=28, p=0.02)\), with male schizophrenia subjects having 9% smaller volumes for the associative striatum relative to male healthy subjects. A partial correlation matrix with total brain volume as a covariate revealed a significant negative correlation between extra-dimensional shift errors and associative striatum volume in male schizophrenia subjects \((r=-0.57, \text{ df}=12, p=0.03)\) but not healthy subjects. The analysis showed that smaller associative striatum volumes were associated with more errors on the extra-dimensional shift (Figure 7A). The same model did not reveal any significant correlations between reversal learning errors or K-BIT composite scores and associative striatum volume.

Parkinsonism scores were compared to sensorimotor striatum volumes using antipsychotic-naïve schizophrenia subjects \((n=12\text{ at the time of ESRS rating})\). This subset also excluded the three schizophrenia subjects taking benztropine, which is an anticholinergic medication. For this subset, sensorimotor striatum volumes were not significantly different between antipsychotic-naïve schizophrenia subjects and healthy subjects. A partial correlation matrix with total brain volume as a covariate revealed a significant negative correlation between Parkinsonism scores and sensorimotor striatum
volume in antipsychotic-naïve schizophrenia subjects \( (r=-0.65, \, \text{df}=9, \, p=0.03) \). The analysis showed that smaller sensorimotor striatum volumes were associated with greater severity of Parkinsonism (Figure 7B). Correlations between limbic striatum volume and the PANSS (total and positive subscale) as well as correlations between associative striatum and the PANSS (total and negative subscale) in antipsychotic-naïve schizophrenia subjects were not significant.
Figure 7: Relationship between extra-dimensional shift errors and associative striatum volume in male schizophrenia subjects (A) and relationship between Parkinsonism scores and motor striatum volume in antipsychotic-naive schizophrenia subjects (B).
4.1 Summary

The basal ganglia are a focal point of schizophrenia research for several reasons. First, the basal ganglia are involved in motor, cognitive, and sensory processes (Yin and Knowlton, 2006)—all of which are considered to be aberrant in schizophrenia (Chatterjee et al., 1995; Mueser and McGurk, 2004). Second, schizophrenia shares a number of similarities with other basal ganglia disorders (Samii et al., 2004; Walker, 2007b). Third, the striatum receives major input from dopamine-containing neurons, and dopamine receptors are copiously found in the striatum (Cote and Crutcher, 1991). Dopamine hyperactivity may result in psychosis, and the therapeutic efficacy of antipsychotic medications is mediated, at least in part, by their action on dopamine receptors (Shenton et al., 2001).

The goal of the present study was to investigate whether basal ganglia abnormalities are present at the onset of schizophrenia. More specifically, the objective was to investigate putative abnormalities using a unified basal ganglia complex that incorporated anterior-posterior divisions, dorsal-ventral divisions, and gray-white matter segmentation. The primary hypothesis was that one or more of the functionally relevant basal ganglia subdivisions (limbic, associative, and sensorimotor) volumes would be different between schizophrenia and healthy subjects, in contrast to no expected differences in total basal ganglia nuclei (caudate, putamen, and globus pallidus) volumes between schizophrenia and healthy subjects. The secondary hypothesis was that gray matter but not white matter volumes would be different (in both nuclei and subdivisions) between schizophrenia and healthy subjects.
4.2 Comments

The present study found that total basal ganglia volumes were not significantly different between first-episode schizophrenia and healthy subjects. This result is congruent with the majority of previous studies that also utilized a first-episode sample (Chakos et al., 1995; Gur et al., 1998; Lang et al., 2001; Gunduz et al., 2002; Glenthoj et al., 2007). These studies are in contrast to previous studies that have reported smaller caudate volumes in antipsychotic-naïve schizophrenia subjects relative to healthy subjects (Keshavan et al., 1998; Shihabuddin et al., 1998). However, the latter two studies are different from the present study in several important ways. Keshavan and colleagues (1998) included a mixed antipsychotic-naïve psychosis sample (schizoaffective disorder, mood disorders, and psychotic disorders not otherwise specified), and their patients had mean illness duration of greater than three years. Alternatively, the present study utilizes a homogenous schizophrenia sample with briefer illness duration. Shihabuddin and colleagues (1998) included an older cohort of schizophrenia and healthy subjects and a different measurement approach for both the caudate and putamen.

