BASAL GANGLIA STRUCTURE AND THE EFFECTS OF NEUROLEPTIC TREATMENT IN SCHIZOPHRENIA

by

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ABSTRACT

Schizophrenia is a complex mental illness of unknown etiology. Clinical research has suggested that abnormalities of the basal ganglia are present in schizophrenia. Whether these abnormalities are present at the beginning of illness or progress with time remains controversial. Concomitantly, antipsychotic treatments, particularly traditional neuroleptics, may exert metabolic effects on the basal ganglia, but the effects of new atypical antipsychotic are unknown. To elucidate the nature of underlying basal ganglia structure and the effects of antipsychotic treatment on striatal morphology, clinical signs and symptoms, three MRI studies of basal ganglia volumes were conducted.

In study A, baseline volumes in a cohort of drug-naïve first episode psychosis (FEP) patients, chronically treated schizophrenia patients and healthy controls were assessed. Chronically treated patients had larger basal ganglia volumes compared to both never-medicated patients and healthy controls. Never-medicated patients' basal ganglia volumes were not different from controls.

In study B, extrapyramidal symptoms (EPS) and their relationship to neuroleptics and striatal volumes were examined. Prior to neuroleptic treatment, 39% of FEP patients had EPS at baseline. FEP patients who presented with parkinsonism had larger left caudate volumes than those who did not. In study C, the effects on basal ganglia volumes and EPS after switching patients from risperidone or typical antipsychotics to olanzapine were examined. Patients previously treated with typicals had decreases in putamen and globus pallidus volume after switching. Patients previously on risperidone had a decrease in caudate volume after switching. Patients maintained on risperidone had no changes in basal ganglia volumes. Severity and prevalence of EPS were unchanged after switching.

No underlying volumetric abnormalities of the basal ganglia in drugnaïve first-episode schizophrenia were observed in the cohort of patients included in this thesis. However, movement disorders were seen in a notable portion of drug-naïve schizophrenia patients, suggesting that abnormalities of the basal ganglia or circuits of the basal ganglia are present and may be subtle.

Atypical neuroleptics do not induce additional EPS at clinically effective doses. Chonic exposure to atypical neuroleptics is not associated with striatal hypertrophy, and in the case of olanzapine, may reduce caudate volumes in some patients.

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LIST OF ABBREVIATIONS

Scanning terms:

MRI	Magnetic Resonance Imaging					
TR/TE	Relaxation time to Echo-time rati					
T1	longitudinal relaxation time					
T2	transverse relaxation time					
SPGR	Spoiled-Gradient echo					
IR	Inversion Recovery					

Statistical terms:

Clinical Measures:

EPS	Extrapyramidal Symptoms
ESRS	Extrapyramidal Symptoms Ratings Scale
PANSS	Positive and Negative Syndromes Scale
SCID	Structured Clinical Interview for Diagnosis

Clinical terms:

central nervous system
Huntington's Disease
Parkinson's Disease
Socioeconomic Status
Diffuse Lewy Body Disease
Progressive Supranuclear Palsy

Others:

FEP	First-episode Psychosis
CPZ	Chlorpromazine
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

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"The important thing is not to stop questioning. Curiosity has its own reason for existing."

Albert Einstein

Dedicated to the memory of Rudy

"My sweet boy"



Chapter 1: General introduction and background

1.1 General Overview:

Schizophrenia is a complex mental illness with an unclear etiology. Multifactorial processes (genetic liability, external environmental insults, neurodevelopmental abnormalities, physical and emotional stressors) interact, resulting in the emergence of the illness. While there is converging evidence from both post-mortem and *in-vivo* imaging studies of brain abnormalities, exactly where and when in the brain abnormalities reside remains unclear (Cleghorn et al 1991; Pearlson et al 1996; Shenton et al 2001). Neurohistochemical studies of antipsychotic-targeted brain regions are highly suggestive of underlying abnormalities of the dopaminergic systems (Dean 2001). The greatest concentration of dopamine targets resides in the subcortical structures known as the basal ganglia. Many symptoms of basal ganglia diseases are strikingly similar to those observed in schizophrenia, particularly movement disorders, executive deficits and memory deficits.

The nature of basal ganglia abnormalities or basal ganglia dysfunction in schizophrenia is controversial. Treatments with traditional antipsychotic medications are known to have measurable physiological effects on basal ganglia volumes and movement disorders, confounding earlier findings of basal ganglia abnormalities in schizophrenia (Harrison 1999a). The purpose of this thesis is to clarify the nature of basal ganglia structure, movement disorders and clinical symptomatology in a cohort of drug-naïve first-episode and

chronically treated schizophrenia patients. This thesis is presented in five major parts. Chapter 1 includes an overview of basal ganglia structure and function, a description of known diseases of the basal ganglia and descriptions of the subjects and techniques employed in the subsequent three studies. Chapters 2, 3 and 4 describe three separate studies of basal ganglia structure, symptoms and/or signs in drug-naïve patients and chronically medicated patients receiving distinct classes of antipsychotic medications. The final chapter includes a summary overview of findings from the previously described studies, a discussion of inherent weaknesses in quantitative MRI investigations in psychiatry research and new directions in investigating the underlying circuitry of schizophrenia.

1.2 Basal Ganglia Structure: Introduction

The basal ganglia consist of five major deep subcortical nuclei (see table 1). In conjunction with other extrapyramidal centres (subthalamic nucleus and substantia nigra), the basal ganglia gives rise to an emerging fibre system with a number of interrelated circuits from which output systems emerge at varying points (Niewenhuys 1985). An illustration of the basal ganglia in the coronal plane is shown on the following page in figure 1.



Figure 1. Illustrated example of basal ganglia structures shown in the coronal plane.

The prominent components of the basal ganglia include the caudate nucleus, the putamen and the globus pallidus. These three nuclei of the basal ganglia are also known as the corpus striatum. Both the subthalamic nucleus and the substantia nigra are anatomically connected to the caudate, putamen and globus pallidus (Manter and Gatz 1992). The terminology of basal ganglia structures and interrelated circuits are numerous. For clarification, a table of basal ganglia nomenclature is presented here (adapted from Manter and Gatz 1992).

Term	Prefix	Suffix	Synonym	Components
Striatum	Strio-	-striate	Neostriatum	Caudate and Putamen
Pallidum	Pallido-	-pallidal	Paleostriatum	Globus Pallidus
Lenticular Nucleus				Putamen and Globus Pallidus
Corpus Striatum				Caudate, Putamen and Globus Pallidus
Subthalamic Nucleus	Subthalamo-	-subthalamic		
Substantia nigra	Nigro-	-nigral		Pars compacta and Pars reticularis

 Table 1. Basal Ganglia Nomenclature

Basal ganglia nuclei demonstrate multimodality of function and have ubiquitous circuitry to widespread regions of the brain. Functionally, striatal structures are involved in the control of movement, affective and cognitive processes. Anatomically, the basal ganglia receive inputs from widespread regions of the cerebral cortex, including the frontal lobes, the temporal lobes and the parietal lobes (Manter and Gatz 1992). The major target of basal ganglia output is the frontal cortex via the thalamus. Additional circuits of the basal ganglia include the oculomotor (involved in control of eye movement), the dorsolateral prefrontal (involved in some aspects of memory related to spatial orientation) and the lateral orbitofrontal (involved in the ability to modify previously learned behavioral sets (Kandel et al 1991)).

More recent work in primates demonstrated an additional output pathway to the visual areas of the inferotemporal cortex, implicating basal ganglia involvement in higher order aspects of visual processing (Middleton and Strick 1996). Injury or disturbance of the striatal system can result in varied clinical symptomatology as a result of its multimodal nature and the complexity of the neural pathways that course through the basal ganglia.

The major inputs to the corpus striatum are from the cerebral cortex, the thalamus and substantia nigra. While neurons from all regions of the neocortex project to the striatum, projections from the frontal and parietal cortices preferentially feed to the putamen (Kandel et al 1991; Manter and Gatz 1992). Axons arising from the frontal eye fields and association areas of the frontal lobes and parietal lobes primarily project to the caudate nucleus (Manter and Gatz 1992).

The basal ganglia have multiple afferent and efferent connections (see figure 2, adapted from Kandel et al 1991). Activation in the frontal cortex related to motor control is mediated by the basal ganglia and thalamus via two significant basal ganglia-thalamocortical feedback loops. These loops comprise the direct and indirect pathways (see figure 3, adapted from Kandel et al 1991). The direct pathway is mediated by the neurotransmitter γ -aminobutyric acid (GABA) in two consecutive connections, which disinhibits the thalamus and releases movement. The indirect pathway has an additional excitatory path from the subthalamic nucleus to the internal globus pallidus mediated by the neurotransmitter glutamate . Activation of this pathway results in inhibition of movement (Graybiel 2001). Additional parallel cortico-basal ganglia loops underlying cognitive and sensory functions are involved in planning, working

memory, learning and attention, and other aspects of higher cognitive function (Middleton and Strick 1996).



Figure 2. Major anatomical connections of the basal ganglia.

- A. The caudate nucleus and putamen receive almost all afferent inputs.
- B. The internuclear connections include connections between all the nuclei.
- C. The principle target of efferent connections is the thalamus.



Figure 3. There are two different pathways throughout the basal ganglia: the direct route from the striatum to the output nuclei and the indirect route through the subthalamic nucleus. This figure shows the possible interactions of different neurotransmitters within the basal ganglia. (Black arrows represent inhibitory pathways; white arrows represent excitatory projections.)

1.3 Diseases of the Basal Ganglia

Many of the symptoms of basal ganglia disease reflect disorder or dysfunction of neurotransmitter systems. The striatum is the central hub for direct excitatory input from the cerebral cortex. The basal ganglia are involved in frontal lobe function by virtue of anatomic connections between cortical and subcortical structures. The putamen is primarily associated with the supplementary motor area and is mainly involved in motor functions, while the anterior caudate nucleus is mainly involved in prefrontal functions (Roberts et al 1993). The globus pallidus is also known to be involved in motor functions (Iwata 1993). Both the caudate and the putamen are heavily populated with dopamine receptors, particularly the D_1 and D_2 subtypes. Nigro-striatal dopaminergic fibres emerging from the substantia nigra target these receptors. Neurotransmitter disruptions may result in both cognitive and motor deficits, such as difficulties with working memory, chorea and dyskinesias (Robbins et al 1998; Skeel et al 2001). The major features of subcortical dementia following basal ganglia malfunction include impaired mood and motivation, altered personality, slowed thinking and impaired reasoning (Robbins et al 1998). The following sections discuss in more detail specific basal ganglia diseases.

1.3.1 Huntington's Disease

Huntington's Disease (HD) is an inherited progressive neurodegenerative disease affecting cognitive, motor and emotional functioning. Transmission of the illness is via a single autosomal dominant gene on chromosome 4. Typically, onset of the illness begins in middle age. The early stages of illness are characterized by alterations in behavior and personality, including depression, anxiety and irritability (APA 1994). Over time, patients with HD go on to develop dementia. Initial signs of movement disorders, such as increased fidgeting and restlessness, progress to generalized choreiform movements consisting of rapid flow-like motion of the fingers, facial grimaces and involuntary crossing and uncrossing of the legs (Manter and Gatz 1992). Neuroanatomically, there are marked degenerative changes in the basal ganglia, particularly in the caudate and putamen. The basal ganglia atrophy progressively in HD, however, there does not appear to be a close association between absolute change in volume over time and severity of neurologic symptoms (Aylward et al 1997). Atrophy of the basal ganglia may begin significantly earlier than the initial presentation of symptoms (Aylward et al 1996). Atrophy of the frontal lobes in HD, which is associated with cognitive impairment, occurs in the later stages of increasing HD symptom severity and is primarily of the white matter (Aylward et al 1998). Measurable cognitive deficits are not restricted to the later stages of illness and patients may exhibit some deficits of executive function and visuospatial memory in early HD (Lawrence et al 1996). The most consistent neuropathological finding

from MRI is reduced caudate and putamen volume, which is present prior to symptom onset and progresses over the course of illness (Aylward et al 2000; Harris et al 1992; Hauser and Olanow 1994). Volume reductions are a result of neuronal atrophy and neuronal loss (Peyser and Folstein 1990).

1.3.2 Parkinson's Disease

Parkinson's disease (PD) is a condition associated with degenerative changes in the substantia nigra and the locus ceruleus (Alegret et al 2001). There is also some evidence for cellular abnormalities within the internal globus pallidus in PD (Hardman and Halliday 1999). The cause of PD is unknown, however the degenerative profile is well characterized. Degeneration of the substantia nigra involves dopaminergic projections to the striatum, resulting in dopamine depletion in the caudate and putamen (Manter and Gatz 1992). The putamen appears to be the most severely affected basal ganglia region in idiopathic PD and bears the brunt of dopamine depletion, resulting in dysfunction in cortico-subcortical motor loops (Kish et al 1988). Clinical symptoms in PD are observed only when striatal dopamine depletion exceeds 80% of normal levels. The caudate, which receives major inputs from the frontolateral association areas, exhibits less dopamine depletion in PD in the later stages of illness, providing a biochemical basis for the clinical observation of only borderline cognitive dysfunction in some cases of late-stage idiopathic PD (Kish et al 1988).

Parkinson's patients develop a number of motor symptoms, including akinesia (absence or loss of voluntary movement), rigidity and tremors. Neuropathologic changes that occur within the basal ganglia in PD can lead to cognitive and behavioural abnormalities (Rauch and Savage 1997). Cognitive deficits in Parkinson's patients include slowed verbal production, decreased attention, impaired judgement and difficulty with problem solving and planning (Stocchi and Brusa 2000). Cognitive changes are reflective of generalized frontal lobe dysfunction resulting from disrupted basal ganglia outflow to the frontal lobes due to dopamine depletion (Owen et al 1998). In some cases, gross cortical atrophy can be seen from magnetic resonance images in PD patients (Agnoli et al 1986). Other neuropathological findings include the presence of Lewy bodies in the substantia nigra and the locus ceruleus (Sano et al 1996).

1.3.3 Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP), first described at the beginning of the 20th century, is characterized by up-gaze paralysis, pseudobulbar palsy (symptoms including mutism, dysphagia and various sensory-motor deficits), neck rigidity and dementia (Sano et al 1996). Onset of symptoms is typically insidious, generally appearing in middle age. Neuropathological findings include neurofibrillary tangles, degeneration of nerve cells, loss of nerve cells and gliosis, particularly in the basal ganglia, substantia nigra and pons (Pahwa 1999). Widespread regions other than the basal ganglia are involved. The

etiology of PSP is unknown. Cognitive symptoms include decreased memory, slowing of thought processes, apathy and depression (Aarsland et al 2001; Sano et al 1996). Some patients also present with delirium, hallucinations and emotional instability (Aarsland et al 2001). Midbrain atrophy is the most consistent magnetic resonance imaging finding in PSP (Soliveri et al 1999).

1.3.4 Diffuse Lewy Body Disease

Diffuse Lewy body disease (DLBD) is characterized neuropathologically by the presence of Lewy bodies. Microscopically, Lewy bodies appear as intracytoplasmic rounded or oval inclusions in the vacuoles of injured or fragmented neurons. Clinical symptoms include dementia, parkinsonism, depression and psychosis (Barber et al 1999). Onset of the disease typically begins after the age of 65. The etiology of Lewy body disease is unclear and few recommended treatments exist (Sano et al 1996). The Lewy bodies are found in brainstem, substantia nigra, other subcortical areas and cortical areas (Kudo et al 1999; Mizukami et al 1999; Sano et al 1996). Recent MRI studies of patients with Lewy body dementia have not found concomitant atrophy of medial temporal lobe structures (amygdala, hippocampus) compared to patients suffering from Alzheimer's dementia and may account for the relative preservation of memory function in DLBD (Barber et al 2001; Barber et al 2000). Hallucinations, delusions and anxiety are common psychiatric disturbances in DLBD, but are not seen in all cases (Sano et al 1996). Gross abnormalities of brain structures are difficult to detect from MRI in DLBD. Subtle changes in the size of cerebral lobes or hippocampal structures in DLBD are not well delineated by *in-vivo* MRI. As in PSP, widespread regions of the brain other than the basal ganglia are affected.

1.4 Schizophrenia: Signs, symptoms and movement disorders

1.4.1 Defining Schizophrenia

Schizophrenia is a serious and debilitating mental illness. It is considered to be a relatively common psychiatric illness, with an estimated prevalence of 1% of the general population. Diagnostically, schizophrenia is a syndrome characterized by a variety of symptoms and signs. According to the current American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, schizophrenia is defined by a wide variety of symptoms, particularly psychotic symptoms, including the presence of delusions and prominent hallucinations occurring in the context of a decline in function over a six month period. These symptoms must be somewhat persistent and cannot be explained by other recognizable psychiatric or medical conditions (Andreasen 1995). The illness of schizophrenia increases sensitivity to stress and is stigmatizing to patients and their families. Medications used to treat the illness often have undesirable side effects, dissuading continued patient adherence (Kane and Marder 1995). Some clinicians have recommended group or family interventions to improve the emotional quality of the patients' personal networks as a means to bolster medication adherence and reduce the impact of stressors that may induce a relapse (Leff et al 1982).

1.4.2 Clinical Signs and Symptoms

Schizophrenia is characterized by a variable constellation of signs and symptoms. The most prominent features of the illness include frank psychosis or positive symptoms (hallucinations, delusions) and negative symptoms (affective flattening, alogia, avolition), associated with marked social and occupational dysfunction (DSM-IV 1994). From a clinical perspective, symptoms are differentiated from signs. Symptoms are manifested as characteristics or elements of the illness that are experienced by the patient and elicit complaints (i.e. auditory or olfactory hallucinations, persecutory delusions). In contrast, signs are manifestations of the illness that are observable to the clinician, but may not elicit complaints from the patient (i.e. cognitive impairment, abnormal smooth-pursuit eye movements, abnormalities of motor reflexes) (Holzman et al 1974; Lane et al 1996; Thaker 2000). No single symptom is pathognomonic of schizophrenia. The positive symptoms include distortions of inferential thinking (delusions), distorted perceptions not based in reality (hallucinations), distortions of thought processes (disorganized language) and distortions of behavioural monitoring (disorganized or catatonic behaviour). Patients with schizophrenia may have hallucinations in any sensory modality (auditory, visual, olfactory, gustatory or tactile), however, auditory hallucinations are the most commonly reported (David 1999; Mueser et al 1990). The most common delusions in schizophrenia are delusions of persecution. Delusions of reference, grandiosity and religiosity are also

common (APA 1994). Bizarre delusions are considered to be particularly characteristic of schizophrenia and are defined by beliefs that are clearly implausible, i.e. involuntary removal or insertion of thought, removal of body organs with no visible signs of physical trauma (Andreasen 1997; A PA 1994). Negative symptoms may include restricted range and intensity of emotional expression (affective flattening), loss of fluency and productivity of thought or speech (alogia) and reduced initiation of goal-directed behaviours (avolition).

While the symptoms of frank psychosis are state-dependent and are relatively amenable to treatment, cognitive and social deficits are more persistent and less responsive to medications (Dickerson et al 1999; Velligan and Miller 1999). Deficits on cognitive tests are related to impaired premorbid functioning, and may predict poor social functioning at outcome (Addington and Addington 2000). Deficits in intellectual capacity may be progressive prior to or during the early years of illness, resulting in deterioration of IQ by 10 or more points from estimated premorbid levels (Sheitman et al 2000; Weickert et al 2000). Neurocognitive abnormalities of attention, memory and planning may reflect an underlying defect of circuit integrity in brain regions involved in these processes (DeLisi et al 1995; Randolph et al 1994).

1.4.3 Movement Disorders

Movement disorders or extrapyramidal symptoms (EPS) are frequently present in schizophrenia. Extrapyramidal symptoms include parkinsonism (tremors, rigidity), akathisia (restlessness), dystonias (abnormal positioning,

spasms of trunk, limbs, neck) and dyskinesias (involuntary chorieform or other rhythmic motions of tongue, jaw, extremities). Extrapyramidal symptoms are the most common side effects of neuroleptic treatment, and are often dosedependent (Kapur et al 2000). While there is clear epidemiological and clinical data that exposure to neuroleptics induces EPS, it is also known that spontaneous EPS can occur in never-medicated schizophrenia patients (Kopala et al 1996; Kopala et al 1997). The rates of spontaneous EPS are variable, ranging from 14 to 23 percent (Conley and Mahmoud 2001; Kopala et al 1997). High-dose exposure to neuroleptic medications, particularly typical antipsychotic medications, and patients' age may contribute to the severity and persistence of EPS (Kapur et al 2000; Srinivasan et al 2001).

1.4.4 Putative Etiologies of Schizophrenia

A number of theories have been proposed to explain both the emergence and the prevalence of schizophrenia, including the evolution of language and laterality (Crow 1995), the introduction of a viral insult to the fetus during early development (Cannon et al 1989), or the combined effect of genetic liability and obstetric complications (Takei et al 1996). The risk of developing schizophrenia is greatly increased in offspring of parents with schizophrenia compared to the general population (McGuffin et al 1994). Although several genetic loci have been linked to schizophrenia, including chromosomes 1,6, 8,11, and 22 (Edgar et al 2001; Kendler et al 1996; Semple et al 2001), no single gene appears to be responsible. Schizophrenia is a

genetically complex illness, and like other complex diseases, it does not follow simple Mendelian patterns of inheritance. Several genes may be involved simultaneously and they may interact with various environmental insults in a heterogeneous manner (Owen and Craddock 1996). Non-genetic insults, including maternal famine, obstetric complications, and season of birth have all been implicated in the etiology of schizophrenia (Dassa et al 1996; Mednick et al 1991; O'Callaghan et al 1992). However, the majority of cases of obstetric complications do not give rise to adult schizophrenia nor do there seem to be neuropathological changes in the brain structure of schizophrenia patients that would be expected following perinatal trauma (Reveley et al 1982).

The underlying causes of schizophrenia are still controversial. The role of fetal stressors in the etiology of schizophrenia is unclear. These events may not be causative, but may set the stage for the later development of schizophrenia. Additional environmental triggers during critical times during normal development may also contribute to derailment of normal brain maturation that could further predispose an individual to schizophrenia. Multiple regions in the brain may be affected. Where and when such events occur in the brain are of significance in understanding the emergence and phenomenology of schizophrenia.

1.5 Historical Perspectives

Modern concepts of schizophrenia are built primarily upon concepts first advanced by Emil Krapelin, Eugen Bleuler and Kurt Schneider in the late 19th

and mid 20th centuries. Verv early recorded histories dating back to Galen (130-200 A.D) were probably the first to describe disturbances of thought, reasoning and intellect as diseases of the mind, but did not describe or define specific forms of mental illnesses. Krapelin was the first modern psychiatrist to emphasize the importance of objective descriptions and classification in psychiatry. Krapelin introduced the concept of studying psychiatric disorders as disease processes, with specific signs emerging at specific times, evolving over the course of illness (Kandel et al 1991). Krapelin focused on three features: (1) the signs the disease presented, (2) the course of the disease, and (3) its outcome. In 1896, Krapelin applied the term dementia praecox to a group of severe mental disorders characterized by reality distortions, resulting in unusual thought patterns and behaviours. He considered the most common characteristic of dementia praecox to be a loss of internal connections of psychic personality, predominantly in the emotional and volitional aspects of mental life (Krapelin (1896) 1971). Krapelin also described dementia praecox as an illness of youth, with a variable course having either a slow, insidious onset or a sudden, acute onset. The course of the illness was further described as having periods of remission and exacerbation over many years (Krapelin (1896) 1971). Krapelin considered dementia praecox to be a form of organic brain deterioration, characterized by morbid changes to the surface of the cortex, and likely, incurable.

Following Krapelin's conception of dementia praecox, Eugen Bleuler, in 1911, introduced the term schizophrenia to replace dementia praecox,

emphasizing the splitting of the mind or the fragmenting of associations (Stotz-Ingenlath 2000). Bleuler described four core symptoms of the schizophrenias, including disturbed associations, disturbed affect, ambivalence and autism or preference of fantasy over reality. Bleuler proposed the idea of a group of schizophrenias, leading to the current understanding of schizophrenia as a heterogeneous group of disorders with similar clinical presentations (Tsuang et al 2000). Bleuler did not consider schizophrenia to be incurable.

Although Krapelin and Bleuler developed full descriptions and definitions of schizophrenia, neither offered concise diagnostic criteria. In response, Kurt Schneider proposed a system of symptom evaluation based on first-rank and second-rank symptoms in 1959 for the purposes of diagnosis (Crow 1998). First-rank symptoms (hallucinations, delusions) were considered to be core symptoms, central to diagnosis and were not explainable by other organic factors (Fish 1984). Second-rank symptoms (i.e. mood disturbances, confused thinking) were symptoms that were not specific to schizophrenia and could be identified in other psychotic illnesses.

1.6 Current DSM-IV Criteria

The American Psychiatric Association bases the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) on multiaxial system involving assessment on five major axes:

- Axis I Clinical disorders, other conditions that may be a focus of clinical attention
- Axis II Personality disorders, mental retardation
- Axis III General medical conditions
- Axis IV Psychosocial and environmental problems
- Axis V Global assessment of functioning

The DSM-IV classification schema groups schizophrenia and other psychotic disorders together and further separates schizophrenia into five subtypes: paranoid, disorganized, catatonic, undifferentiated and residual. DSM-subtyping of schizophrenia is based on the predominant symptomatology at the time of evaluation. The subtyping may be variable over time. The duration of the disturbance is central to a diagnosis of schizophrenia. The DSM-IV criteria for schizophrenia are presented in table 2. If criteria A, D and E for schizophrenia are met, and the episode of the disorder lasts at least one month, but less than six months, a provisional diagnosis of schizophreniform disorder is assigned.

Table 2. DSM-IV Diagnostic Criteria for Schizophrenia

A. *Characteristic Symptoms* : 2 or more of the following, present for a significant portion of time during a 1-month period with some signs of the disorder persisting for a least 6 months (criteria A&C):

- 1. Delusions
- 2. Hallucinations
- 3. Disorganized speech
- 4. Grossly disorganized or catatonic behaviour
- 5. Negative symptoms (affective flattening, alogia, avolition)
- B. Social/Occupational Dysfunction: For a significant period of the time since onset of the disturbance, one or more major areas of functioning (i.e. work, interpersonal relationships, self-care) are markedly below levels achieved prior to onset, or if onset is early, failure to achieve expected levels of interpersonal, academic or occupational achievement.
- **C.** *Duration:* Continuous signs of the disturbance persist for a minimum of 6 months. The 6month period must include at least 1 month of symptoms (unless successfully treated) that meet criterion (A) and may include periods of prodromal or residual symptoms.
- D. Schizoaffective and Mood Disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features ruled out because either 1) no major depressive, manic or mixed episodes have occurred concurrently with symptoms or 2) if mood episodes have occurred with symptoms, their duration was brief relative to active and residual periods.
- **E.** Substance and medical condition exclusion: The disturbance is not a result of direct physiological effects of a substance or a general medical condition.
- **F.** *Relationship to a pervasive developmental disorder*: If there is a history of autism or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are present for at least 1 month (or less if successfully treated).

1.7 Imaging in Schizophrenia – A Quarter Century of Structural Research

When Krapelin first described dementia praecox, he believed that brain abnormalities would ultimately be linked to the etiology of schizophrenia. Unfortunately, post-mortem studies in the late 19th and early 20th centuries had equivocal findings, perhaps due to the crudeness of the available measurement techniques or the expectation of large abnormalities. Specific neuropathological findings had been inconsistently reported and difficult to reproduce (Halliday 2001). Research investigating brain abnormalities in schizophrenia fell out of favour until the advent of CT technology. Johnstone and colleagues published a landmark CT study of ventricular volume in schizophrenia in 1976, confirming early pneumonencephalography findings of increased ventricular size (Haug 1962; Johnstone et al 1976).

Interest in brain abnormalities in schizophrenia expanded with the proliferation of CT and, later the development of magnetic resonance imaging (MRI). The newer MRI technology offered researchers the ability to study grey and white matter *in vivo*. Throughout the mid 1980's to the end of the 1990's, numerous MRI studies in schizophrenia have provided some of the most compelling evidence for structural brain abnormalities (Shenton et al 2001). Ventricular dilation is the most replicated finding and is more prominent on the left side (Andreasen et al 1990; Buchsbaum et al 1997; Cannon et al 1998; McNeil et al 2000). Ventricular enlargement is not exclusive to schizophrenia and may occur in other conditions (Alzheimer's disease, hydrocephalus, myocardial infarction). Additionally, ventricular dilation may be induced by

chemotherapy, corticosteroids and alcohol. Given the frequency of the finding, ventricular enlargement does suggest either a loss of tissue in the periventricular regions or a developmental anomaly in schizophrenia. Metaanalyses have demonstrated a small, but statistically significant overall reduction of brain and intracranial size, without concomitant reductions in extracranial size and a moderate trend towards ventricular dilation (Elkis et al 1995; Ward et al 1996; Wright et al 2000).

Third ventricle enlargement is another frequently reported MRI finding in schizophrenia (Baare et al 2001; Dauphinais et al 1990; Marsh et al 1994; McNeil et al 2000). Dilation of the third ventricle is suggestive of a loss of volume in the adjacent thalamic tissue. This has generated considerable interest in schizophrenia research, as alterations in the interconnectivity could make the thalamus a critical site in the underlying neuropathology and clinical and cognitive dysfunctions in schizophrenia (Andreasen et al 1998; Volz et al 2000). Third ventricle enlargement suggests either abnormal development or neurodegeneration of the thalamus in schizophrenia. Third ventricle dilation is also observed in multiple sclerosis, anorexia and alcoholism (Bakshi et al, 2000, Golden et al, 1996, Visser et al, 1999).

The temporal lobes and the medial structures of the temporal lobes are also regions of interest in schizophrenia. Both delusions and auditory hallucinations may be associated with temporal lobe abnormalities. Abnormalities of the superior temporal gyrus (STG) and alterations of normal sylvian fissure asymmetry are associated with hallucinations (Matsumoto et al

2001a; McCarley et al 1993). A number of MRI studies revealed abnormalities of the posterior STG, particularly planum temporale, an important substrate for language (Hirayasu et al 2000; Hirayasu et al 1998; Menon et al 2001). Reductions in left STG and left amydala volume have been observed in young patients and these reductions were inversely correlated with severity of auditory hallucinations (Barta et al 1990). Reductions in the medial structures (amygdalae, hippocampi) are present in schizophrenia (Maier et al 2000; Marsh et al 1994) and may be associated with development of psychosis. A recent meta-analysis has reported a general trend for bilateral reductions of the hippocampi in schizophrenia (Nelson et al 1998). These findings are paralleled in post-mortem studies demonstrating tissue loss in the hippocampal and parahippocampal complexes (Arnold et al 1995; Bogerts et al 1990). The amygdala and the hippocampus are involved in emotional valence and memory, both of which are affected in schizophrenia. Like ventricular dilation, hippocampal volume reductions are more marked on the left side and are not restricted to schizophrenia (Hirayasu et al 1998; Jellinger 2000).

Hippocampal volume reductions are present both in the early and chronic stages of illness (Matsumoto et al 2001b; Velakoulis et al 1999). The causes of volumetric reductions in the hippocampi are unclear, although postmortem studies have demonstrated alterations of dendritic and neuronal morphology (Luts et al 1998; Zaidel 1999), as well as loss of synaptic proteins (Young et al 1998). As with ventricular dilation, hippocampal abnormalities may be developmental in origin, as there is little evidence of gliotic scarring that
typically accompanies neurodegeneration or neuronal injury (Arnold 1999; Bogerts 1999; Falkai et al 1999). Overall reductions in hippocampal volumes may be small (less than 10%) and accurate detection from MRI would be affected by small sources of measurement error (Nelson et al 1998).

Abnormalities of frontal lobe tissues, particularly of the prefrontal cortex, have been another region of interest in schizophrenia. Cognitive and behavioural deficits associated with measures of frontal lobe damage are observed in schizophrenia (Pantelis et al 1997; Velligan and Bow-Thomas 1999). Some, but not all MRI studies have reported frontal lobe abnormalities (Breier et al 1992; Sanfilipo et al 2000; Vita et al 1995). Small, subtle differences, complexity of frontal structures and varying methodologies may be contributing to equivocal findings.

Subcortical structures (basal ganglia, thalamus, corpus callosum, olfactory bulbs) have become more important regions of focus in schizophrenia. For the purposes of this thesis, only findings pertaining to basal ganglia structures will be discussed in detail. The basal ganglia have become a region of primary research interest in schizophrenia because of the extensive dopaminergic inputs into the caudate and putamen, the clinical efficacy of antipsychotic medications acting on dopamine receptors and the significance of the basal ganglia in cognitive, motor and sensory processing (Keshavan et al 1998).

Post-mortem studies have suggested both increased and decreased basal ganglia volumes in schizophrenia (Bogerts et al 1985; Heckers et al

1991). Prior exposure to neuroleptic treatment is an important factor in findings of increased basal ganglia volumes in schizophrenia. Chronic exposure to typical antipsychotic medications (older generation antipsychotics with a high propensity to induce extrapyramidal side effects) was associated with striatal enlargement in patients who were previously drug-naïve (Chakos et al 1995; Chakos et al 1998; Keshavan et al 1994). Enlarged striatal volumes decreased when typical antipsychotics were switched to the atypical antipsychotic, clozapine (Chakos et al 1995; Chakos et al 1998; Frazier et al 1996; Keshavan et al 1994). The term atypical refers to newer generation antipsychotics that have a reduced propensity to induce extrapyramidal side effects. (A more complete discussion of typical and atypical neuroleptics is provided in section 1.9). Over a two-year period Corson and colleagues (Corson et al 1999b) observed increased basal ganglia volumes during treatment with typical antipsychotics (seven different drugs) and decreased volume over time in patients treated with atypical antipsychotics (clozapine, risperidone and olanzapine). In studies of never-medicated subjects, some have reported decreased volume in the caudate compared to healthy comparison subjects (Keshavan et al 1998; Shihabuddin et al 1998), but others have not (Flaum et al 1995). Increased basal ganglia volumes are not induced by all neuroleptic medications. Exposure to typical antipsychotics induces the greatest change in volumes, but preliminary studies of exposure to atypical antipsychotics indicates the latter do not increase basal ganglia volumes over time (Gur et al 1998b; Keshavan et al 1994).

The increases in basal ganglia volumes may reflect the effects of some neuroleptic medications, yet decreased volumes reported in first-episode neuroleptic-naïve patients with schizophrenia suggest underlying abnormalities prior to the introduction of neuroleptics. As with all previously described volumetric reductions, basal ganglia volume reductions are not exclusive to schizophrenia (Aylward et al 1996; Baumann et al 1999). The specificity of basal ganglia abnormalities requires further investigation, given the diversity of symptoms seen in basal ganglia disorders and the sensitivity of these structures to antipsychotic treatment.

1.8 First-Episode Schizophrenia – Advantages to Studying the Early Phases of Illness

Studying schizophrenia in the early stages of illness offers several advantages. In patients chronically treated with neuroleptics it is often difficult to disentangle brain changes associated with schizophrenia from brain changes associated with disease-related insults, such as alcoholism, drug abuse and malnutrition. Scans performed prior to long-term administration of neuroleptic medication offer researchers the opportunity to investigate regional abnormalities of the brain without the confounding effects of medications (Chakos et al 1995; Chakos et al 1998). The dose and length of neuroleptic exposure required to induce regional volume changes may vary, depending on the region in question. Preliminary studies recommend a maximum of 12 weeks

of continuous exposure to neuroleptics as an appropriate limit for studies of first-episode schizophrenia for relative drug-naïve status (Chakos et al 1994).

Progressive changes in specific brain regions may occur during the early phases of illness (DeLisi et al 1998; DeLisi et al 1997). Chronicity of psychosis may confer some level of neurotoxicity, resulting in progressive changes (Madsen et al 1999). Baseline brain abnormalities in early schizophrenia may be different than in later schizophrenia and have different predictive values on long-term clinical outcome. The terms early and late schizophrenia are not specifically defined in the DSM-IV or in psychiatry literature per se. For the purposes of this thesis, the first one to three years from first onset of illness will be defined as early schizophrenia, whereas illness beyond the fifth year will be defined as later schizophrenia.

Third, there are both gender- and age-related effects on the volumes of specific brain regions, and age effects vary depending on the region (Bartzokis et al 2001; Jernigan et al 2001; Raz et al 2001). Normal brain aging may be altered by schizophrenia (Buchsbaum and Hazlett 1997; Pfefferbaum and Marsh 1995). Studying schizophrenia at the onset of illness ameliorates the confounds of medication and to some extent aging, since most first-episode patients are relatively young.

1.9 Antipsychotics

1.9.1 Typical versus Atypical – Differentiating 2 Major Subclasses of Antipsychotic Medications

The introduction of chlorpromazine into clinical practice more than 40 years ago was a revolutionary step in the management of schizophrenia. Chlorpromazine and other early drugs (see table 3) were labeled antipsychotics or neuroleptics to differentiate them from classic CNS depressants, such as sedatives, opiates, anesthetics and hypnotics (Anderson et al 1998). Over a period of a few weeks, treatment with antipsychotic drugs reduces hallucinations, mental confusion and delusions without inducing physical or psychological dependence (Bezchlibnyk-Butler and Jeffries 1999). Traditional or typical antipsychotics are relatively effective in treating the positive symptoms of psychosis, but are considerably less efficacious in treating negative symptoms and cognitive impairment. Unfortunately, conventional or typical antipsychotics are accompanied by unwanted neurologic side effects, including involuntary extrapyramidal movements and tardive dyskinesia (Blin et al 1996; Glazer 2000; Laux et al 1990). Extrapyramidal movement disorders are elicited by typical antipsychotics in a dose-dependent manner (Kopala 1996; Marsalek 2000).

Pharmacologically, the exact mechanism of antipsychotic action is unclear. Primary action has been attributed to dopamine receptor blockade, particularly of the D₂ subtype, seen in high concentration in basal ganglia structures (Busatto and Kerwin 1997; Hall et al 1994; Hurd et al 2001).