For the present study, caudate volumes were 5% smaller in schizophrenia subjects relative to healthy subjects. However, this small difference was not statistically significant (Table 5). Previous studies have not reported volumetric differences between first-episode schizophrenia and healthy subjects for the putamen, globus pallidus, or nucleus accumbens (Shenton et al., 2001; Gunduz et al., 2002; Ballmaier et al., 2004; Glenthoj et al., 2007).
Functionally relevant basal ganglia volumes were not significantly different between first-episode schizophrenia and healthy subjects. Although, for the associative striatum there was a 6% difference approaching statistical significance, with schizophrenia subjects having smaller associative striatum volumes relative to healthy subjects. The present study is the only study to have examined limbic, associative, and sensorimotor subdivisions in schizophrenia. Previous studies of dopamine transmission have examined functionally relevant basal ganglia subdivisions in healthy subjects (Mawlawi et al., 2001; Martinez et al., 2003).

The results for the segmented volumes were different for the caudate versus the other basal ganglia nuclei. Putamen and globus pallidus gray matter volumes were not significantly different between first-episode subjects and healthy subjects. However, caudate gray matter volumes were 6% smaller in schizophrenia subjects compared to healthy subjects. The technology used in classifying and segmenting tissue into gray, white, and CSF components is fairly novel. Consequently, there are relatively few studies that have applied this paradigm.

One previous study of gray-white matter proportions in the striatum of schizophrenia subjects observed increased relative white matter volumes in the caudate and nucleus accumbens as well as increased relative gray matter volume in the putamen (Tamagaki et al., 2005). However, the aforementioned study is different from the present study in several important ways. First, Tamagaki and colleagues (2005) included a chronic schizophrenia sample (as opposed to a first-episode sample), with a mean age of 40 years and mean illness duration of 15 years. Second, they did not
measure basal ganglia nuclei beyond the striatum (i.e., the globus pallidus). Third, and most notably, their schizophrenia subjects had been exposed to typical and/or atypical antipsychotic medications for a substantial period of time. Previous studies indicate that antipsychotic medications (especially the typical class) have a hypertrophic effect on the striatum (Chakos et al., 1994; Gur et al., 1998; Lang et al., 2001). In addition, antipsychotic medications (including the atypical class) increase gray matter volumes in both the striatum (Massana et al., 2005) and cortex (Molina et al., 2005). Another previous study of gray-white matter content found decreased gray matter volumes in the caudate of first-episode schizophrenia subjects relative to healthy subjects (Jayakumar et al., 2005). However, this voxel-based morphometry study noted more global losses in gray matter volumes, as other brain regions were affected as well.

The results for the segmented volumes were different for the associative striatum versus the other functionally relevant basal ganglia subdivisions. Limbic striatum and sensorimotor striatum gray matter volumes were not significantly different between first-episode subjects and healthy subjects. However, associative striatum gray matter volumes were 8% smaller in schizophrenia subjects compared to healthy subjects. The present study is the only study to have segmented functionally relevant basal ganglia subdivisions.

Reductions in gray matter volumes in the caudate and associative striatum may reflect cellular changes, including neuronal loss or atrophy. Postmortem studies suggest both reduced striatal spine size (Roberts et al., 1996), and reduced prefrontal cortical spine density in schizophrenia (Glantz and Lewis, 2000). Reduced spine size or density
would effectively reduce neuronal size, which might result in lower overall gray matter.

Congruent with lower gray matter volumes in schizophrenia, is evidence indicating lower mitochondrial profile in the striatum of postmortem schizophrenia subjects (Kung and Roberts, 1999). Lower mitochondrial profile would suggest decreased metabolism in the striatum in schizophrenia. Gray matter, which may include dendrites (plus spines), cell bodies, and synapses, is considered to be the metabolically active component of neurons (Squire et al., 2003).