Extrapyramidal symptoms typically appear after D₂ receptor occupancy levels exceed 65 to 78% (Busatto and Kerwin 1997; Hall et al 1994; Hurd et al 2001; Kapur and Remington 2001; Kapur et al 2000), putatively altering normal activity of both the direct and indirect pathways of the basal ganglia. Optimal D₂ receptor occupancy levels vary between individuals, however, therapeutic concentrations of antipsychotics generally occupy close to 70% of the brain's D₂ receptors (Seeman 2001). Some researchers have speculated that oxidative stress may contribute to EPS in schizophrenia, however results from adjunct antioxidant treatments are contradictory (Eranti et al 1998; Lerner et al 2001).

Nonconventional or atypical antipsychotics were designated as atypical on the basis of their reduced propensity to elicit extrapyramidal side effects. The most widely cited pharmacologic model for atypicality is clozapine (Masellis et al 2000). While atypicality is conferred upon antipsychotics with a decreased incidence of EPS at therapeutic doses, the boundaries between typical and atypical are not definitive. Atypical antipsychotics target a wider range of receptors (see table 3) and may affect different classes of receptor subtypes (Anderson et al 1998; Ashby and Wang 1996). Atypical antipsychotics generally have a lower affinity to D₂ receptors compared to typical antipsychotics and are more readily displaced by endogenous dopamine (Kapur and Remington 2001). Treatment with atypical antipsychotics, such as clozapine and olanzapine, may have some benefits compared with typical antipsychotics in treating the negative symptoms in schizophrenia (Ashby and Wang 1996; Cuesta et al 2001). It has been postulated that the salient feature of atypicality is not

receptor target profiles, but rather the rapid rate of dissociation from D₂ receptors (Kapur and Remington 2001).

1.9.2 Risperidone and Olanzapine – Brief Profiles of Two Atypical Antipsychotics

1.9.2a Risperidone

Risperidone (trade name Risperdal) or risperidone tartrate is an atypical antipsychotic with a high affinity to seroton type 2 (5-HT₂), D₂ and α_{1-} noradrenergic receptors (CPA 2000). It binds with lower affinity to histamine H₁ and α_2 -noradrenergic receptors and has no affinity for either D₁ or muscarinic cholinergic receptors. Optimal therapeutic dosage varies, depending on the target patient group. Typically, first-episode patients receive low or moderate clinical doses (2-4 milligrams per day) and these doses are sufficient to elicit 60-70% D₂ occupancy levels (Kapur et al 1999). Treatment resistant chronic patients may receive up to 16 milligrams of risperidone per day, however dosages above 5 to 6 milligrams per day increase the probability of medicationinduced EPS (Kapur et al 1999). At doses up to 4 milligrams of risperidone per day, 60–90% 5-HT₂ total receptor occupancy is achieved (Bezchlibnyk-Butler and Jeffries 1999). The implications for serotonin blockade as a treatment for psychosis remain controversial (Kapur et al 1999; Seeman 2001). Risperidone's interactions with dopamine, serotonin and histamine receptors may also affect appetite leading to weight gain (Baptista 1999), which is a

common adverse side effect with most atypical antipsychotics (McIntyre et al 2001; Sussman 2001).

1.9.2b Olanzapine

Olanzapine (trade name Zyprexa) is another atypical antipsychotic with pleotrophic pharmacology and affects the dopaminergic, serotonergic, muscarinic and adrenergic systems (Green 1999). Olanzapine has a high affinity for D₂, D₃ and D₄ receptors, as well as all 5-HT₂ subtypes and the muscarinic receptor subtype, M₁ (Bymaster et al 1999). At doses between 10-20 milligrams of olanzapine per day, D₂ receptor occupancy levels fall between 59-80% and 5-HT₂ receptor occupancy levels are greater than 90% (Bezchlibnyk-Butler and Jeffries 1999). Olanzapine has a very high affinity for serotonin receptors and saturation is achieved at doses in the 5-10 milligram per day range (Kapur and Remington 2001). As with other antipsychotic agents, therapeutic dosage for clinical response to olanzapine corresponds with D₂ receptor occupancy levels between 65-80% (Kapur and Remington 2001). Olanzapine does elicit EPS at higher doses (Jauss et al 1998; Leucht et al 1999). Additionally, olanzapine appears to cause substantial weight gain, greater than is associated with risperidone treatment (Ganguli 1999; Lund and Perry 2000).

Medication	Receptor Targets	Recommended Therapeutic Dosage (Milligrams/Day)				
A) Typicals, Early Atypicals*						
Chlorpromazine	D ₂ , D ₃ , D ₄ , D ₁ ,H ₁ , mACH, α1	300+				
Haloperidol	D ₂ , D ₃ , D ₄ , α1, H ₁	2				
Loxapine	D ₂ , D ₄ , 5-HT _{2A} , 5-HT ₂	15				
Fluphenazine	D ₂ , D ₃ , D ₄ , D ₁ , NMDA	2				
Pimozide	D ₂ , 5-HT ₂ , H ₁ , α2	2				
*Thioridazine	D ₂ , D ₃ , D ₄ , D ₁ , mACH, H ₁	200+				
*Sulpride D ₂ , D ₃ , D ₄ , D ₁		400+				
B) Atypicals						
Clozapine	D_2 , D_1 , 5-HT _{2A} , $\alpha 1$, $\alpha 2$, H_1 , ACH	300+				
Olanzapine	D ₁ , D ₂ , D4, 5-HT _{2A} , α2, H ₁	10				
Risperidone	5-HT _{2A} , H ₁ , D ₂ , α1, α2	2.5				
Quetiapine	5-HT _{2A} , D ₂ , D ₁	300+				

Table 3. Pharmacology of Common Typical and Atypical Drugs

(Table adapted from Anderson et al, 1998 – recommended dosages based on D_2 occupancy rates as suggested by Bezchlibnyk-Butler & Jeffries, 1999).

D-class = dopamine receptor subtypes 5-HT-class = serotonin receptor isoforms α-class = adrenergic receptor isoforms H-class = histamine receptor isoforms x-ACH = Acetylcholine receptor isoforms NMDA -- N-Methyl-D-aspartate receptor

1.10 Dopamine hypothesis and implications for the involvement of basal ganglia abnormalities in schizophrenia

The classical dopamine hypothesis of schizophrenia postulates dopamine hyperactivity as a central feature of psychosis. This hypothesis gives emergence to the supposition that increased dopamine is responsible for the symptoms of schizophrenia, however the exact mechanism remains unknown (Harrison 1999b). The dopamine hypothesis arose from the efficacy and usefulness of D₂-blocking agents in treating psychosis and the effects of amphetamine as a pro-dopaminergic model of psychosis. The pharmacology of both typical and atypical antipsychotic medications share D_2 receptor blockade as a common feature. D₂-blockade alone may be sufficient to produce antipsychotic effects (Kapur and Seeman 2001; Schotte et al 1993.). Several studies have shown that clinical potencies of antipsychotic agents correlate with their ability to block D₂ receptors (Kapur et al 2000; Seeman 2001). Dopamine is of particular interest, given its role in both cognition and movement disorders (Mozley et al 2001; Wong et al 1996). Given the high proportion of D_2 receptors found in basal ganglia structures, abnormalities of striatal functioning and striatal morphology may play essential roles in the presentation and the treatment of schizophrenia (Menon et al 2001).

1.11 Tools and Techniques: MRI – Acquisition and Protocols

The following chapters describe three separate MRI-based studies, conducted to explore the nature of basal ganglia structures before and after the

introduction of atypical antipsychotics. The same MRI protocols were applied in all three studies. All scans were performed at the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia. Subjects were scanned with a Seimens Magnaton Vision 1.5 Tesla MRI scanner as part of a First Episode Psychosis Program and Study. Funding for the scans of this research project was provided by Janssen-Ortho of Canada for the Dalhousie site. T2 weighted axial images were obtained with the following sequence; TR/TE = 4000/90, field of view = 220, and matrix = 238x256. Slice thickness for all T2 weighted images was 5 mm with a 1mm interslice gap, 22 slices were obtained for T2 weighted sequence. An additional inversion recovery (IR) sequence in the coronal plane was obtained for each subject. The IR sequence was obtained as follows: TR/TE = 2000/20, field of view = 200, and matrix = 168 x 256. A total of 18 slices, 4 mm thick with a 1mm interslice gap were available for this sequence. The follow-up scans were acquired a mean of 1.06 years after baseline (sd=0.4). Digitized slices were measured using a Macintosh G3/350Mz computer. While scanning protocols were specified to re-align follow-up scans to baseline scans as closely as possible, it was necessary to confirm the level of scan to rescan matching by a trained rater. Re-scan matching was assessed by visual inspection of pre-determined landmarks (position of the anterior horns, the presentation of the anterior commissure, the presentation of the anterior caudate, the presentation of globus pallidus, the presentation of the hippocampal formation) on the five IR slices used to assess basal ganglia volumes (see below). Re-scans that were not matched bilaterally on a minimum of 4 out of 5 markers were not included. Re-scans were performed no earlier than 6 months after baseline and no later than 18 months after baseline.

A two-dimensional imaging modality was chosen over a threedimensional imaging modality. By using two-dimensional imaging to cover the entire brain (T2 axial images) we were able to acquire images with high sensitivity to focal pathology and good demarcation of the cerebrospinal fluid (CSF) containing spaces. These spaces provided us with reliable, easily recognizable internal landmarks. Inversion recovery sequences (coronal IRweighted) were obtained for anatomical detail and clear gray-white tissue differentiation. The white-to-grey pixel intensity ratio in these scans is 1.42, compared with a value of 0.89 obtained using an SPGR sequence obtained on a 1.5T GE scanner of similar quality.

1.12 Region of Interest measurement protocols

The following region-of-interest measurement protocols were used to assess basal ganglia volumes in the proceeding studies. Measurements of basal ganglia regions were made by a single rater (DL) blind to diagnosis, treatment, scan interval and gender. Two raters (DL and VG) measured total intracranial volumes. The inter-rater correlation for total intracranial volumes was high (r = .99). Prior to measurement, films were visually inspected for motion artifact, head tilt, rotation and for slice matching at follow-up. One subject was excluded due to head tilt. Slice-to-slice matching of the baseline to follow-up scans was assessed by visual comparison of placement of the

anterior commissure slice and placement of the first presentation of the anterior horns of the lateral ventricles. This approach was used in a serial scan followup study of lesions in multiple sclerosis (Paty and McFarland 1998).

Bilateral areas of the caudate, putamen and globus pallidus were measured on five consecutive slices from IR weighted coronal scans. This sequence was selected over the T2-axial sequence because grey and white matter tissue contrast was better visualized in this sequence. All regions of interest (ROI) were manually selected by using interactive shareware (NIH Image 1.61ppc) (Rasband 1997). Measures of the basal ganglia began two slices anterior and ended two slices posterior to the anterior commissure slice. All basal ganglia measures were the mean of four measures from each brain slice. Structural boundaries were selected based on Duvernoy's MRI atlas (Duvernoy 1991). Only three out of a total of 145 scans included in the following studies had potiential assessable volumes on a sixth slice, however these potentially assessable volumes would have been minimal (less than 10% of the total possible volumes). No subjects had volumes that were not visible on all five consecutive slices. To maintain consistency of technique, no sixth slices volumes were included.

The caudate, putamen and globus pallidus were visually determined on each slice (see Figure 4). The most anterior slice showed the head of the caudate-putamen complex, however, these nuclei could not be separated at this level. The total bilateral caudate-putamen complex on this slice was therefore divided into two halves. The nucleus accumbens was included in the total caudate volume. Demarcation of putamen and globus pallidus was determined by presence of the lateral medullary lamina. Total volumes were calculated by multiplying each measure by absolute slice thickness and summing over five slices. This method interpolated volumes within the interslice gaps and assumed a uniformity of shape between slices. Partial volume effects, particularly pixels containing two or more kinds of tissue, are an inherent source of noise related to edge detection of specific structures. To account for this noise intra-class correlations were assessed for all regions by regression analysis on a randomly selected subset of 10 scans (ICC >0.84 for all regions). Total intracranial volumes were acquired from T2 weighted axial slices. Total intracranial volume included the cerebellum, pons, medulla oblongata, hemispheres, ventricular spaces and sulcal spaces.





1.13 Subjects – Recruitment

All schizophrenia subjects included in the following three studies were recruited in Halifax, Nova Scotia as part of the Schizophrenia Research and Early Psychosis Program in conjunction with the Department of Psychiatry of Dalhousie University. Specific populations of patients with schizophrenia were selected for investigation for each study presented in this thesis. A brief description and tabulation of subjects included for each separate study are provided at the beginning of each study description. Age and gender-matched healthy comparison subjects were recruited from hospital staff and the local community.

Exclusion criteria for schizophrenia subjects were a history of significant head injury or loss of consciousness exceeding five minutes, any history of facial or nasal trauma, a history of central nervous system infection or neurologic disorder, a history of significant substance abuse or seizure disorders. Exclusion criteria for healthy comparison subjects were similar with the addition of a history of psychiatric illness or of psychiatric disorder in the family. These criteria were reviewed by the treating psychiatrist and a qualified research assistant at the time of intake. Signed consent was obtained from all participants and the Dalhousie University Research Ethics Committee approved the studies.

1.14 Clinical Assessments

Clinical assessments of signs and symptoms before and after beginning treatment were based on two assessment tools, the Positive and Negative Syndrome Scale (PANSS) and the Extrapyramidal Symptom Rating Scale. The following descriptions provide an overview of their structure and function. Complete copies of these assessment tools are provided in Appendix A and B.

1.14.1 PANSS – Positive and Negative Syndrome Scale

The Positive and Negative Syndrome Scale was developed and standardized for typological and dimensional assessment of schizophrenic phenomena (Kay et al 1987). The PANSS is a comprehensive rating instrument with 30 items, based on a 7-point rating scale. It evaluates positive, negative and other symptom dimensions (general psychopathology) based on a formal semistructured clinical interview. The PANSS is based on the totality of information pertaining to a specified period of time, generally, the previous week prior to assessment. Information may be derived from clinical interviews, reports of the primary-care hospital staff and/or family members. The seven points of the rating scale represent increasing levels of psychopathology as follows in table 4:

Score	Degree of Psychopathology
1	Absent
2	Minimal
3	Mild
4	Moderate
5	Moderate Severe
6	Severe
7	Extreme

The scoring system is based on the following criteria. A rating of 2 (minimal) denotes questionable or suspected psychopathology, or it may allude to the extreme range of normal. A rating of 3 (mild) is indicative of clear presence of psychopathology, but it is not a serious impediment to daily functioning. A rating of 4 (moderate) indicates that the pathology is serious, but occurs only occasionally or impedes daily functioning to only a modest extent. A rating of 5 (moderate severe) indicates that the psychopathology has a definite impact on normal functioning, but it is not all consuming and can be controlled by will. A rating of 6 (severe) indicates gross pathology present very frequently and is very disruptive of daily functioning and requires direct supervision or intervention. A rating of 7 (extreme) refers to the most severe level of psychopathology, which drastically impedes most or all major life functions and requires close supervision and assistance. Of the 30 items included in the PANSS, 7 items constitute the positive scale, 7 items constitute the negative scale and the remaining 16 items constitute the general psychopathology scale (Kay et al 1987). The PANSS

scoring was performed by a trained psychiatrist and were reviewed regularly with two other trained researchers to maintain intra-rater reliability (ICC=.81).

1.14.2 ESRS – Extrapyramidal Symptom Rating Scale

The Extrapyramidal Symptom Rating Scale is composed of a multi-item checklist of several items to assess the presence and severity of parkinsonism, dystonia, dyskinesia and akathisia. This scale provides a very comprehensive assessment of movement disorder and may be more sensitive than other available scales because of the increased number of extrapyramidal symptoms included for assessment. The ESRS includes physicians' overall or global behavioural ratings for 12 items for parkinsonism, dystonia and dyskinesia (see Appendix B) scored on a 4-point scale. A score of 0 means the behaviour is absent, a score of 1 indicates mild presentation of the symptom, a score of 2 indicates a moderate severity of symptom presentation and a score of 3 indicates the symptom is severe. Subsections of the ESRS assess discrete elements of movement disorders based on severity (7-point scale) and frequency (never, occasional, frequent, constant or almost constant) Subsections of the parkinsonism scale include bradykinesia, rigidity, gait & posture, expressive automatic movements, akathisia, sialorrhea, postural stability. Subsections of the dyskinesia scale include lingual movements, jaw movements, bucco-labial movements and truncal movements. Subsections of the dystonia scale include acute torsion dystonia and non-acute or tardive dystonia of the trunk, limbs,

head, jaw tongue and lips. All items are scored for the left and right side. Global scores for parkinsonism, dystonia, dyskinesia and akathisia are based on the rater's overall impression of all the subscale scores.

For the purposes of the studies conducted for this thesis, only global scores of the four main sections (parkinsonism, dystonia, dyskinesia and akathisia) were reported. Raters' global ratings were consistent with summarized scores based on the individual items inventoried for each major component of the full ESRS scale (ICC=0.79). This scale has been used successfully in a multi-centred study and yielded similar prevalence rates of EPS in independent studies of drug-naïve schizophrenia patients (Caligiuri et al 1993; Honer et al 2002; Kopala et al 1998). The four global ESRS scores are summed to give a total ESRS score. All ratings were performed by a trained clinician (LK) at Dalhousie University. The intrarater (test-retest) reliability for these ratings was high (ICC =0.84). The scale for the overall global assessment of parkinsonism, dystonia, dyskinesia and akathisia is applied as follows in table 5:

 Table 5. Global Ratings Scale for Parkinsonism, Dystonia, Dyskinesia and Akathisia.

C	
Score	Severity of Movement Disorder
0	Absent
1	Borderline
2	Very Mild
3	Mild
4	Moderate
5	Moderately Severe
6	Marked
7	Severe
8	Extremely Severe

The scoring system for this modified ESRS scale is based on the both the frequency and the severity of any observable movement disorder. The rating is based on clinical judgement and should be understood as a nonlinear scale. A rating of 1 (borderline) denotes a barely detectable level of movement disorder, or it may allude to the extreme range of normal. A rating of 2 (very mild) is indicative of definite presentation of some movement disorder, but disorder is very minor and does not interfere with normal levels of social and physical functioning. A rating of 3 (mild) is indicative of clear and definite presentation of movement disorder, but the disorder may not be sufficient to interfere with normal functioning. A rating of 4 (moderate) is indicative that movement disorder is serious and is noticeable to the patient, but may only impede normal functioning to a modest extent. A rating of 5 (moderately severe) indicates that the disorder is severe enough to interfere with normal functioning, but is not an unmanageable impediment. A rating of 6 (marked) indicates very serious movement disorder that disrupts normal functioning enough to require continuous management or intervention. A rating of 7 indicates acutely serious movement disorder that markedly disrupts normal functioning and requires continuous intervention and close monitoring. A rating of 8 indicates the most extreme presentation of movement disorders and would completely preclude normal functioning and requires intensive intervention and monitoring (see Chouinard, 1995 for a description of the application of the ESRS).

Chapter 2: Study A: An MRI study of basal ganglia volumes in firstepisode schizophrenia patients treated with risperidone.