For the present study, exploratory analyses were performed. The goal was to establish relationships between functionally relevant basal ganglia subdivisions and related functional measures. The first exploratory analysis compared PANSS scores (particularly, positive subscale scores) to limbic striatum volumes in antipsychotic-naïve schizophrenia subjects. The rationale was that the limbic subdivision is an integral part of the dopamine transmission pathway and would play a critical role in the pathophysiology of the psychotic state (Mawlawi et al., 2001; Squire et al., 2003). Previously medicated subjects were excluded because the clinical efficacy of antipsychotic medications are thought to be quite rapid (Kapur et al., 2000). However, it takes longer (weeks if not months) for antipsychotic medications to change basal ganglia morphology, so that these changes can be measured (Chakos et al., 1994). Despite these precautions, there were no significant correlations between limbic striatum volumes and PANSS scores or even positive subscale scores.

The second exploratory analysis compared associative striatum volumes to cognitive measures in schizophrenia subjects. The rationale was that the associative subdivision relates to cognitive function, specifically pertaining to the dorsolateral
prefrontal cortex-associative striatum circuit (Yin and Knowlton, 2006). Performance at the extra-dimensional shift stage is sensitive to structural or neurochemical changes in this circuit (Dias et al., 1996; Chudasama and Robbins, 2006). Whereas the reversal learning stages are sensitive to structural or neurochemical changes in the orbitofrontal cortex-ventral striatum circuit (Dias et al., 1996; Cools et al., 2004; Chudasama and Robbins, 2006).

There was a significant negative correlation between extra-dimensional shift errors and associative striatum volumes in schizophrenia subjects, but this finding was not retained after total brain volume was taken into account. A subsequent analysis was performed using male subjects. For this subset, a statistically significant result for associative striatum volumes was observed, with male schizophrenia subjects having 9% smaller associative striatum volumes than male healthy subjects. The subsequent analysis showed that smaller associative striatum volumes were associated with more errors on the extra-dimensional shift. However, the same model did not reveal any significant correlations between reversal learning errors or K-BIT composite scores and associative striatum volumes. The lack of correlations showed that there was dissociation between the different neuropsychological tests. First, there was dissociation between the extra-dimensional shift and K-BIT (an estimate of overall cognitive ability). Furthermore, and perhaps more importantly, there was dissociation between the extra-dimensional shift stage and reversal learning stages of the ID / ED shift.

Neuropsychological evidence for frontostriatal dysfunctions in schizophrenia has already been established (Elliott et al., 1995). However, the present study is the first to show a link between associative striatum volumes and extra-dimensional shift errors.
Interestingly, impaired performance at the extra-dimensional shift is exhibited in both early un-medicated Parkinson’s disease patients (Downes et al., 1989; Owen et al., 1992) and asymptomatic Huntington’s disease (Lange et al., 1995). A study of basal ganglia structures in Huntington’s disease showed that gene-positive subjects who were far from onset had lower caudate and putamen volumes than gene-negative subjects (Aylward et al., 1996).

The third exploratory analysis compared Parkinsonism scores to sensorimotor striatum volumes in antipsychotic-naïve schizophrenia subjects. The rationale was that the sensorimotor subdivision relates to motor function (Mawlawi et al., 2001; Squire et al., 2003). Previously medicated subjects were excluded because antipsychotic medications can cause immediate changes in motor functioning (Fitzgerald et al., 2000). The analysis showed that smaller sensorimotor striatum volumes were associated with greater severity of Parkinsonism. According to the literature, this is the only study to show such a relationship.

4.3 Caveats

There are a number of limitations to the present study. A ubiquitous limitation in MRI studies is that results may be influenced by acquisition and measurement techniques, as well as tissue contrast. Despite this limitation, there was high intra-rater reliability for basal ganglia volumes, as well as high inter-rater reliability for basal ganglia and sub-region volumes. Sub-region volumes, in particular, are small and only represent a fraction of the total striatum. There was also a strong positive correlation between basal ganglia volumes and total brain volumes. Basal ganglia volumes from postmortem and MRI studies are provided in Tables 7 and 8, respectively. Table 7
shows that the mean values for the present study are quite similar to postmortem
values. Table 8 also reveals that the present study has the highest values among all the
MRI studies. However, there is a broad range and studies that utilized the axial plane
and thinner slices (such as the present study) report larger volumes.

Another limitation for the present study is the sample size. Given the
heterogeneous nature of schizophrenia, this is probably the single biggest factor that led
to the rejection of the primary hypothesis. However, only two studies have had positive
findings with a first-episode schizophrenia sample, and both these studies had fewer or
equivalent number of schizophrenia subjects (Keshavan et al., 1998; Shihabuddin et al.,
1998). Similarly, a study by Aylward and colleagues (1996) found lower basal ganglia
volumes in Huntington’s disease using fewer subjects (Table 8). The current
methodology was sufficiently powered to detect significant differences in gray matter
volumes of the caudate and associative striatum. These measures are proportions of
larger volumes making detection of significant differences more challenging.

A final limitation for the present study pertains to the definition of the anatomical
sub-regions. The sub-regions were obtained by reference to another brain structure (the
anterior commissure) and via a geometric approach. As a result, the sub-regions may
not have exact correspondence to the part of the striatum they are supposed to
represent. However, there is precedence for both approaches in both the structural
(Gilbert et al., 2001; Khorram et al., 2006; Lang et al., 2006) and functional (Mawlawi et
al., 2001; Martinez et al., 2003) neuroimaging fields. Additionally, as mentioned, this
approach was specific enough to detect significant differences in gray matter volumes of the caudate and associative striatum.
Table 7: Review of postmortem basal ganglia volumes from healthy subjects.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects (healthy subjects)</th>
<th>Caudate and nucleus accumbens (mm³)</th>
<th>Putamen (mm³)</th>
<th>Globus pallidus (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bogerts et al., 1985</td>
<td>22 (9)</td>
<td>9626</td>
<td>10118</td>
<td>3278</td>
</tr>
<tr>
<td>Bogerts et al., 1990</td>
<td>39 (21)</td>
<td>9936</td>
<td>11200</td>
<td>3907</td>
</tr>
<tr>
<td>Heckers et al., 1991</td>
<td>46 (23)</td>
<td>N/A</td>
<td>N/A</td>
<td>3620</td>
</tr>
<tr>
<td>Lauer and Beckmann, 1997</td>
<td>18 (9)</td>
<td>9680</td>
<td>11260</td>
<td>N/A</td>
</tr>
<tr>
<td>Baumann et al., 1999</td>
<td>16 (8)</td>
<td>10350</td>
<td>10800</td>
<td>3400</td>
</tr>
<tr>
<td>Bielau et al., 2005</td>
<td>22 (42)</td>
<td>9897</td>
<td>10565</td>
<td>3173</td>
</tr>
</tbody>
</table>
Table 8: Review of MRI basal ganglia volumes from healthy subjects.