Baseline comparisons of basal ganglia volumes in a cohort of healthy controls, drug-naïve and chronically treated schizophrenia patients - Are there differences?

2.1 Background Rationale

In last 25 years, the predominance of MRI as tool of investigation into brain abnormalities in psychiatry has resulted in a moderate number of studies of the basal ganglia in schizophrenia. In a recent review by Shenton and colleagues (Shenton et al 2001), 25 published studies were reviewed. Most (68%) of these studies reported increased basal ganglia volumes in schizophrenia. Because of medication effects, a number of the studies reviewed may have observed drugeffects (particularly effects of typical antipsychotics) as opposed to drug-free abnormalities of basal ganglia volumes (Chakos et al 1994).

Abnormalities in striatal volume prior to medication treatment in schizophrenia are not well characterized. Some (Corson et al 1999a), (Keshavan et al 1998), but not all (Gur et al 1998b; Shihabuddin et al 1998) recent MRI studies reported decreased caudate volumes in antipsychotic-naïve patients with schizophrenia. Several longitudinal MRI studies of basal ganglia volumes in schizophrenia during treatment with typical antipsychotics (e.g. chlorpromazine, haloperidol, trifluoperazine) or atypical antipsychotics (e.g. olanzapine, risperidone, clozapine, quetiapine) have been performed. Chronic exposure to typical antipsychotic medications was associated with striatal enlargement in patients who were previously drug-naïve (Chakos et al 1995; Chakos et al 1998; Keshavan et al 1994). Enlarged striatal volumes decreased when typical antipsychotics were switched to the atypical antipsychotic, clozapine (Chakos et al 1995; Frazier et al 1996). Over a two-year period Corson and colleagues (Corson et al 1999b) observed increased basal ganglia volumes during treatment with typical antipsychotics (seven different drugs) and decreased volume in patients treated with atypical antipsychotics (clozapine, risperidone and olanzapine). It is unclear if the variability of these results is due to differences in image acquisition, regional selection protocols, medication effects or subject selection biases. The following study was conducted to investigate the presence of baseline abnormalities and the effects of the atypical antipsychotic, risperidone, compared to typical antipsychotics with respect to basal ganglia volumes and movement disorders.

2.2 Hypotheses

- Basal ganglia volumes in drug-naïve patients are reduced compared to healthy controls.
- Basal ganglia volumes in patients treated chronically with typical antipsychotics are greater than first-episode patients' baseline basal ganglia volumes.

 Based on pharmacologic profile (similar D₂ receptor occupancy rates compared to typical neuroleptics), long-term exposure to clinically efficacious doses of risperidone will increase basal ganglia volumes compared to baseline volumes.

2.3 Subjects

Demographic characteristics of the 30 FE, 12 chronic and 23 control subjects appear in Table 6. Ratings of socio-economic status (SES) were based on the Canadian National Occupation and Classification System. (Canada 1993). Parental SES ratings were based on the highest rated parent. Diagnoses were made according to the DSM-IV criteria, based on the Structured Clinical Interview for Diagnosis (SCID). All FE and chronically treated patients were diagnosed with schizophrenia, except for one FE subject diagnosed with schizoaffective disorder.

First-episode (FE) patients were included if lifetime exposure to antipsychotic medication did not exceed 12 weeks (Chakos et al 1994). Ten of 30 FE patients received limited antipsychotic treatment over the previous span of illness, none received in excess of six weeks of continuous antipsychotic treatment immediately prior to the day of scanning (see Table 4). The 12 chronically ill patients received 10 or more weeks of continuous typical antipsychotic medication treatment immediately prior to the baseline scan. Dosage of antipsychotic medication was converted to chlorpromazine (CPZ) equivalents (Bezchlibnyk-Butler and Jeffries 1999). Mean dose for chronically treated patients was 261 milligrams CPZ units per day. Twenty-three healthy control subjects were recruited from hospital staff and the local community.

2.4 Treatment and Clinical Measures

All ratings of psychiatric and extrapyramidal signs and symptoms were completed by Dalhousie University research clinicians. Twenty-four FE patients were subsequently treated with risperidone (dose range 1.0 – 6.0 mg/day, mean dose 2.7 mg/day). Fifteen FE patients remained on risperidone for a minimum of 6 months of continuous treatment and these patients were used to study the effects of risperidone on basal ganglia structures. Some preliminary ESRS scores are provided in table 6. Analysis of the ESRS data in non-medicated first episode patients will be presented in a subsequent chapter.

Fable 6. Demographic and treatment characted	eristics of cor	ntrol, first episode and	l chronic	subjects at ba	seline scan	
<u>Characteristics</u>	Controls	FE Schizophrenia		Chronic Schize	phrenia	
Mean Age (sd) years	27.7 (7.2)	22.9 (6.4)		38.4 (11.6)		
Gender	11 F 12 M	9F 21M		5F 7M		
Ethnicity						
Caucasian	n=22	n=26		n=11		
African-American		n=2				
Asian	n=1			n=1		
Aboriginal		n=1				
Other		n=1				
Baseline Medication Treatment – Lifetime Exposure	None	Typical or Atypical Medi	cations	Typical Antipsyc	chotics	
Mean: weeks (sd) exposure Range: weeks		3.7 weeks (2.7) 0.0-11.0 weeks		307 weeks (340 12.5-1040.0 we	.7) eks	
Medication Trials * Mean Dose (CPZ equivalents	NIA	36 5 ma/day +66 0m/	(110)0	061 moldav	cp/pm ()/2+/	1/10
			g/uay)	zo i ng/uay	(エンキリ IIIG/ua	ay)
Risperidone		2.5 –6 mg/day (n=5)			()	
I rifluoperazine		5 -20 mg/day (n=1)		9-Zu mg/day	(n=4)	
Haloperidoi		3 –15 mg/day (n=3)		30 mg/day	(n=2)	
Loxapine		20 mg/day (n=1)		10-70 mg/day	(n=4)	
Chlorpromazine				200 mg/day	(n=2)	
Fluphenazine		-		.8-1.3 mg/day	(n=30)	
Mean ESRS scores						
a) Admission* (prior to new medication trials)	N/A	2.0 (2) Range:0-6 N	V=23⁺	7.0 (6) Range	:0-20 N=11	• _
b) Post-risperidone treatment [*]		1.0 (1) Range:0-5 N	1=14*	N/A		

Mean PANSS scores				
a) Admission ⁺ (prior to new medication trials) b) Post-risperidone treatment ⁺	N/A	100.9 (18) 56.1 (27)	Range:70-141 N=24 Range:32-118 N=13	67.4 (22) Range:32-102 N=11 N/A
Mean Parental Socioeconomic status (sd) (**see note)				
High	n=11	n=9		n=4
Moderate	n=7	n=9		n=2
Low	n=1	n=9		n=1
Mean Subject SESstatus (sd) (**see note)				
High	n=13	n=1		
Moderate	n=2	n=1		
Low	0=u	n=13		
Currently in School	n=5	n=15		

*Some patients received short durations of multiple medications prior to scanning.

** SES based on Canadian National Occupation Classification System (High = Professional/Managerial, Moderate = Skilled Clerical/Technical, Low = Manual Labour/ Untrained Clerical). Data were not available in all cases.

nb: School - subject currently enrolled in elementary, high school or in process of obtaining undergraduate degree

2.5 Data Analysis – Statistical Methods

Continuous demographic variables were analyzed by omnibus analysis of variance (ANOVA). A single ANOVA test was performed with age entered as a dependent measure and group (FE, Chronic, Control) entered as a main effect. Group differences in gender, SES and ethnicity were analyzed using Chi-square goodness-of-fit tests. Measures of total intracranial volume and baseline regional brain volumes were analyzed by an omnibus analysis of covariance. For analysis of total intracranial volume, group and gender were entered as main effects, with age entered as a covariate. For regional brain volumes, total (left+right) caudate, putamen and globus pallidus volumes were entered as dependent measures, with group entered as a main effect and total intracranial volume entered as a covariate. Post hoc analyses of significant main effects were performed using Bonferroni inequality/Dunn's tests (between groups) and paired t-tests for comparisons between baseline and follow-up volumes.

2.6 Results: Population characteristics, basal ganglia volumes

Age was significantly different between the three comparison groups (F(2)=7.1, p.=.002). Chronically treated patients were significantly older than both FE patients (p.<.001) and controls (p.<.05), however there was no age difference between FE and controls (p.>.06). Subsequent analyses have included age as a covariate as normal aging processes result in volumetric changes in subregional brain volumes over time (Bartzokis et al 2001; Courchesne et al 2000; Matochik

et al 2000). Gender distributions did not differ between FE patients, chronically treated patients and controls ($X^2(1)=1.76$, p.=ns). There were no differences in parental SES between groups ($X^2(4)=6.2$, p.=ns). Both FE and chronic patients had lower SES than control subjects ($X^2(4)=42.2$, p.<.01). Ethnicity did not differ between groups ($X^2(8)=6.9$, p.=ns).

Individual volumes of regions of interest at baseline and follow-up are shown in Figure 6 and Figure 7. Mean volumes for all regions of interest are given in Table 7. Outliers, particularly subjects whose basal ganglia volumes changed in opposing direction to non-outliers at follow-up, were re-assessed to confirm the accuracy of the reported volumes. The intraclass correlation for reassessed outlier basal ganglia volumes was high (caudate ICC = 0.91, putamen ICC = 0.93, globus pallidus ICC = 0.89). Post-hoc comparisons of age, neuroleptic dosage, baseline PANSS scores and baseline ESRS scores did not reveal any differences between outliers and non-outliers (all Fisher's PLSD pvalues > 0.1).

Males had larger intracranial volumes than females (F(1)=32.10, p.<.01), but no differences were found between groups and no association was found between age and intracranial volume (F(2)=1.62, p.=ns). To control for gender effects, all subsequent ANCOVA analyses included both gender and total intracranial volume as covariates for all regions of interest. Baseline basal ganglia volumes in neuroleptic-naive patients were not different from FE patients who had received less than 12 weeks of antipsychotic medications at scan (pvalues for all regions >.05). Therefore, subsequent intergroup comparisons include all FE patients.

A significant group effect was observed for caudate (F(2,1)=3.18, p.=.048), putamen (F(2,1)=3.41, p.=.039) and globus pallidus (F(2,1)=11.88, p.=.0001) volumes. Post-hoc analyses revealed significantly larger caudate, putamen and total globus pallidus volume in chronically treated patients compared with the FE group (see Figure 6). Post-hoc analysis also revealed significantly greater putamen and globus pallidus volumes, but not caudate, in chronically treated patients compared with controls. Caudate, putamen and globus pallidus volumes in FE patients compared to controls were not different (p.>1 for all regions).

Repeat scans were not available for the chronically treated group. Only FE patients and controls were included in risperidone follow-up analyses. No changes in total caudate, putamen or globus pallidus volumes were observed in either FE (all p-values >.2) or controls (all p-values >.2) at follow-up.

Twenty-four baseline PANSS scores were collected prior to the start of neuroleptic medications. These scores were used in the subsequent PANSS analyses. FE patients had greater drug-naïve baseline PANSS scores than chronically medicated patients t(33)=-4.8, p.<.01). PANSS scores were collected for 14 patients after a mean of one year of exposure to risperidone. First-episode patients had significantly reduced PANSS scores after risperidone treatment t(13)=8.4, p.<.001). PANSS scores for risperidone-treated patients did not differ

from PANSS scores for patients chronically treated with typical antipsychotics

(t=1.1, p.>.2, df=23).

Table 7.	Mean intracranial and basal ganglia volumes at baseline and follow-up
	in patients with schizophrenia and in normal controls.

Group	Caudate (mm ³)	Putamen (mm³)	Globus Pallidus (mm³)	Total Intracranial Volume (mm³)
A) Baseline	(L+R)	(L+R)	(L+R)	
First Episode Schizophrenia (N=30)	5880 (664)	8514 (1169)	2524 (402)	1467965 (114369)
Chronically Treated Schizophrenia (N=12)	6390 (630) *	9325 (620) *	3101 (341)* *	1457172 (16408)
Normal Controls (N=23)	6088 (489)	8689 (924)	2478 (400)	1460174 (114369)
B) Follow-up	(L+R)	(L+R)	(L+R)	
First Episode Schizophrenia (N=15)	6025 (835)	8643 (1041)	2562 (313)	1445684 (139674)
Normal Controls+ (N=17)	5974 (534)	8636 (833)	2648 (383)	1455274 (96610)

- ◆ ◆ Significantly larger than normal controls at baseline (p.<.01)
- Significantly larger than FEP at baseline (p.<.01)
- Volumes unchanged from baseline (all p-values>0.1)









2.7 Summary of Findings – Study A

Three main findings emerged from this study. First, the observation of increased basal ganglia volumes in patients chronically treated with typical antipsychotic medication was replicated, as hypothesized. Second, no baseline differences in basal ganglia volumes between first-episode patients with schizophrenia and healthy control subjects were observed. The data did not support the hypothesis of baseline differences in striatal volumes in never-medicated patients. Third, significant changes in basal ganglia volumes in previously drug-naïve patients after a mean of 1.06 years exposure to risperidone were not observed. The hypothesis for increased basal ganglia volumes after risperidone treatment was not supported by the current data.

Studies of non-human striatal complex demonstrated that haloperidol treatment increased the number of neurons immunoreactive for the Fos-like protein in the caudate nucleus and putamen (Deutch et al 1996; MacGibbon et al 1994). A recent study demonstrated striatal enlargement in response to haloperidol treatment in rats after one month of exposure to medication (Chakos et al 1998). Both studies suggest increased neuronal activation in the striatum after exposure to typical antipsychotics. Additionally, functional brain studies in humans have demonstrated haloperidol-induced increases in deoxyglucose metabolism in striatal regions (Bartlett et al 1994; Holcomb et al 1996). Both increased neuronal activation and increased neuronal metabolism may contribute to basal ganglia enlargement following exposure to typical antipsychotics. While other studies have not reported greater enlargement of one striatal substructure over any other, in this study enlargement varied between subregions. The globus pallidus exhibited a notable increase in volume in chronic patients, with a mean volume 623 mm³ (25%) larger than mean volumes in healthy controls. In comparison, caudate and putamen volumes were increased by a mean of 302 mm³ (6.8%) and 636 mm³ (7.8%) respectively in chronically treated subjects compared to healthy controls. All three regions were significantly larger compared to healthy controls. While proportionally, the increase in the globus pallidus appears the greater, the reason for a regionally specific preferential increase is unclear. Measurement limitations may be contributing to the observed increases, as a small increase in a small region is proportionally greater compared to a small increase in a larger region.

Chakos and colleagues (Chakos et al 1994) reported a correlation between basal ganglia volumes and dose of fluphenazine in first episode schizophrenia. Enlargement of striatal structures may occur relatively rapidly and reach plateau in the early phases of antipsychotic treatment. There is evidence to suggest that even low dose exposure to a typical agent may result in hypertrophy of the basal ganglia (Keshavan et al 1994).

Putative progressive brain changes related strictly to chronicity of illness in schizophrenia are not well characterized and there is a lack of definitive data to demonstrate increased subregional brain volumes after onset of puberty (Abi-Dargham et al 1991; Castellanos et al 1994; Zipursky et al 2001). With respect to

those papers that have reported progressive brain changes in schizophrenia, data suggests schizophrenia patients have an increased rate of volume loss compared to healthy controls (Gur et al 1998a; Mathalon et al 2001). This volume loss probably occurs in the prodromal phase of illness, prior to onset of symptoms and remains relatively stable during the course of illness (Woods 1998). It is unlikely that the basal ganglia hypertrophy observed chronically treated patients in the current study is related to either aging or chronicity of illness.

The current assessment of baseline volumes in this study did not reveal abnormalities of the gross morphology of caudate, putamen or globus pallidus in the early phases of illness. This finding does not support the hypothesis of gross baseline abnormalities of the basal ganglia prior to neuroleptic exposure. Alternate studies of antipsychotic-naïve subject groups have reported both reduced and similar baseline basal ganglia volumes compared to healthy controls (Corson et al 1999b; Gur et al 1998b).

FE patients who were classified as neuroleptic-naive in this study did not exhibit striatal enlargement after mean of 1.06 years of continuous risperidone treatment. One study reported that patients titrated off typical antipsychotic medications onto newer generation atypical antipsychotics (risperidone, olanzapine, clozapine) exhibited a reduction in basal ganglia volumes after two years (Corson et al 1999b). Studies contrasting the effects of typical neuroleptics and the atypical neuroleptic, clozapine, suggest that striatal enlargement induced
by typical neuroleptics is reversible (Chakos et al 1995; Frazier et al 1996). A longer-term follow-up of the effects of risperidone on the basal ganglia will be described later in this thesis to further explore these phenomena.

With respect to outliers at follow-up, re-assessment of ten randomly selected data points did not reveal inherent measurement confounds that would explain why some subjects had increased basal ganglia volumes at follow-up. Neither healthy controls nor FE outliers differed in age or years of education from non-outliers. Furthermore, FE outliers did not differ from FE non-outliers when comparing baseline medication dosage, baseline PANSS scores or baseline ESRS scores. One contributing factor may be individual heterogeneity of metabolic and clinical response to neuroleptic treatment.

Chapter 3 Study B: Extrapyramidal Symptoms in Drug-naïve Schizophrenia Subjects

Relationship of baseline basal ganglia volumes and clinical signs – movement disorders in schizophrenia

3.1 Background and Rationale

A number of previous studies have documented pre-existing movement disorders occurring in some drug-naïve schizophrenic patients (Caligiuri et al 1993; Cassady et al 1998; Chatterjee et al 1995; Kopala et al 1998; Kopala et al 1997). The presentation of movement disorders in schizophrenia and the underlying mechanisms involved have not been well understood. Some of the difficulty in understanding movement disorders in schizophrenia relates to the concept of two distinct etiologies, either psychiatric or neurological, being the cause of motor disorders (Rogers 1985). Confounding the issue more, preexisting movement disorders in schizophrenia may be masked by antipsychotic drug effects. However, studies of large psychiatric and mental handicap populations have suggested that neuroleptic medication itself does not make a major contribution to the amount of motor dysfunction observed and that neuroleptics are neither necessary nor sufficient to cause all observed motor deficits (Rogers 1985; Rogers et al 1991). Studies of early childhood developmental patterns in patients prior to the onset of schizophrenia have demonstrated long-standing abnormalities of motor function in this population (Erlenmeyer-Kimling et al 2000; Walker et al 1999). In an earlier study of

childhood home movies of adult-onset schizophrenia patients by Walker and Lewine (Walker and Lewine 1990), diagnosis-blind raters were able to reliably identify pre-schizophrenic children based on behavioural differences compared to normal siblings (decreased emotional response, abnormal motor posturing of limbs, delay or normal developmental motor milestones).

In studies of chronic and first-episode schizophrenia patients, high rates of parkinsonism (31% to 36% of all subjects) were reported (Kopala et al 1997; McCreadie et al 1982; van Harten et al 1996). Other movement disorders, such as dystonia and dyskinesia are not as commonly observed in either neuroleptically naïve or previously treated schizophrenia patients (Honer et al 2002; van Harten et al 1996). These data suggest an underlying abnormality of the striatal region may be present at first break and that the phenomena of movement disorders in schizophrenia is not restricted to medication effects.

Recent reports from addiction studies suggest that dopamine depletion may be related to extrapyramidal symptoms and that increased frequency of EPS is also associated with striatal enlargement, particularly in the caudate (Jacobsen et al 2001). In contrast, those studies that have reported striatal abnormalities in drug-naïve FE patients have more frequently reported a reduction in caudate volume compared to healthy controls (Corson et al 1999a; Keshavan et al 1994; Shihabuddin et al 1998). Volume reductions in the caudate and putamen are also seen in Parkinson's patients (Drayer 1989; Hauser and Olanow 1994; Lisanby et al 1993).

In the initial sample of drug-naïve first episode patients described in chapter 2, the phenomena of pre-existing movement disorders were measured. Some initial exploratory comparisons between medication dosages and ESRS scores in FE patients and chronic patients in presented in chapter 2 were made with unpaired student t-tests. Follow-up ESRS scores in risperidone-treated patients were assessed by a paired t-test. These ESRS scores were obtained as described previously in section 1.14.2. In this data set, over 90% of chronically treated patients were experiencing some movement disorder at baseline. ESRS scores were available for 23 never treated FE patients and 11 chronically treated patients (see Table 6). Ten FE neuroleptic-naïve patients (43%) had pre-existing extrapyramidal movement disorders. Ten (91%) chronically treated patients had extrapyramidal movement disorders at the time of their initial clinical evaluation.

Chronically treated patients had significantly greater ESRS scores than never medicated patients (t(32)=-3.4, p.<.01). ANOVA did not reveal differences in baseline basal ganglia volumes between never-medicated patients who presented with signs or with definite extrapyramidal symptoms (ESRS>0) and those who did not (ESRS=0); (all p-values >0.1). Thirteen risperidone-treated patients had repeated ESRS scoring after one year of treatment (mean dose =2.7 mg/d). Total ESRS scores after treatment were not different from unmedicated ESRS scores (t(12)=1.4, p.=ns). After-treatment ESRS scores were decreased in four patients, which is in keeping with prior reports (Kopala et al

1998), very slightly increased in two patients and unchanged in the remaining seven patients.

Of the FE patients in this study who had no previous medications at baseline, 43% presented with baseline extrapyramidal movement disorders. This is a higher proportion than reported in a previous study (Kopala et al 1998). This observation suggests either underlying basal ganglia pathology or dysfunction in schizophrenia may be related to the development or motor abnormalities in some patients. Overall, patients experienced improvement of EPS with risperidone treatment alone. The finding of no difference in basal ganglia volumes between FE patients with or without EPS is in contrast with increased striatal volumes in chronically treated patients with EPS. The neurobiological mechanism of EPS in untreated FE patients may be different from EPS related to antipsychotic medication in chronically treated patients. Enlargement of striatal structures following treatment with typical antipsychotics may be closely related to the likelihood of movement disorders with traditional antipsychotic medications.

Exploratory correlational analyses of ESRS scoring and baseline basal ganglia volumes in the chronically treated patients did not reveal any statistically significant relationships between basal ganglia volumes and total length of antipsychotic exposure, total lifetime dosage or total length x total lifetime dosage (converted to CPZ units). However, a positive correlation between globus pallidus volume and total length of antipsychotic exposure approached significance (r=0.57, p.=0.06). An increased sample size may be necessary to

evaluate putative neuroleptic dose and duration effects on both EPS severity and striatal enlargement.

To further investigate these initial observations, an expanded study of EPS in a group of drug-naïve and chronically treated schizophrenia patients was conducted. A full description of the subjects, measures and results are presented in the following sections.

3.2 Hypotheses

- 1. Never-medicated first-episode schizophrenia patients have detectable extrapyramidal symptoms.
- Drug-naïve first-episode schizophrenia patients with extrapyramidal symptoms will have decreased basal ganglia volumes compared to those drug-naïve patients without EPS.
- 3. Severity of extrapyramidal symptoms is positively correlated to dose and duration of treatment in chronic schizophrenia patients.

3.3 Subjects

As previously described, all subjects were recruited at Dalhousie University as part of the Early Psychosis Program. For the initial comparison of baseline medication-naïve extrapyramidal symptom scores, 41 patients with drug-naïve ESRS scores were included. Baseline MRI scans were completed for 34 of a total of 41 first-episode patients with concomitant ESRS scores. Demographic characteristics for the total group of these 34 first-episode subjects are provided in Table 8. A cohort of 19 chronically treated schizophrenia patients was included as a separated positive control group to investigate the relationship of neuroleptic dose and duration of treatment to EPS severity. A total of 18 out of 19 chronically treated subjects completed ESRS scoring for this study. Baseline chronic-treatment scans (12 or more continuous weeks of typical neuroleptic treatment) were available for all 19 chronic patients.

3.4 Treatments and Clinical Measures

First-episode patients were subsequently treated with a variety of neuroleptics (30 received risperidone, 1 received haloperidol, 4 received olanzapine and 6 received quetiapine). Mean duration of neuroleptic treatment in the FE subjects at time of baseline scan is provided in Table 8. The chronic patients had been treated with a variety of typical neuroleptics at the time of scanning. Mean dose and duration of treatment at time of scan and additional demographic information for chronically treated patients in provided in table 9. Extrapyramidal symptoms were assessed using the ESRS as described in the previous study.

Variable	Mean Values (SD)
Age (years)	23.5 (5.0) <i>Range</i> : 13.7-34.8
Gender	
Male Female	24 10
Duration of Treatment (Days) Baseline Scan	30.0 (29.7) <i>Range</i> : 0.0-87.0
Dose (CPZ equivalents – mg/d) baseline scan	236.4 (293.3) Range: 0.0-1300.0
Drug-naïve Baseline ESRS Score (Total)	2.1(2.7)
Baseline Subscores: Parkinsonism Dystonia Dyskinesia Akathisia	1.2 (1.5) 0.5 (1.1) 0.3 (0.8) 0.2 (0.7)
Subjects with Baseline EPS*	15
Subjects without Baseline EPS*	19
Baseline PANSS Score (Total)	95.2 (19.9)

Table 8. ESRS Study – Demographic characteristics and symptom severity infirst-episode subjects (N=34).

* Score of 2 or greater for any of the four individual ESRS subscores

Variable	Mean (SD)
Age (years)	33.3 (10.9)
Gender	
Male Female	12 7
Duration of Treatment (weeks)	451.3 (452.3) Range: 12.0 – 1181.6
Dose (CPZ equivalents – mg/d)	327.2 (353.6) Range: 40.0 -1278.0
Lifetime dose (dose x duration) – total CPZ units	1243571.4 (1980611.8) <i>Range:</i> 16250.0 – 7618000.0
Baseline ESRS Score – Total (N=18)	6.8 (5.7) <i>Range</i> : 0.0 – 20.0
Subscores: Parkinsonism Dystonia Dyskinesia Akathisia	2.6 (1.9) 0.8 (1.6) 1.5 (2.1) 2.0 (1.7)
Subjects with Baseline EPS*	13
Subjects without Baseline EPS*	5
Baseline PANSS Score – Total	68.1(18.1)

Table 9. ESRS Study – Medication, symptom and demographic information for a
cohort of 19 chronically treated schizophrenia patients.

* Score of 2 or greater for any of the four individual ESRS subscores

3.5 Data Analysis: Statistical Methods

Baseline comparisons of drug-naïve basal ganglia volumes were restricted to first-episode schizophrenia subjects who were scanned before receiving no more than 12 weeks of continuous treatment. All medication doses in the chronically treated subjects were converted to chlorpromazine units as described in the previous study. For the purposes of statistical comparisons, the presence of extrapyramidal symptoms was defined by a score of 2 or greater for any individual subscale ESRS rating for parkinsonism, dystonia, dyskinesia or akathisia. A score of 2 indicates the presence of mild, but definite presentation of extrapyramidal dysfunction. This approach was taken to account for the nonlinearity of the ESRS scale. Basic descriptive statistics were calculated to measure the rates of EPS in drug-naïve schizophrenia patients at baseline. Baseline basal ganglia volumes were analyzed by ANOVA. Total intracranial volume, age and were gender entered as covariates, group (with or without baseline EPS) was entered as a main effect and total basal ganglia volumes were entered as dependent measures. A total of 34 FE patients had both baseline scanning and completed ESRS scores prior to initiation of neuroleptic treatment. Exploratory linear correlations of total ESRS scores, ESRS subscores, medication dose and duration were performed to investigate putative relationships of symptom severity and medication dosage in the cohort of chronically treated subjects. To maximize the probability of detecting a relationship if one existed (i.e. minimize the probability of type II errors), alpha

levels were not adjusted for multiple comparisons in this study because of the exploratory nature of the approach. This methodology has been recommended by others (Lawrence et al 1998).

3.6 Results

In the total sample of 34 FE patients, 15 (44.0%) drug-naïve patients had baseline extrapyramidal symptoms. The mean total ESRS score was 2.1. The mean total PANSS score at baseline was 95.2 in the first-episode group and 68.0 in the chronically treated group (see tables 8 and 9). Covarying for age, gender and total intracranial brain volume, the initial ANOVAs of basal ganglia volumes revealed no significant differences between those subjects with EPS compared to those without EPS at baseline (Caudate: F(1,29)=3.3, p.>0.08, Putamen: F(1,29)=0.3, p.>0.6, Globus pallidus: F(1,29)=2.0, p.>0.1).

Spearman's correlation did not reveal any significant relationships between neuroleptic dose, lifetime dose and basal ganglia volumes in chronically treated subjects (all p-values >0.2). A modest positive correlation of lifetime dosage and subscore for dystonia was found (r=.475, p.=0.05), however there were no relationships between severity of parkinsonism, dyskinesia or akathisia to lifetime neuroleptic dosage (all p-values >0.3).

The summary data showed that parkinsonism was the largest component of the total ESRS score (see table 8). To improve the homogeneity of comparison groups a secondary analysis was performed using the parkinsonism item to define comparable groups. The presence of parkinsonism was defined as a threshold ESRS score of 2 or more for this subscore. New ANOVAs with parkinsonism group (parkinsonism + or -) entered as a main effect, gender, age and total intracranial volumes were entered as covariates and baseline basal ganglia volumes were entered as dependent measures were performed. Subjects with parkinsonism at baseline had significantly larger caudate volumes than those who did not (F(1,29)=8.9, p.=.006). Baseline putamen volumes were not different between parkinsonism (+) and (-) subjects (F(1.29)=.07, p.>0.7), nor were globus pallidus volumes (F(1,29)=1.8, p.>0.1). All basal ganglia volumes in total EPS +/- groups and EPS-parkinsonism +/- groups are shown in figures 8-10 (see table 10 for mean basal ganglia volumes in Total EPS +/- subjects and EPSparkinsonism +/- subjects). **Table 10.** Mean baseline basal ganglia volumes in Total EPS positive and
negative EPS-Parkinsonism positive and negative drug-naïve
subjects with first episode schizophrenia.

Region	Volume – mm3 (SD)	Volume – mm3(SD)
Grouping:	Total EPS (+) N=15	Total EPS (-) N=19
Caudate	6249.8 (463.9)	6033.7 (487.7)
Putamen	8843.6 (1084.3)	8756.0 (1196.5)
Globus Pallidus	2692.8 (430.5)	2454.7 (536.0)
Total Intracranial Volume	1438045.8 (160328.9)	1500361.2 (149511.4)
Grouping:	EPS-Parkinsonism (+) N=10	EPS-Parkinsonism (–) N=24
Caudate	6414.2 (488.2) [*]	6010.2 (526.5)
Putamen	8974.8 (1173.2)	8719.7 (1077.7)
Globus Pallidus	2749.2 (469.7)	2480.8 (518.9)
Total Intracranial Volume	1495020.6 (136191.1)	1463639.3 (164304.6)

• Significantly larger than ESP-Parkinsonism (-) group (p.=.006)





Volume - mm³



volume - mm³





and EPS-parkinson positive or negative defined subject groups in a cohort of neuroleptic-Figure 10. Total globus pallidus volumes in Total-EPS positive or negative defined subject groups naïve first-episode schizophrenia patients.

3.7 Summary of Findings – Study B

The hypothesis of increased prevalence of baseline movement disorders in never-medicated first-episode schizophrenia patients was confirmed. This parallels findings from a larger study by Honer and colleagues (Honer et al 2002), who reported the presence of extrapyramidal symptoms (defined by a score of 2 or more on any individual ESRS item) in 44.9% of neuroleptic nonexposed schizophrenia patients. The current study also paralleled the finding of a greater degree of parkinsonism than dystonia, dyskinesia or akathisia by Honer and colleagues (Honer et al 2002). This finding is suggestive of underlying basal ganglia abnormalities as research in Parkinson's disease have shown that bradykinesia, a cardinal manifestation of Parkinson's, may result from a failure or loss of basal ganglia output to reinforce cortical mechanisms that ready and execute movement commands (Beradelli et al 2001).

The hypothesis of decreased basal ganglia volumes in drug-naïve subjects with baseline EPS was not confirmed. While two studies have reported reduced caudate volumes in neuroleptic-naïve first-episode subjects (Corson et al 1999a; Keshavan et al 1998), others have not (Falke et al 2000; Shihabuddin et al 2001). Contrasting results between the current study and previous studies may be due to methodological issues related to volume assessment and image acquisition, which are not standardized across studies. The current finding of increased caudate volume at baseline in a subset of patients is paralleled by functional studies showing increased metabolism in the caudates of schizophrenia patients (Kircher et al 2001; McGuire et al 1998). Studies of caudate and putamen-specific lesions have indicated that both may result in parkinsonism, however caudate lesions are also frequently associated with emotional and behavioural disturbances (Bhatia and Marsden 1994).

In the current cohort of chronically treated schizophrenia patients, daily neuroleptic dose and total lifetime dose for typical neuroleptics were not correlated with striatal volumes, nor was the severity of EPS related to total lifetime dosage, except in the case of dystonia. The lack of any relationship of neuroleptic exposure to striatal volume and EPS severity may be related to a relatively rapid metabolic response to typical neuroleptic treatment, which induces changes within the first few weeks of exposure (Benes et al 1985). The chronically treated patients in the current cohort had received a mean of 451.3 weeks of treatment prior to scanning and was not optimal for the detection of rapid early changes in striatal volumes. Additionally, the small sample size may be a limiting factor. Both the severity of EPS and the magnitude of striatal enlargement may reach plateau very early in the course of typical neuroleptic treatment. The mean dose of neuroleptics for the chronically treated group in this study was 327.2 chlorpromazine units per day. An earlier study reported increased basal ganglia volumes in a cohort of patients treated with low-dose haloperidol (equivalent to 100 chlorpromazine units per day) (Keshavan et al 1994). Very moderate doses of typical antipsychotics appear to be sufficient to induce metabolic changes in animal models (Atkins et al 1999). The relationship

of striatal enlargement and EPS remains unclear. Subtle underlying abnormalities in specific basal ganglia regions may predispose some schizophrenia patients to EPS. In particular, abnormalities of the left-sided basal ganglia structures may preferentially predispose subjects to both EPS and psychiatric problems, including memory dysfunction and altered affective functioning (Haley et al 2000; Jacobsen et al 2001).

Basal ganglia abnormalities are suggestive of disruption or dysfunction of fronto-striatal circuits in both schizophrenia and Parkinson's disease, which share overlapping characteristics (Pantelis et al 1997). These circuits subserve both motor and cognitive processes that are involved in smooth pursuit eye movements, affective disturbance (emotional blunting), altered perception (hallucinations) and the execution of learned motor tasks (Buchsbaum et al 1999; Middleton and Strick 2000). The complexity and multiplicity of fronto-striatal loops may provide a parsimonious explanation for the heterogeneous symptoms of schizophrenia, as alteration of a single subcortical region could be reflected by a wide variety of neurological and neurocognitive disturbances (Middleton and Strick 2000; Robbins 1990).

Chapter 4: Study C: A follow-up study of basal ganglia volumes in schizophrenia patients switched from risperidone or typical antipsychotics to olanzapine

Effects of switching to an alternate atypical antipsychotic – contrasting the effects of olanzapine and risperidone on basal ganglia structures

4.1 Background and Rationale

Olanzapine is a more recently introduced atypical neuroleptic agent and is considered to be a well-tolerated medication with low propensity to induce EPS (Sanger et al 1999). There are some reports of improved clinical efficacy of olanzapine compared to both risperidone and typical antipsychotics, however the data are contradictory (Cuesta et al 2001; Geddes et al 2000; Green 1999). Like risperidone, olanzapine also induces movement disorders at higher doses (Chambers et al 1998; Conley and Mahmoud 2001). Olanzapine is believed to induce a lower rate of EPS at clinical doses than risperidone (Leucht et al 1999), and some studies reported superior efficacy of olanzapine over risperidone in treating negative symptoms, however this finding is controversial (Bhana et al 2001; Kopelowicz et al 2000). Although there are a number of studies of olanzapine's clinical effects, its effects on basal ganglia structures have not been investigated. A MEDLINE search with the key words "olanzapine" and "basal ganglia" or "MRI" region-of-interest assessments resulted in no citations.

Both risperidone and olanzapine share similar pharmacologic profiles and recent research suggest that they have similar effects on the basal ganglia

(Markowitz et al 1999; Tarazi 2001). To investigate the effects of olanzapine on striatal structures, three separate treatment regimes in chronically treated patients were investigated. Schizophrenia patients being treated with either risperidone or typical antipsychotics were subsequently switched over to a trial of olanzapine or maintained on risperidone. The three treatment protocols consisted of risperidone to risperidone at follow-up, risperidone to olanzapine at follow-up, or typical antipsychotics to olanzapine at follow-up.

4.2 Hypotheses

- 1. Basal ganglia volumes decrease after switching from typical antipsychotics to olanzapine.
- 2. Basal ganglia volumes remain stable after switching from risperidone to olanzapine.
- Switching medications from typical antipsychotics and risperidone reduces the severity of extrapyramidal symptoms

4.3 Subjects

As described previously, patients for this study were recruited as part of the Early Psychosis Program at Dalhousie University. These patients were a separate cohort from those introduced in studies A and B. Thirty-seven schizophrenia patients and the previously reported cohort of 17 healthy control subjects were included in this study. The mean age of patients was 27.6 years. Ten patients were female and 27 were male. All subjects were scanned at baseline, either receiving risperidone or typical antipsychotics for a mean of 198.7 weeks at the date of scan. Patients were subsequently rescanned at follow-up at a mean interval of 45.6 weeks post-baseline. Demographic data for patients is provided in table 11 and is grouped by follow-up medication protocols.