<table>
<thead>
<tr>
<th>Study</th>
<th>Slice thickness (mm) and plane</th>
<th>Number of subjects (healthy subjects)</th>
<th>Caudate and nucleus accumbens (mm³)</th>
<th>Putamen (mm³)</th>
<th>Globus pallidus (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>1.5 axial</td>
<td>50 (25)</td>
<td>11197</td>
<td>11212</td>
<td>3005</td>
</tr>
<tr>
<td>Chakos et al., 1994</td>
<td>3.1 coronal</td>
<td>39 (10)</td>
<td>5590 (caudate only)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hokama et al., 1995</td>
<td>1.5 coronal</td>
<td>30 (15)</td>
<td>9130</td>
<td>8370</td>
<td>2260</td>
</tr>
<tr>
<td>Aylward et al., 1996</td>
<td>3.0 axial</td>
<td>47 (27)</td>
<td>5980</td>
<td>9000</td>
<td>2520</td>
</tr>
<tr>
<td>Gur et al., 1998</td>
<td>1.0 axial</td>
<td>224 (128)</td>
<td>10128</td>
<td>9209</td>
<td>994</td>
</tr>
<tr>
<td>Keshavan et al., 1998</td>
<td>2.8 axial</td>
<td>42 (17)</td>
<td>10810</td>
<td>5280</td>
<td>N/A</td>
</tr>
<tr>
<td>Corson et al., 1999</td>
<td>1.5 coronal</td>
<td>79 (43)</td>
<td>5959 (caudate only)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lang et al., 2001</td>
<td>4.0 (1.0 inter-slice gap) coronal</td>
<td>65 (23)</td>
<td>6088</td>
<td>8689</td>
<td>2478</td>
</tr>
<tr>
<td>Rosas et al., 2001</td>
<td>1.5, coronal</td>
<td>51 (24)</td>
<td>8500</td>
<td>9200</td>
<td>N/A</td>
</tr>
<tr>
<td>Tamagaki et al., 2005</td>
<td>1.5, coronal</td>
<td>114 (56)</td>
<td>5310</td>
<td>8924</td>
<td>N/A</td>
</tr>
</tbody>
</table>
4.4 Future Directions

In science, a balance should be struck between data and theory. It is important to have good theories to test, and the requisite data to prove or disprove those theories. There is compelling evidence for brain abnormalities and pathologies in schizophrenia. Many different structures have been implicated including the frontal lobe, temporal lobe, hippocampus / para-hippocampus complex, thalamus, and basal ganglia. No single structure parsimoniously explains all the signs and symptoms of schizophrenia. Additionally, the heterogeneous nature of this disorder means that no cluster of structures can be implicated in every single case.

Although many aspects of schizophrenia reflect an aberrant frontostriatal circuitry, the pathophysiology of this disorder remains unclear. Given the heterogeneous nature of schizophrenia, it might be best to dichotomize patients based on different features, such as level of functioning or response to treatment. Furthermore, current and future experimental paradigms should focus on studying multiple brain regions and the connectivity between these brain regions. This could be done by using, and perhaps even improving, existing techniques such as structural MRI, functional MRI, and DTI. One interesting approach might be to study psychoses that have known pathophysiology (e.g., encephalitis, multiple sclerosis, and psychoactive drug-induced), particularly those that share broader features with schizophrenia. Then, based on these studies, develop new ideas to investigate the mechanism of illness of schizophrenia and schizophrenia spectrum disorders, which have a more elusive and less understood pathophysiology.
4.5 Conclusions

The present study suggests that total basal ganglia nuclei volumes and functionally relevant basal ganglia volumes are not different in first-episode schizophrenia. Although, for associative striatum volume there was a small difference approaching statistical significance, with schizophrenia subjects having smaller associative striatum volumes relative to healthy subjects. In all probability, with more subjects and an improved methodological approach, a statistically significant result would be attained.

Segmented volumes suggest that caudate gray matter volumes and associative striatum gray matter volumes are significantly different between first-episode schizophrenia and healthy subjects. First-episode schizophrenia subjects had smaller caudate gray matter volumes and associative striatum gray matter volumes. Altered gray-white matter proportions involving the caudate or associative striatum may lead to disrupted frontostriatal functional circuits in schizophrenia.

Exploratory analyses suggest that there is significant negative correlation between volume of the associative striatum and extra-dimensional shift errors. Smaller volumes of the associative striatum are associated with more errors on this neuropsychological test. This test was specific to the associative striatum, as other neuropsychological tests (e.g., reversal learning) did not reveal any correlations. An additional exploratory analysis suggests that there is a significant negative correlation between volume of the motor striatum and severity of Parkinsonism. Smaller volumes of the motor striatum are associated with increased severity of Parkinsonism. Structural abnormalities in functionally relevant subdivisions may lead to aberrant functioning.
References


Davis JM, Chen N, Glick ID (2003) A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 60:553-564.


myelination in schizophrenia detected in vivo with MRI, and post-mortem with

Abnormal Involuntary Movement Scale (AIMS) and Extrapyramidal Symptom
Rating Scale (ESRS): cross-scale comparison in assessing tardive dyskinesia.
Schizophr Res 77:119-128.