4.4 Treatment and Clinical Measures

At baseline, 10 patients were being treated with various typical antipsychotics (loxapine, trifluphenazine, chlorpromazine, fluphenazine, haloperidol) and 27 patients were being treated with risperidone (see table 11 for dose and duration of treatments). Some patients were also receiving adjunctive anticholinergic medications to ameliorate EPS at the time of baseline scanning (see table 11). No subjects were receiving anticholinergic medications at followup. At follow-up, all patients on typical medications and 13 of the risperidonetreated patients had been switched to olanzapine. The remaining 14 patients remained on risperidone. Medications were switched based on the clinical evaluations of a psychiatrist. Those patients switched from risperidone to olanzapine presented with more severe EPS and more severe psychiatric symptoms compared to those who were not switched (see table 11). Patients being treated with typical antipsychotics at baseline also had more severe EPS and psychiatric symptoms than the group maintained on risperidone (see table 11). Clinical symptoms (PANSS scores) and extrapyramidal symptoms (ESRS

scores) were assessed at baseline. Outcome PANSS and ESRS scores were performed a mean of 51.5 weeks after baseline. Baseline-matched follow-up assessments were available for all 10 typicals to olanzapine patients, 11 out of 14 risperidone-to-risperidone patients and 12 out of 13 risperidone-to-olanzapine patients. Mean PANSS and ESRS scores are provided in table 11. Dosage information for typical medications was converted to chlorpromazine units for statistical purposes. Baseline basal ganglia measures and total intracranial volumes were performed as previously described in study (A). Follow-up basal ganglia volumes were assessed a mean of 45.6 weeks after baseline. Mean basal ganglia volumes for all groups are shown in table 12.

matched hea	Ithy comp						
Riable	speridone N=	-Risperidone	Risperidone N=	-Olanzapine 13	Typicals- O	lanzapine 0	Healthy Controls N=17
	3aseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline Follow-up
Weeks Treatment (SD) 38	.5 (16.1)	52.1(6.9)	58.5 (15.4)	42.2 (12.1)	577.3 (478.5)	41.0 (17.3)	
Range	.3-67.4	32.0-64.0	13.4-154.3	21.6-59.0	58.9-1181.6	7.0-63.0	
Medication Dose (SD) 2.3	3 (1.1)	2.1 (1.3)	3.3(1.1)	15.0 (1.6)	360.1 (263.7)	17.0 (6.4)	
Range 0.4	5-4.5	0.3-5.0	1.0-5.0	7.5-25.0	154.0-1000.0	7.5-25.0	
Total PANSS 49	.9 (18.5)	48.5 (19.1)	67.2 (23.1)	56.2 (13.7)	64.6 (15.8)	59.4 (16.1)	
Range 34	0-93.0	30.0-98.0	42.0-118.0	38.0-77.0	38.0-88.0	37.0-86.0)	N/A
Total ESRS (SD) 0.4	5 (1.0)	0.4 (0.7)	3.5 (3.3)	4.2 (3.3)	9.6 (5.8)	5.9 (4.3)	
Range 0.(0-3.0	0.0-2.0	0.0-10.0	0.0-11.0	1.0-20.0	0.0-11.0	
	2		10(17)	2 E (1 G)		2 6 (1 E)	
	(0.1)	0.4 (0.0)	(7.1) 0.1	(0.1) C.7	0.0 (1.1) 0.0	(0.1) 0.7	
Dystonia 0.0	0 (0.0)	0.0 (0.0)	0.1 (0.3)	0.4 (0.8)	1.4 (2.0)	1.2 (1.3)	
Dyskinesia 0.0	0.0)	0.0 (0.0)	0.4 (1.0)	1.1 (1.5)	2.7 (2.2)	1.4 (1.6)	
Akathisia 0.0	0 (0.0)	0.0 (0.0)	1.3 (1.9)	0.2 (0.6)	2.5 (1.7)	0.7 (1.1)	
Anticholinergics							
Yes 1((7.1%)		2 (15.4%)		5 (50%)		
No 13	~	14	11	13	5	10	
Age -Years (SD)	22.6	(4.7)	25.5	(8.1)	35.3 (8.8)	24.6 (7.6)
Range	10.8	-30.7	15.3-	47.7	18.6-4	16.8	13.0-37.0
Gender							
Male	-	0	÷	0	7		თ
Female	•	4		8	3		8
Tahla 12 Baseline and f		total (left + ri	oht) hasal d	andia volum	SAL		
		10(d) (10(1 - 1)	<u> </u>	Butamon (S	01 mm ³		Dallidue (SD) mm ³

Table 11. Clinical and demographic data for subjects in 3 separate treatment protocols and a cohort of age-

	2 db 10101 bi					
	Caudate	i (SD) mm³ 👘 👘	Putamen	(SD) mm ³	Glóbus Pallic	ius (SD) mm ³
Treatment Group	Baseline (SD)	Follow-up (SD)	Baseline (SD)	Follow-up (SD)	Baseline (SD)	Follow-up (SD)
Risperidone-Risperidone	5979.3 (948.9)	6119.0 (735.8)	9068.3 (1132.9)	8729.1 (1249.1)	2626.8 (320.7)	2704.2 (481.8)
Risperidone-Olanzapine	6329.1 (623.6)	6115.8 (653.6)	9144.2 (704.6)	8642.4 (718.6)	2672.8 (249.9)	2504.0 (428.2)
Typicals-Olanzapine	5988.3 (486.3)	5971.4 (452.3)	9175.9 (648.3)	8241.9 (731.5)	3029.8 (343.4)	2731.4 (248.6)
Controls	6040.1 (444.5)	5973.6 (534.0)	8653.5 (989.5)	8636.0 (202.1)	2540.5 (382.8)	2647.8 (225.6)

4.5 Data Analysis: Statistical Methods

All basic descriptive statistics are presented in tables 11 and 12. Baseline comparisons of age, total intracranial volume, dosage, basal ganglia volumes, PANSS scores and ESRS scores were performed with omnibus ANOVAs with treatment group entered as a main effect and age and total intracranial volume entered as covariates for volumetric comparisons. A Chi-square analysis of anticholinergic treated and nontreated at baseline was performed to investigate baseline differences in EPS severity between groups. Baseline to follow-up comparisons of basal ganglia volumes, total PANSS scores and ESRS scores were performed for each separate treatment group with paired t-tests. Post-hoc analyses were performed with Fisher's PLSD. Additional descriptive statistics of anticholinergic usage at follow-up were tabulated.

4.6 Results

4.6.1 Baseline Comparisons

An initial ANOVA of age revealed a significant difference between groups (F(3,50)=6.5, p.=.0008), with the typicals-olanzapine group being oldest (see table 11). There were no differences between groups for total intercranial volume (F(3,50)=0.7, p.>0.5). Complete medication dose information was available for 10 Typicals-olanzapine subjects, 14 Risperidone-risperidone subjects and 12 Risperidone-olanzapine subjects. An initial omnibus ANOVA revealed a significant difference in baseline chlorpromazine equivalents between treatment

groups, (F(2,33)=12.3, p.=.0001), with Typicals-olanzapine patients receiving significantly higher doses than Risperidone-risperidone patients (Fisher's p.<.0001) and Risperidone-olanzapine patients (Fisher's p=.0008). Examining medication in risperidone-treated patients alone, baseline risperidone dose was significantly higher in the Risperidone-olanzapine subjects compared to the Risperidone-risperidone subjects (F(1,25)=4.8, p.=.04). A subsequent correlational analysis of baseline risperidone dose and baseline basal ganglia volumes found a moderate correlation of dose and globus pallidus volume (r = 0.41, p. =.05), however, this did not remain after Bonferroni correction for multiple comparisons. No statistically significant correlations between baseline caudate or putamen volumes and baseline risperidone dose were observed (all p-values >.09). Initial comparisons of left and right volumes did not reveal any significant left-right asymmetries, therefore subsequent analyses were based on total (left + right) volumes. There were no group differences in baseline caudate (F(3)=0.7, p.>0.5) or putamen (F(3)=2.1, p.>.1) volume, nor were there significant effects of age (F(1)=0.03, p.>0.5) or total intracranial volume (F(1)=0.6, p.>.5). However patients in the typicals-olanzapine had significantly larger globus pallidus volumes compared to all other groups (F(3,50)=6.8, p.=.0007), Fisher's p. \leq .01 for all between-group comparisons. Total ESRS scores were significantly different between treatment groups (F(2,29)=8.4, p.=.001). Typicals-olanzapine subjects had the highest total ESRS at baseline (Typicals-olanzapine vs. Risperidoneolanzapine Fisher's p.=.0008; Typicals-olanzapine vs. Risperidone-risperidone

Fisher's p.<.0001). Because these initial results were likely due to medication effects, a separate analysis of ESRS between the two risperidone treatment groups was performed. At baseline, Risperidone-olanzapine subjects had significantly higher ESRS scores compared to Risperidone-risperidone subjects (F(1,25)=8.1, p.=.01). ANOVAs of the four ESRS subscores revealed the greatest proportion of EPS in the Risperidone-olanzapine subjects were due to parkinsonism (F(1,24)=4.3, p.=.05). The Risperidone-risperidone subjects did not have detectable levels of dystonia, dyskinesia or akathisia (see table 11).

4.6.2 Follow-up Comparisons

Follow-up medication doses are shown in table 11. The two groups receiving olanzapine at follow-up were not receiving significantly different doses of antipsychotic (F(1,20)=0.6, p.>0.4). Follow-up comparisons of basal ganglia volumes, PANSS scores and ESRS scores were performed on individual treatment groups, as preliminary results from the baseline comparisons revealed substantive differences in baseline clinical profiles. Baseline and follow-up volumes are shown for each region of interest in figures 11-13. Paired t-tests revealed no differences in follow-up caudate volumes in the Risperidonerisperidone treatment group (t(13)=-1.7, p.>0.2), the Typicals-olanzapine treatment group (t(9)=0.1, p.>0.9) or the healthy controls (t(16)=0.1, p.>0.8). However, risperidone patients switched to olanzapine had a significant reduction in caudate volumes (t(12)=2.6, p.=.03). Putamen volumes were significantly reduced at follow-up in the Risperidone-olanzapine group (t(12)=3.5, p.=.004) and the Typicals-olanzapine group (t(9)=4.7, p.=.001). Putamen volumes were also reduced in the Risperidone-risperidone group at follow-up, but this reduction did not reach statistical significance (t(13)=2.0, p.=.07). There was no change in the putamen volumes in healthy controls at follow-up (t(16)=0.1, p.>0.9). Globus pallidus volumes remained unchanged at follow-up in the Risperidonerisperidone group (t(13)=-1.0, p.>0.3), the Risperidone-olanzapine group (t(12)=1.4, p.>0.1) and the healthy controls (t(16)=-1.1, p.>0.2). Only the subjects in the Typicals-olanzapine groups had a significant reduction in globus pallidus volumes at follow-up (t(9)=2.2, p.=.05).

None of the treatment groups had any significant change in total PANSS scores at follow-up (all p-values >.08). The prevalence of adjunct anticholinergic treatment at baseline differed significantly between groups ($X^2(2)=6.8$, p.=.03). Fifty percent of the Typicals-olanzapine patients were receiving adjunct anticholinergic medications, compared to only 15.4% of the Risperidone-olanzapine patients and 7.1% of the Risperidone-risperidone patients. Total ESRS scores remained unchanged in the Risperidone-risperidone and the Risperidone-olanzapine groups at follow-up (both p-values >0.5). There was a non-significant trend towards reduced total ESRS scores also remained unchanged in the Risperidone-olanzapine groups at follow-up (all p-values >0.1). The Typicals-olanzapine patients did have

statistically significant reductions in dyskinesia (t(9)=2.8, p.=.02) and akathisia (t(9)=2.9, p.=.02), however parkinsonism and dystonia remained unchanged (both p-values >0.5).













4.7 Summary of Results – Study C

As predicted, basal ganglia volumes were reduced at follow-up in the patients switched from typical medications to olanzapine. Data presented in figures 11 – 13 illustrates a heterogenic structural response to olanzapine within groups. As in the study (A), 10 random data points were resampled in case of measurement error, however, retested volumes remained equivalent.

The reduction in striatal volumes was restricted to the putamen and globus pallidus regions in patients previously treated with typicals. This finding was different from an earlier report of the effect switching from haloperidol to clozapine (Chakos et al 1995), which specifically demonstrated volume reduction in the caudate nuclei. Mean total PANSS score at baseline (64.6) was not significantly different after switching from typicals to olanzapine (59.4). Given the chronicity of illness in this group (having received a mean of over 11 years of treatment at baseline), their symptoms may have been relatively stable. The mean total ESRS score for patients treated with typicals was 9.6 at baseline and 5.9 at follow-up, supporting olanzapine's atypicality.

With respect to the second hypothesis, the current data showed that caudate volumes were reduced in patients switched from risperidone to olanzapine, contradicting the hypothesis that striatal volumes would remain stable in the presence of an alternate atypical neuroleptic. This finding may be related to inherent baseline differences in the clinical profiles of the two separate risperidone treatment groups.

Patients maintained on risperidone treatment for the entire length of this study had a mean baseline PANSS score of 49.9 and a mean follow-up PANSS score of 48.5 (a change of 2.8%). The mean total ESRS score for risperidone-maintained patients was .5 at baseline and .4 at follow-up. As demonstrated previously, continuous exposure to moderate doses (less than 4 or 5 mg per day) does not induce additional EPS (Lang et al 2001). The risperidone-risperidone patient group had stable basal ganglia volumes, stable symptom severity and minimal EPS during the course of this study.

Risperidone patients switched to olanzapine had a mean baseline PANSS score of 67.2 and a mean follow-up PANSS score of 56.2 (equivalent to a change of 16.4%). While this magnitude of symptom improvement does not meet criteria for medication responsiveness in refractory patient populations (20% or greater symptom improvement), the overall symptom improvement with olanzapine was paired with caudate volume reduction. The mean total ESRS score for risperidone patients switched to olanzapine was 3.5 at baseline and 4.2 at follow-up. This increase was not statistically significant and may be related to decreased exposure to anticholinergic medications at follow-up.

Patients switched from risperidone to olanzapine, perhaps due to an underlying pathophysiology of the caudate region, were not responding robustly to risperidone treatment. The change in caudate volume is of interest as decreased dopamine activity within the caudate appears to have significant implications for attention, memory, affect and depression (Haley et al 2000;

Martinot et al 2001). A recent study by Martinot and colleagues (Martinot et al 2001) reported decreased dopaminergic function in the left caudate of depressed patients with both affective flattening and psychomotor retardation (i.e. slowness of movement attributable to psychic disturbance). In a separate study, Scheepers and colleagues (Scheepers et al 2001) examined caudate volumes in schizophrenic patients treated with typical antipsychotics and were switched to clozapine. After 52 weeks of continuous clozapine therapy Scheepers et al (Scheepers et al 2001) reported a significant decrease in caudate volumes restricted to the left side in clozapine responders, but not in nonresponders. This finding suggests that neuroleptic responsiveness may be linked to observed caudate volume decreases with atypical neuroleptic treatment.

With respect to the third hypothesis, generally, neither overall symptom severity nor overall EPS severity changed when patients were switched to olanzapine, however, patients previously on typicals did have moderate reductions in dyskinesia and akathisia. The persistence of parkinsonism, which accounts for the most prominent feature of movement disorders seen in schizophrenia, may not respond as readily to atypical antipsychotic therapy in populations that have experienced chronicity of illness and may be more resistant to neuroleptic treatment.

A previous study reported decreased dopamine activity in the caudate coincided with both increased presentation of EPS and is associated with caudate enlargement (Jacobsen et al 2001). Data from the present study cannot

confirm a relationship between decreased EPS and reduction in caudate volume. This relationship may have been confounded by adjunct anticholinergic treatments in the current study. A number of the Typicals-olanzapine patients (5 out of 10) were receiving adjunct anti-parkinson medications at baseline, and the severity of baseline EPS in this population may have been partially masked. It is also of interest that 2 of 13 subjects in the Risperidone-olanzapine group were also receiving adjunct anticholinergics while on risperidone monotherapy. Both these subjects no longer required additional antiparkinson medications after being switched over to olanzapine. These observations suggest that olanzapine treatment did ameliorate the severity of EPS to a greater degree than indicated by the current data.
Chapter 5: Conclusions, Future Directions

5.1 General Conclusions

The purpose of this thesis was to clarify the nature of basal ganglia structure, movement disorders and clinical symptomatology in a cohort of drugnaïve first-episode and chronically treated schizophrenia patients. Interest in the role of the basal ganglia was initially stimulated by the similarities between symptoms of schizophrenia and symptoms seen in diseases of the basal ganglia. Overlapping phenomenology include abnormal cognitive, motor and emotional functioning and psychosis. More compelling evidence came from studies of the properties of antipsychotic medications. Traditional antipsychotics (i. e. chlorpromazine, haloperidol) primarily block D2 receptors in the striatum where they exist in the highest concentration in the brain, strongly suggesting that dopamine overactivity in striatal regions is a significant contributing factor to psychosis. Conversely, these observations also suggest that a primary underlying abnormality of the basal ganglia could be part of the schizophrenia phenotype. A confounding problem with traditional antipsychotic treatment is their propensity to induce movement disorders, such as parkinsonism or dyskinesias. Newer generation atypical antipsychotics (i. e. clozapine, risperidone, olanzapine) are less prone to induce extrapyramidal symptoms, however, at sufficient dose they also can increase the prevalence of parkinsonism and dyskinesias. Another confounding issue in understanding the relationship of

observed signs and symptoms in schizophrenia and medications is the fact that most studies are of patients with exposure to multiple medications, making it difficult to delineate the effects of any single medication. To better understand the phenomenology of schizophrenia and basal ganglia structures in schizophrenia, the studies conducted for this thesis specifically targeted subjects with no previous exposure to neuroleptics or subjects who were receiving monotherapy to compare with chronically treated subjects receiving only typical neuroleptics.

Study A specifically looked at non-medicated first-episode schizophrenia patients, with the expectation of both abnormal basal ganglia volumes and increased prevalence of movement disorders. While an increased prevalence of EPS was seen in never-medicated patients, basal ganglia volumes were no different compared to healthy age and gender-matched controls. Only patients chronically treated with typical medications had increased baseline basal ganglia volumes, particularly in the globus pallidus. One year of continuous exposure to risperidone monotherapy did not increase or decrease striatal volumes in the previously drug-naïve subjects, nor was there a clear relationship between total lifetime dosage and striatal volumes or severity of EPS in chronically treated patients.

The lack of gross volumetric differences between healthy controls and drug-naïve FE patients does not support the hypothesis of early progressive degenerative processes in schizophrenia. Any abnormality of the basal ganglia at first-break appears to be functional or metabolic in nature, given the prevalence

of EPS in the drug-naïve patients. Basal ganglia enlargement, which was clearly associated with exposure to typical neuroleptics in the first study, was not well correlated to dose or length of exposure, perhaps due to a rapid physiological response that reach plateau levels in the first few weeks of treatment. This hypothesis is supported by data from animal studies (Angulo et al 1990; Delfs et al 1994).

In study B, a more comprehensive investigation of movement disorders was performed in an expanded cohort of neuroleptic-naïve first episode patients and another group of chronically treated schizophrenia patients. It was unclear from study A whether small baseline differences in basal ganglia volumes would be related to the presence of EPS in drug-naïve schizophrenia patients. Again, a significant proportion of untreated schizophrenia patients presented with EPS at baseline (39%). A general comparison of basal ganglia volumes in subjects with or without EPS at baseline did not reveal overall differences in striatal volumes between these two subgroups. Looking more closely at the predominant element of EPS, parkinsonism, FE patients with parkinsonism had significantly larger caudate volumes than those without. As in the previous study, in this cohort of chronically treated subjects, there were no clear relationships between severity of EPS, life-time dosage and striatal volumes.