Thalamic volumes in patients with first-episode schizophrenia. Am J Psychiatry
158:618-624.

Glantz LA, Lewis DA (2000) Decreased dendritic spine density on prefrontal cortical
pyramidal neurons in schizophrenia. Arch Gen Psychiatry 57:65-73.


Glenthoj A, Glenthoj BY, Mackeprang T, Pagsberg AK, Hemmingsen RP, Jernigan TL,
Baare WF (2007) Basal ganglia volumes in drug-naive first-episode
schizophrenia patients before and after short-term treatment with either a typical


Goldman AL, Pezawas L, Mattay VS, Fischl B, Verchinski BA, Zoltick B, Weinberger
DR, Meyer-Lindenberg A (2007) Heritability of Brain Morphology Related to
Schizophrenia: A Large-Scale Automated Magnetic Resonance Imaging Segmentation Study. Biol Psychiatry.


Jayakumar PN, Venkatasubramanian G, Gangadhar BN, Janakiramaiah N, Keshavan MS (2005) Optimized voxel-based morphometry of gray matter volume in first-


Lange KW, Sahakian BJ, Quinn NP, Marsden CD, Robbins TW (1995) Comparison of executive and visuospatial memory function in Huntington's disease and


Appendix I: University of British Columbia Research Ethics Board Certificate of Approval

The University of British Columbia
Office of Research Services
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

**ETHICS CERTIFICATE OF EXPEDITED APPROVAL: RENEWAL WITH AMENDMENTS TO THE STUDY**

<table>
<thead>
<tr>
<th>PRINCIPAL INVESTIGATOR:</th>
<th>DEPARTMENT:</th>
<th>UBC CREB NUMBER:</th>
</tr>
</thead>
<tbody>
<tr>
<td>William G. Honer</td>
<td>UBC/Medicine, Faculty of Psychiatry</td>
<td>H01-70454</td>
</tr>
</tbody>
</table>

**INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:**

<table>
<thead>
<tr>
<th>Institution</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancouver Coastal Health (VCHRI/VCHA)</td>
<td>Vancouver General Hospital</td>
</tr>
<tr>
<td>Vancouver Coastal Health (VCHRI/VCHA)</td>
<td>UBC Hospital</td>
</tr>
</tbody>
</table>

Other locations where the research will be conducted:
N/A

**CO-INVESTIGATOR(S):**

- Allen Thornton
- Donna Jane M Lang
- James L. Kennedy
- Thomas Ehmann
- Jehannine Austin
- Robert Holt
- Rhonda Low
- G. William MacEwan
- Richard Williams
- Lakshmi N. Yatham
- Lili C. Kopala
- Alexander L. MacKay

**SPONSORING AGENCIES:**

- British Columbia Mental Health Society - "Interactions of Development, Early Life Experience & Genetic Predisposition in Schizophrenia"
- Eli Lilly Canada Inc. - "Early Psychosis Identification and Intervention"
- Michael Smith Foundation for Health Research - "Early Psychosis Identification and Intervention"

**PROJECT TITLE:**

Early Psychosis Identification and Intervention
The current UBC CREB approval for this study expires: March 8, 2008

<table>
<thead>
<tr>
<th>Consent Forms</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject_07Feb26</td>
<td>Version1</td>
<td>February 26, 2007</td>
</tr>
<tr>
<td>ParentofControl07Feb26</td>
<td>Version1</td>
<td>February 26, 2007</td>
</tr>
<tr>
<td>ParentofSubject07Feb26</td>
<td>Version1</td>
<td>February 26, 2007</td>
</tr>
<tr>
<td>Control07Feb26</td>
<td>Version1</td>
<td>February 26, 2007</td>
</tr>
</tbody>
</table>

**CERTIFICATION:**

In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal by the UBC Clinical Research Ethics Board.

Approval of the Clinical Research Ethics Board by one of:

Dr. James McCormack, Associate Chair