In the final study, the effects of switching medication from either typicals to olanzapine or switching from risperidone to olanzapine were investigated. These subject groups were compared to subjects maintained on risperidone treatment

and healthy matched controls. Patients treated with olanzapine after long-term exposure to haloperidol and other typical neuroleptics had a significant reduction in putamen and globus pallidus volume, confirming the reversibility of typical neuroleptic-induced hypertrophy. Switching patients from risperidone to olanzapine also resulted in a reduction in caudate volume, whereas patients maintained on risperidone did not show any change in striatal volumes over time. The severity of baseline EPS was difficult to ascertain in the subjects included in this study as a proportion were receiving adjunct antiparkinson medications to control EPS. There was no evidence to show that olanzapine worsened EPS severity at low to moderate dosage. Some caveats are necessary for this final study, as treatment crossovers were not based on random assignment. Those patients who were clinically judged as poorly responding to risperidone were preferentially switched to olanzapine. Potentially, risperidone patients who were selected out for a trial of olanzapine may have shared a similar underlying metabolic dysfunction of the striatal system that was better targeted by olanzapine.

In the context of all three of the studies presented in this thesis, there is insufficient evidence to support the hypothesis of generalized gross abnormalities of basal ganglia morphology and there is no evidence of progressive basal ganglia degeneration over the course of 1 to 2 years. The data suggests that much more subtle differences of basal ganglia are present within populations with first-episode schizophrenia. There appear to be subgroups of FE

schizophrenia patients that have different basal ganglia volumes depending on extrapyramidal symptom profile. As well, data presented in study C suggests that poor treatment response to risperidone may be associated with a subtle degree of striatal abnormality. Those patients who were selected by clinicians to receive olanzapine therapy were not responding to risperidone treatment as well as those patients who remained on risperidone. Mean baseline PANSS scores (shown in table 11) in the risperidone to olanzapine group were 34.6% higher compared to patients maintained on risperidone. After switching to olanzapine, this group experienced a decrease in mean PANSS scores and a concomitant decrease in caudate volume.

A study by Gur and colleagues (Gur et al 1998b), which included a cohort of 21 neuroleptic-naïve schizophrenia patients, 48 patients chronically treated with typicals and 29 patients treated with either risperidone or clozapine, paralleled the findings reported in this thesis. Gur and colleagues (Gur et al 1998b) found significant increases in striatal volume only in patients treated with typical neuroleptics. In contrast, both Corson et al (Corson et al 1999a) and Keshavan et al (Keshavan et al 1998) observed decreased caudate volumes in never-medicated schizophrenia patients.

In the current data, patients chronically treated with typical antipsychotics had a greater degree of globus pallidus enlargement than in the caudate or putamen. In a cohort of 15 neuroleptic-treated schizophrenia patients, similar results were reported by Hokama and colleagues (Hokama et al 1995).

Functionally, pallidal structures are the major outflow center of the basal ganglia (see figure 14 below). Metabolically, D₂ receptor antagonism via antipsychotic exposure is known in increase striato-pallidal GABA transmission (O'Connor 2001). Functional studies conducted by Early and colleagues (Early 1993; Early et al 1987) have demonstrated hyperactivity in the left globus pallidus in drug-naïve schizophrenia patients. When compared to animal models of unilateral lesions of the ascending dopaminergic systems, schizophrenic patients shared common features including increased blood flow to the left globus pallidus, impaired ability to disengage attention from the left side and dopamine receptor supersensitivity in the left striatum of drug-naïve patients (Early 1993). The metabolic and functional characteristics of the globus pallidus may be contributing to attenuated response to neuroleptic exposure.



excitatory (+) loops via the internal globus pallidus (adapted from Hurwitz, 2002). Figure 14. Basic anatomy of fronto-subcortical pathways, mediated by inhibitory (-) and

Data included in this thesis confirms that neither risperidone nor olanzapine induce striatal hypertrophy. Patients treated with olanzapine after long-term exposure to haloperidol and other typical neuroleptics had a significant reduction in putamen and globus pallidus volume. A number of earlier studies also reported increased basal ganglia volumes in patients treated with typical neuroleptics (Breier et al 1992; Buchanan et al 1993; Chakos et al 1994). Data presented in this thesis parallels other MRI studies of patients switched from typical antipsychotics to clozapine (Chakos et al 1995; Corson et al 1999b; Frazier et al 1996), supporting the hypothesis of atypical neuroleptics reversing striatal hypertrophy induced by exposure to typical neuroleptics.

The relationship between medication, dosage and basal ganglia volume remains obscure. Studies suggest that typical antipsychotics, particularly haloperidol, induce both morphological and metabolic changes in the caudate and putamen (Konradi and Heckers 2001). Multiple metabolic effects appear to be contributing to striatal hypertrophy after neuroleptic exposure. Animal studies have been particularly helpful in understanding the effects of both acute and chronic administration of antipsychotics in the striatum and its proximal regions. A brief table of current metabolic and cellular response to antipsychotic challenge is shown below. Up-regulation of substructures is indicated by (\uparrow) and down-regulation is indicated by (\downarrow). Atypical medications induce up-regulation or redistribution of receptors, but they are not known to induce gross morphological changes to cell structure in the striatum (see table 13).

Table 13. Review of metabolic and cellular response to antipsychotic challenge.

ł	Tissue Type	Antipsychotic	Dendrites Dendritic Size *	Cell Body Size	Receptors/ Synaptic	Glucose Metabolism
			*		Vesicles	
edith et al)	Kal NACC	Паюрепион				
es et al 1983)	Rat SubNr	Haloperidol	*	~	•	
es et al 1985)	Rat Striatum	Haloperidol	÷	←	•	
comb et al	Human Striatum	Haloperidol				← .
ett et al 1994)	Human Caudate	Haloperidol				~
ingelo et al	Human GP, SubNr	Haloperidol				->
ingelo et al	Human Caudate	Clozapine				→
n et al 2001)	Rat Striatum	Haloperidol			D ₂ †	
ai et al 2001)	Rat Striatum	Haloperidol			D₂↑	
can et al 2000)	Rat NAcc, Amyg	Olanzapine				1
le et al 2000)	Human Striatum	Risperidone				Ŷ
n et al 2002)	Human Cortex	Risperidone				→
ns et al 1999)	Rat Medial PFC	Risperidone,			5-HT₂A↑	
		Olanzapine,			5-HT₂A↑	
		Clozapine			5-HT₂A↑	

NAcc – Nucleus Accumbens Amyg – Amygdala

Abbreviations:

SubNr – Substantia Nigra PFC – Prefrontal Cortex

GP – Globus Pallidus

The earlier studies conducted by Benes and colleagues (Benes et al 1985; Benes et al 1983) described increased neuronal size, larger dendritic diameters and concomitant increases in the numbers of associated synaptic vesicles. This finding suggests that haloperidol induces terminal remodeling or sprouting and that the remodeling may underlie the observed increases in striatal volume and the presentation of neuroleptic-induced oral dyskinesias.

One study suggests that differences in the temporal organization or metabolic responses to haloperidol administration may contribute to the heterogeneity of findings (Bartlett et al 1996). These authors described decreased glucose metabolism in the limbic cortex and the caudate 12 hours post-haloperidol challenge in healthy normal subjects, but in their more recent 1996 study they observed no significant metabolic changes in any region 2 hours post-haloperidol challenge in healthy subjects. These subjects did experience significant extrapyramidal side effects within the 2-hour time period, suggesting that differential timing in behavioural and metabolic responses to typical neuroleptic medication may occur (Bartlett et al 1996).

Chronic haloperidol administration also induces upregulation of the immediate early gene transcription factor Δ FosB in the caudate-putamen complex (Atkins et al 1999; McGibbon et al 1994). This observation is of interest as the clinical effects of antipsychotic medications are believed to be mediated in part by the regulation of gene expression (Hyman and Nestler 1996). Chronic treatment with haloperidol is also known to elevate extracellular concentrations of

glutamate in the striatum by decreasing glutamate transporter activity in the rat striatum (Souza et al 1999). Increased glutamate extracellularly, coupled with decreased glutamate transport may result in increased glutamate neurotransmission and may be part of the mechanism involved in the therapeutic action of haloperidol (Souza et al 1999). Whether other typical antipsychotics act similarly upon striatal morphology and metabolism is unknown.

Recent studies suggest that both risperidone and olanzapine decrease glucose utilization in widespread regions, including lateral frontal cortex, the medial frontal cortex, the striatum, the hippocampus and in limbic cortical regions (Duncan et al 2000; Liddle et al 2000; Ngan et al 2002). Interestingly, each specific medication appears to preferentially reduce metabolism in different regions. Ngan et al (2002) did not observe reduced metabolism in the basal ganglia after exposure to risperidone, whereas Liddle et al (2000) did see reduced glucose metabolism in the ventral striatum, thalamus and frontal cortex after exposure to risperidone. In contrast, Duncan et al (2000) reported that while risperidone had little effect on deoxyglucose metabolism in the limbic areas or the nucleus accumbens after ketamine challenge, olanzapine decreased metabolism in these same regions. Preferential targeting by specific neuroleptics may contribute to the variance in both medication response and changes in caudate volumes after switching from risperidone to olanzapine, particularly in EPS-positive risperidone-resistant patients.

The data presented here also confirms the observation of pre-neuroleptic movement disorders in a significant portion of first-episode schizophrenia patients. Forty-three percent of neuroleptic-naïve subjects in study (A) and 39% of neuroleptic-naïve subjects in study (B) had EPS at baseline. The relationship of drug-naïve EPS and pre-treatment basal ganglia volumes remains unclear. The current data cannot confirm a clear relationship between striatal volumes and severity of EPS per se. With respect to EPS and medications, the atypicality of risperidone and olanzapine is supported by the data presented in this thesis. The prevalence and severity of extrapyramidal symptoms were not increased when drug-naïve patients were treated chronically with a mean of 2.7 mg per day of risperidone. Similarly, patients switched from risperidone to olanzapine (mean dose = 15.0 mg per day) had no change in EPS severity, and those switched from typicals to olanzapine (mean dose = 17.0 mg per day) had a decrement in EPS prevalence and severity (see table 11).

By examining the phenomena of EPS more closely, the data in Study B demonstrated that baseline striatal differences within groups of FE patients exist. In particular, parkinsonism, the predominant form of EPS, could distinguish a subsample of never-medicated FE patients with underlying caudate enlargement. Treatment with risperidone did not worsen pre-existing movement disorders in the studies presented here, nor did they significantly induce additional movement disorders. In contrast, exposure to typical medications was associated with greater severity and prevalence of EPS, which were ameliorated by switching to

atypical medications. These observations suggest that mechanisms for preexisting and persistent EPS seen in drug-naïve patients may be different from EPS induced by neuroleptic treatment.

Although improvement in EPS and reduction in striatal hypertrophy were concomitant with switching to olanzapine, a clear relationship between striatal enlargement and EPS was not demonstrated in either Study A or Study C. A steep, rapid response to typical medications would not be identifiable in patients treated for several months to several years prior to assessment.

Clearly, the clinical effects of typical and atypical antipsychotics vary. Both classes of medications are efficacious in ameliorating psychosis, but their metabolic effects, side effect profiles and receptor targets differ. Kapur et al (2000) has suggested that D₂ blockade is the common underlying feature of all antipsychotic therapy and that the distinguishing feature of atypical medications is lowered dopamine receptor affinity (i.e. fast dissociation), hence their decreased propensity to induce EPS. This hypothesis does not provide a parsimonious explanation of treatment resistance. If D₂ blockade alone was sufficient to improve the symptoms of psychosis neither switching medications nor augmenting medications ought to improve clinical response. This is refuted by numerous studies of antipsychotic augmentation in refractory psychosis (Raskin et al 2000; Silver et al 2000; Taylor et al 2001). Atypical antipsychotics may exert modulatory effects in serotonergic systems and other dopamine receptor subtypes that are beneficial in treating psychosis, particularly in

treatment refractory populations (Chong and Remington 2000). Atypical medications exhibit a diversity of pharmacologic profiles (see table 3) and have associated side effects that vary between medications. As previously stated, both risperidone and olanzapine can induce both weight gain and EPS at higher doses. In contrast, clozapine does not appear to induce EPS at any dosage.

5.2 Methodology and Scanning Protocols

Methodologies applied to obtain subregional volumes of interest from MRI vary from study to study. This heterogeneity of measurement approaches makes cross-study comparisons difficult. An examination of volumes reported in other MRI studies revealed a wide range of volumes and intra-rater reliabilities for specific striatal volumes. Both slice thickness and slice orientation affect the accuracy and reliability of reported volumes. The general consensus amongst psychiatric imaging researchers has been that thinner slices (typically 1 to 2 mm) are better than thicker slices and 3-dimensional acquisitions are better than 2dimensional acquisitions to maximize the data (personal communication from Dr. Robert Bilder). A thin-sliced, 3-dimensional acquisition protocol does offer the greatest amount of data, but it does not offer the highest resolution of data. Both image clarity and tissue contrast are compromised with this approach. Conversely, 2-dimensional, thicker-sliced images introduce a higher degree of partial volume effects, particularly when examining gyral structures. Partial volume effects occur when two or more different densities of tissues are being

represented within a single pixel or voxel (i.e. cerebrospinal fluid and grey matter). This phenomenon interferes with the rater's ability to accurately detect edges and perimeters of convoluted structures of the brain. Scan clarity is a limiting factor in edge-detection, particularly for volumes under 10 cubic centimetres in size. Because basal ganglia volumes are relatively small and are imbedded within other brain tissues, an inversion recovery sequence was chosen to maximize the contrast between white and grey matter.

Post-mortem studies of striatal volumes provide the highest degree of accuracy. Three postmortem studies were reviewed, where the variability in measured control volumes between studies was +/- 5% for the striatum, and +/- 9% for the globus pallidus (see table 14 below). Post-mortem volumes are compared to MRI-based volumes in table 15.

Study	Caudate	Caudate and NAcc	Putamen	Globus Pallidus
Bogerts et al, 1985	7770	9626	10118	3278
Bogerts et al, 1990	8603	9936	10179	3907
Heckers et al, 1991				3620
Postmortem mean	8187	9781	10149	3602

Table 14. Review of post-mortem striatal volumes in schizophrenia (cubic millimetres).

Table 15. Comparison of post-mortem and MRI-based striatal volumes in healthy controls (cubic millimetres).

	Slice thickness	Differences from postmortem			rtem
MRI Study	20/30	mean values			
macualy	orientation	Caudate	Caudate + NAcc	Putamen	Globus pallidus
Present	4.0, 2D, coronal	-38%		-14%	-31%
Corson et al, 1999	1.5, 3D, coronal	-28%			
Chakos et al, 1994	3.1, 3D, coronal	-32%			
Keshavan et al, 1998	2.8, 3D, axial		+11%	-48%	
Gur et al, 1998	1.0, 3D, axial		+4%	-9%	-72%
Hokama et al, 1995	1.5, 3D, coronal		-7%	-18%	-37%
Aylward et al, 1997	5.0, 2D, axial		+2%	-4%	-4%

The values presented in this thesis are similar to those obtained with thinner slices and 3D acquisition protocols. The majority of MRI studies underestimate volumes relative to the postmortem reports. Of note, the most accurate study (Aylward et al, 1997) used relatively thick slices, obtained with a proton density sequence. The inherent problems of comparing between imaging studies appear to apply to the present study to about the same extent as to other studies.

Another inherent problem with all MRI-based studies of specific brain structures is related to level of specificity. In larger structures, such as the lateral

Another inherent problem with all MRI-based studies of specific brain structures is related to level of specificity. In larger structures, such as the lateral ventricles, partial volume effects along the perimeter are less of a confound because these structures are easily identified and relatively large compared to the total brain volume. As well, the image intensity of the fluid pixels in the lateral ventricles has a high level of contrast compared to its surrounding tissues. These factors contribute to the consistency of the finding of moderate ventricular enlargement in populations with schizophrenia (Shenton et al 2001). Some current software packages have been developed to perform some automated region-of-interest (ROI) selections based on Talairach templates, however the gold-standard approach to ROI assessment of subcortical structures is based on manual tracing by a trained rater. A manual tracing approach was used to collect data for this thesis. To ameliorate rater-error, measurements were repeated over multiple trials (4 trials per ROI) to get a best averaged score for each selection. By applying a standardized approach and a rigorous assessment protocol, the intra-rater reliability for striatal volumes was maximized. The intrarater reliabilities (performed by DL) were: caudate .99, putamen .97, globus pallidus .96. These compare favourably with two other studies that also report intraclass correlations for measures of these structures (see table 16). The reliability for striatal identification along the longitudinal axis was not problematic, as the volume sampled was determined a priori to be two slices anterior and two slices posterior to the reference slice that contained the anterior commissure. Reference to

delineate the boundaries of individual structures of the basal ganglia. This further

improved reliability.

Table 16. Reported intraclass correlations for basal ganglia volumes from various MRI studies.

Study	ICC: Caudate	ICC: Putamen	ICC: Globus Pallidus
Current studies	.99	.97	.96
Corson et al, 1999	.81	.70	N/A
Giedd et al, 2000	.85	.82	.80
Keshavan et al, 1998	.94	.93	.26
Gur et al, 1998	.98	.99	.94
Rosenberg et al, 1997	.95	.87	N/A

5.3 Subject Selection

Multiple factors affect brain morphology including, but not limited to, gender, age, education, history of serious head injury, neurological illnesses, CNS infection, alcohol consumption, corticosteroid treatment, fetal hypoxia and previous antipsychotic exposure (Cowell et al 1994; Filipek et al 1994; Reite et al 1997). Careful subject selection and detailed medication histories in patient populations are required to produce valid interpretations of MRI-based volumes. Conversely, age and gender-matching of control subjects is equally critical. A number of the control subjects included in this thesis were recruited from within the hospital community. This group of subjects generally had a higher level of education and health than the general community. Comparisons between schizophrenic patients and the current control group may have been biased by hyper-normal brain structure in the controls. However, attempts to match controls based on educational and socio-economic levels would introduce other based on educational and socio-economic levels would introduce other confounds, as non-schizophrenic subjects with equivalent education or socioeconomic status are likely to suffer from other developmental or medical conditions (i.e. mental retardation, autism). Schizophrenia itself may seriously interfere with normal age-appropriate expected levels of educational and social attainment (ADA 1994). Alternatively, the parental educational and socioeconomic levels of control-parents and patient-parents were matched in the studies presented for this thesis. No differences were seen in parental socioeconomic status between patients and controls.

5.4 Implications for Future Studies

Careful consideration to methodology, scanning protocols and subject selection will be required if meaningful cross-study comparisons are desired. Additionally, understanding medication effects on striatal structures will require studies based on monotherapy. The effects of neuroleptic interactions on striatal morphology are unknown and may confound volumetric data. With respect to understanding the brain morphology of schizophrenia, researchers may find subgrouping FE patients according to extrapyramidal symptom profile and unmedicated basal ganglia volumes of value when trying to ascertain a schizophrenia phenotype.

5.5 Advantages to Atypical Neuroleptics

Second-generation atypical antipsychotics offer a number of advantages in treating first-episode psychosis. Clinically, the first psychotic episode in patients with schizophrenia is the most responsive to treatment, however, these patients are also more likely to develop motor side effects, even at low medication doses (DeQuardo 1998). Data from this thesis suggests that atypical antipsychotic medications are effective in the treatment of first-episode schizophrenia and are well tolerated. Both risperidone and olanzapine had a lower propensity to increase or induce additional EPS than typical antipsychotics. A recent study by Bhana and colleagues (2001) suggested that in large, wellcontrolled trials in schizophrenia patients, olanzapine was superior to haloperidol in overall improvements in psychopathology rating scales and in the treatment of depressive and negative symptoms, and was comparable in effects on positive psychotic symptoms. Bhana et al (2001), found the 1-year risk of relapse (rehospitalisation) was significantly lower with olanzapine than with haloperidol treatment. The tolerability of moderate doses of risperidone and olanzapine contribute to patients ability to stay on medication for longer periods, decreasing the need for more frequent hospitalizations (DeQuardo 1998; Malla et al 2001; McCreadie 1996)

5.6 New Directions - Investigating an Underlying Circuitry of Schizophrenia

The evidence for underlying brain abnormalities or brain pathology in schizophrenia is compelling. While multiple sites of abnormality have been identified (frontal lobes, hippocampal complex, lateral ventricles, thalamus, superior temporal gyrus, increased prevalence of minor developmental midline anomalies), it is clear no single focal lesion provides a parsimonious explanation for the diverse presentation of symptoms seen in schizophrenia. However it has been suggested that a dysfunction or disruption to the multiple fronto-striatal pathways may be sufficient to explain the heterogeneous signs and symptoms of the illness (Middleton and Strick 2000; Robbins 1990).

Cortico-striatal pathways also are known to subserve neurocognitive functions (i.e. working memory, executive planning, speed of thought processing), which are abnormal in schizophrenia as well as in Parkinson's and Huntington's diseases (Lawrence et al 1998; Pantelis et al 1997). Cognitive deficits in schizophrenia may predate the onset of illness (Erlenmeyer-Kimling et al 2000). Similarities of cognitive deficits in schizophrenia to those seen in Parkinson's and Huntington's diseases are intriguing, as their neuropathology is clearly defined. A final common pathway to neurocognitive deficits in all three illnesses further supports the hypothesis of disrupted or dysfunctional basal ganglia circuitry.

Functional imaging data does suggest that the pathophysiology of schizophrenia reflects an aberrant activity in, or integration of components of

distributed circuits involving the frontal cortex, the hippocampus and some subcortical structures (Harrison 1999b). It can be hypothesized that neuropathological features represent anatomical substrates of functional abnormalities in neural connectivity. Evidence from studies of the mechanisms of action of antipsychotic drugs further supports this hypothesis. As well, specific circuits of the basal ganglia may underlie aspects of both movement disorders and psychotic symptoms (see figure 15 and 16).



Striatal Thalamocortical Motor Circuit



Striatal Thalamocortical Limbic Circuit

Both the striatal thalamocortical motor and limbic circuits suggest that dysfunction in multiple pathways between several key hubs (striatum, thalamus, cortical regions) are involved in the emergence of motor signs and psychotic symptoms in schizophrenia (Walker 1994). While the reports of striatal abnormalities in unmedicated FE schizophrenia patients remains controversial, there is a growing body of evidence for the presence of thalamic abnormalities in schizophrenia, independent of medication effects (Konick and Friedman 2001).

Reduction in thalamic size is related to decreased speed of cognitive processes (Van Der Werf et al 2001). In schizophrenia, reductions in thalamic volumes have been reported at the onset of psychosis in some, but not all, studies (Arciniegas et al 1999; Ettinger et al 2001; Gilbert et al 2001). Varying methodologies may contribute to the heterogeneity of findings in thalamic volumes. Additionally, treatment with neuroleptics may induce thalamic hypertrophy as a physiological response to receptor blockade (Gur et al 1998b). Structural MRI findings are paralleled by reports of reduced concentrations of the neuronal marker n-acetyl aspartate (*NAA*) in the thalamus of patients with schizophrenia (Ende et al 2001). Similar reductions of *NAA* have been reported in the dorsolateral prefrontal cortex of schizophrenia patients (Bertolino et al 1998).

The convergence of evidence from both frontal lobe and thalamic deficits in schizophrenia is suggestive of a disruption of fronto-thalamic loops or a reduction of circuit integrity. The functionality and the integrity of fronto-thalamic

circuits have not been fully quantified in drug-naïve first-episode schizophrenia. With currently available technology we can assess neuronal and axonal integrity, myelin and thalamic structure and function in FES patients. *In vivo* corticothalamic circuit integrity can be measured with a new MRI modality to measure the myelin-water specific short-T2 relaxation signal (similar to ansiotropy) and proton magnetic resonance spectroscopic imaging (MRS) of neuron-specific N-acetyl aspartate compounds (NAAs) in specified regions-ofinterest. Understanding neural circuitry and neural networks in schizophrenia will require multiple approaches to elucidate the nature of the underlying dysconnectivity of psychosis.

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Appendix A – Positive and Negative Syndrome Scale

EARLY PSYCHOSIS IDENTIFICATION AND INTERVENTION

SUBJECT	RATER	DATE:
NUMBER:	INITIALS:	(d/m/y)

POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS)

Inst	Instructions for Rating:							
			evere	<u>o – a</u> (Ci	rcle o	<u>e / -</u> one)		
	Delusions	1	2	3	4	5	6	7
2	Conceptual Disorganization		2	3	4	5	6	7
2	Hallucinatory Behaviour	1	2	3	4	5	6	7
		1	2	3	4	5	6	7
	Grandiosity		2	3	4	5	6	7
6			2	3	4	5	6	7
7	Hostility	1	2	3	4	5	6	7
NE	GATIVE SCALE	<u> </u>	-	(Ci	rcle (one)	<u> </u>	l
		1	2	3	4	5	6	7
2	Emotional Withdrawl		2	3	4	5	6	7
3	Poor Rannort	1	2	3	4	5	6	7
4	Passive Pathetic Withdrawl	1	2	3	4	5	6	7
5	Difficulty in Abstract Thinking	1	2	3	4	5	6	7
6	Lack of Spontaneity and Flow of Conversation	1	2	3	4	5	6	7
7	Stereotyped Thinking	1	2	3	4	5	6	7
GENERAL PSYCHOPATHOLOGY SUBSCALE (Circle one)					·			
1	Somatic Concern	1	2	3	4	5	6	7
2	Anxiety	1	2	3	4	5	6	7
3	Guilt Feelings	1	2	3	4	5	6	7
4	Tension	1	2	3	4	5	6	7
5	Mannerism and Posturing	1	2	3	4	5	6	7
6	Depression	1	2	3	4	5	6	7
7	Motor Retardation	1	2	3	4	5	6	7
8	Uncooperative	1	2	3	4	5	6	7
9	Unusual Thought Content	1	2	3	4	5	6	7
10	Disorientation	1	2	3	4	5	6	7
11	Poor Attention	1	2	3	4	5	6	7
12	Lack of Judgment and Insight	1	2	3	4	5	6	7
13	Disturbance of Volition	1	2	3	4	5	6	7
14	Poor Impulse Control	1	2	3	4	5	6	7
15	Preoccupation	1	2	3	4	5	6	7
16	Active Social Avoidance	1	2	3	4	5	6	7
		T	otal	PANS	SS sc	ore:_		
Medication at time PANSS was completed Dose (mg/d)] [Durati	on (w	/ks)	

Appendix B – Extrapyramidal Symptoms Ratings Scale

EARLY PSYCHOSIS IDENTIFICATION AND INTERVENTION

SUBJECT	RATER	DATE:
NUMBER:	INITIALS:	(d/m/y)

EXTRAPYRAMIDAL SYMPTOM RATING SCALE (ESRS)

Medication at time ESRS was completed	Dose (mg/d)	Duration (wks)

PA	PARKINSONISM, DYSTONIA AND DYSKINESIA						
Qu	Questionnaire and behavioural scale: (Physician)						
Inq	uire into the status of each symptom and rate accordingly						
Sta	itatus: 0 = Absent 1 = Mild 2 = Moderate 3 = Severe						
1.	1. Impression of slowness or weakness, difficulty in carrying out routine tasks.						
2.	2. Difficulty walking or with balance.						
3.	3. Difficulty swallowing or talking.						
4.	4. Stiffness, stiff posture.						
5.	5. Cramps or pains in limbs, back or neck.						
6.	6. Restless, nervous, unable to keep still.						
7.	7. Tremours, shaking.						
8.	8. Oculogyric crisis, abnormal sustained posture.						
9.	9. Increased salivation.						
10.	10. Abnormal involuntary movements (dyskinesia) of extremities or trunk.						
11.	11. Abnormal involuntary movements (dyskinesia) of tongue, jaw, lips or face.						
12.	12. Dizziness when standing up (especially in the morning)						

EARLY PSYCHOSIS IDENTIFICATION AND INTERVENTION DATE:

SUBJECT NUMBER:

RATER INITIALS:

(d/m/y)

EXTRAPYRAMIDAL SYMPTOM RATING SCALE (ESRS) CONTINUED

PARKINSONISM: PHYSICIAN'S EXAMINATION

For each item please insert and/or circle	the rating number which best describes the subject's condition.
Expressive automatic	0 = Normal
movements: (facial	1 = Very mild decrease in facial expressiveness.
mask/speech)	2 = Mild decrease in facial expressiveness.
	3 = Rare spontaneous smile, decreased blinking, voice slightly monotonous.
	 4 = No spontaneous smile, staring gaze, low monotonous speech, mumbling.
	5 = Marked facial mask, unable to frown, slurred speech.
	6 = Extremely severe facial mask with unintelligible speech.
Bradykinesia:	0 = Normal
	1 = Global impression of slowness in movements.
	2 = Definite slowness in movements.
	3 = Very mild difficulty in initiating movements.
	4 = Mild to moderate difficulty in initiating movements.
	5 = Difficulty in starting or stopping any movements, or freezing on initiating voluntary act.
	6 = Extremely severe (nearly frozen).
Rigidity:	0 = Normal.
(Rate each extremity separately)	1 = Very mild, barely perceptible.
Right Arm:	2 = Mild (some resistance to passive movements).
Left Arm:	3 = Moderate (definite resistance to passive movements).
Right Leg:	<pre>4 = Moderately severe (moderate resistance but still easy to move limb.)</pre>
Total	5 = Severe (marked resistance with definite difficulty moving limb).
	6 = Extremely severe (nearly frozen).
Gait & posture:	0 = Normal.
	1 = Mild decrease of pendular arm movement.
	2 = Moderate decrease of pendular arm movement, normal steps.
	3 = No pendicular arm movement, head flexed, steps more or less normal.
	4 = Stiff posture (neck, back), small step (shuffling gait).
	5 = More marked festination or freezing on turning.
	6 = Triple flexion, barely able to walk.

EARLY PSYCHOSIS IDENTIFICATION AND INTERVENTION					
SUBJECT R/	ATER		DATE:		
NUMBER: IN	ITIALS:		(d/m/y)		
EXTRAPYRAMIDAL SYN	IPTOM	RATING SC	ALE (ESRS) CO	NTINUED	
PARKINSONISM: PHYSICIA	N'S EXA	MINATION			
Tremor: Assign a rating number for eac	h region ac	cording to the sc	oring table below.		
Right upper arm	Hea	d			
Left Upper Arm	Jaw	'Chin			
Right Lower Leg	Ton	gue			
Left Lower Leg	Lips	,	Total		
Tremor: Scoring Table	I	Occasional	Frequent	Constant or almost so	
None	0				
Borderline	1				
Small amplitude		2	3	4	
Moderate amplitude		3	4	5	
Large amplitude		4	5	6	
For each item below please circle the ra	iting numbe	r which best des	cribes the subject's co	ondition.	
Akathisia:	0 = Nor	mal			
	1 = Loo	ks restless, ner	vous, impatient, und	comfortable.	
	2 = Nee	ds to move at I	east one extremity.		
	3 = Ofte pos	en needs to mo ition.	ve one extremity or	to change	
	4 = No spontaneous smile, staring gaze, low monotonous speech, mumbling.				
	5 = Unable to sit down for more than a short period of time.				
	6 = Move or walks constantly.				
Sialorrhea:	0 = Normal				
	1 = Ver	y mild.			
	2 = Milc	l.			
	3 = Moo	lerate; impairs	speech.		
	4 = Moo	lerately severe			
	5 = Sev	ere.			
	6 = Ext	emely severe;	drooling.		
Postural Stability:	0 = Nor	mal.			
	1 = Hes	itation when pu	ushed but no retropu	Ilsion.	
	2 = Ret	ropulsion but re	ecovers unaided.		
	3 = Exa	ggerated retrop	oulsion without failin	g.	
	4 = Abs	ence of postura examiner.	al response, would f	all if not caught	
	5 = Uns	table while sta	nding, even without	pushing.	
	6 = Unable to stand without assistance.				

EARLY PSYCHOSIS IDENTIFICATION AND INTERVENTION						
SUBJECT	RATER			DATE:		
NUMBER:	INIT	TIALS:		(d	/m/y)	-
EXTRAPYRAMID	AL SYMF	PTOM RA	TING	<u>SCALE (E</u>	SRS) COM	NTINUED
DYSTONIA: PHYSICI	AN'S EX	AMINATI	ON			
Acute Torsion Dystonia:						
Assign a rating number for each	ch region ac	cording to th	e scoring	table below.		
Right upper arm		Head				
Left Upper Arm		Jaw/Ch	nin			
Right Lower Leg		Tongue	9			
Left Lower Leg		Lips			Total	
Acute Torsion Dystonia: Sco	oring Table					
0 = Absent. 1 = Very Mild. 2 = Mild. 3 = Moderate.	4 = Mc 5 = Se 6 = Ex		oderately sev vere. tremely seve	vere. ere		
Assign a rating number for ea	ch region ac	cording to th	ne scoring	table below.		
Right upper arm		Head				
Left Upper Arm		Jaw/Cł	nin			
Right Lower Leg		Tongue				
Left Lower Leg		Lips			Total	
Non-acute or Chronic or Tar	dive Dysto	nia: Scoring	g Table			
0 = Absent. 1 = Very Mild. 2 = Mild.	4 = M 5 = S 6 = F		4 = Mo 5 = Se 6 = Ex	oderately sev vere. tremelv seve	vere. ere	
3 = Moderate.				•		

EARLY PSYCHOSIS IDENTIFICATION AND INTERVENTION

SUBJECT NUMBER: RATER INITIALS:

(d/m/y)

DATE:

EXTRAPYRAMIDAL SYMPTOM RATING SCALE (ESRS) CONTINUED

DYSKINETIC MOVEMENTS: PHYSICIAN'S EXAMINATION

For each item below please circle the rating number which best describes the subject's condition.				
		Occasional*	Frequent**	Constant or almost so
Lingual movements (slow lateral or torsion movem	ent	of tongue).		
None.	0			
Borderline.	1			
Clearly present, within oral cavity.		2	3	4
With occasional partial protrusion.		3	4	5
With complete protrusion.		4	5	6
Jaw movements (lateral movement, chewing, bitin	g, cle	enching).		
None.	0			
Borderline.	1		1	
Clearly present, small amplitude.		2	3	4
Moderate amplitude, but without mouth opening.		3	4	5
Large amplitude, but with mouth opening.		4	5	6
Bucco-labial movements (puckering, pouting, smacking, etc.).				
None.	0			
Borderline.	1			
Clearly present, small amplitude.		2	3	4
Moderate amplitude, forward movement of lips.		3	4	5
Large amplitude, marked, noisy smacking of lips.		4	5	6
Truncal movements (rocking, twisting, pelvic gyrations).				
None.	0			
Borderline.	1			
Clearly present, small amplitude.		2	3	4
Moderate amplitude.		3	4	5
Greater amplitude.		4	5	6

* When activated, rarely spontaneous

** Frequently spontaneous and present when activated

EARLY PSYCHOSIS IDENTIFICATION AND INTERVENTION

SUBJECT NUMBER:

INITIALS:

RATER

DATE: (d/m/y)

EXTRAPYRAMIDAL SYMPTOM RATING SCALE (ESRS) CONTINUED

DYSKINETIC MOVEMENTS: PHYSICIAN'S EXAMINATION

For each item below please circle the rating number which best describes the subject's condition.					
		Occasional*	Frequent**	Constant or almost so	
Upper extremities (choreoathetoid movements on	y: arı	ms, wrists, hand	ls and fingers).		
None.	0				
Borderline.	1				
Clearly present, small amplitude, movement of one limb.		2	3 .	4	
Moderate amplitude, movement of one limb or movement of small amplitude involving two limbs.		3	4	5	
Greater amplitude, movement involving two limbs.		4	5	6	
Lower extremities (choreoathetoid movements only: legs, knees, ankles and toes).					
None.	0				
Borderline.	1				
Clearly present, small amplitude, movement of one limb.		2	3	4	
Moderate amplitude, movement of one limb or movement of small amplitude involving two limbs.		3	4	5	
Greater amplitude, movement involving two limbs.		4	5	6	
Other involuntary movements (swallowing, irregul sighing, etc.).	ar re	spiration, frown	ing, blinking, gr	imacing,	
None.	0				
Borderline.	1				
Clearly present, small amplitude.		2	3	4	
Moderate amplitude.		3	4	5	
Greater amplitude.		4	5	6	
		* \\/hammative/	had verely energy	*****	

When activated, rarely spontaneous

** Frequently spontaneous and present when activated

EARLY PSYCHOSIS IDENTIFICATION AND INTERVENTION					
SUBJECT RATER	DATE:				
NUMBER: INITIALS	: (d/m/y)				
EXTRAPYRAMIDAL SYMPTOM	I RATING SCALE (ESRS) CONTINUED				
CLINICAL GLOBAL IMPRESSION	OF SEVERITY OF PARKINSONISM				
Considering your clinical experience, how	0 = Normal.				
sever is the parkinsonism at this time?	1 = Borderline.				
	2 = Very Mild.				
	3 = Mild.				
	4 = Moderate.				
	5 = Moderately Severe.				
	6 = Marked				
	7 = Severe.				
	8 = Extremely Severe.				
CLINICAL GLOBAL IMPRESSION	OF SEVERITY OF DYSTONIA				
Considering your clinical experience, how	0 = Normal.				
sever is the dystonia at this time?	1 = Borderline.				
	2 = Very Mild.				
	3 = Mild.				
	4 = Moderate.				
	5 = Moderately Severe.				
	6 = Marked				
	7 = Severe.				
	8 = Extremely Severe.				

,

CLINICAL GLOBAL IMPRESSION OF SEVERITY OF DYSKINESIA				
Considering your clinical experience, how sever is the dyskinesia at this time?	0 = Normal.			
	1 = Borderline.			
	2 = Very Mild.			
	3 = Mild.			
	4 = Moderate.			
	5 = Moderately Severe.			
	6 = Marked			
	7 = Severe.			
	8 = Extremely Severe.			