NEUROPSYCHOLOGICAL FUNCTIONING AND NEUROMORPHOMETRY IN NON-KRAEPELINIAN AND KRAEPELINIAN SCHIZOPHRENIA

by

ADAM M. BRICKMAN

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

2004

INFORMATION TO USERS

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleed-through, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

ProQuest Information and Learning Company
300 North Zeeb Road
P.O. Box 1346
Ann Arbor, MI 48106-1346

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

6/25/04
Date

Joan C. Borod
Joan C. Borod, Ph.D.
Chair of Examining Committee

6/26/04
Date

Executive Officer

Nancy S. Foldi, Ph.D.
Monte S. Buchsbaum, M.D.
Lina Shihabuddin, M.D.
Gwenn Smith, Ph.D.

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

NEUROPSYCHOLOGICAL FUNCTIONING AND NEUROMORPHOMETRY IN NON-KRAEPELINIAN AND KRAEPELINIAN SCHIZOPHRENIA

by

ADAM M. BRICKMAN

Advisor: Professor Joan C. Borod

The clinical heterogeneity of schizophrenia has prompted many attempts to establish valid subtypes. One classification system characterizes patients as either "Kraepelinian" or "non-Kraepelinian" based on longitudinal analysis of self-care deficits. Kraepelinian patients have poor outcome, defined as unremitting symptomatology and dependence on others for food, clothing, and shelter over a continuous five-year period or more. Non-Kraepelinian patients have better functional outcome and are independent for these needs. Preliminary neuroimaging studies demonstrated that Kraepelinian patients have enlarged ventricles, reduced posterior cortex, and diminished posterior anisotropy compared to non-Kraepelinian patients and normal controls. Non-Kraepelinian patients have reduced frontal matter and anisotropy compared to normal controls. These findings suggest a "two-hit" model for poor functional outcome: circuitry involving both anterior and posterior systems is characteristic of Kraepelinian patients.

The purpose of the current three-part series of studies was to extend these findings by examining neurocognition and neuromorphometry of the thalamus and internal capsule with high-resolution structural magnetic resonance imaging. In Study 1, neuropsychological functioning was examined in Kraepelinian and non-Kraepelinian patients. Kraepelinian patients were more impaired on most measures, including

immediate memory, executive functioning, and intrusive errors. Impairments in these domains were the best predictors of Kraepelinian status, correctly classifying close to 80% of the patients. For Study 2, the thalamus was traced at five axial levels in dorsal-to-ventral directions. Compared to controls, schizophrenia patients had smaller thalami at ventral levels, and these effects were most marked in Kraepelinian patients. Thalamic size was positively associated with frontal and temporal lobe size. For Study 3, a new protocol was developed to measure the size of the anterior limb of the internal capsule at five levels. Size of the structure was similar between normal controls and non-Kraepelinian patients, and significantly reduced in the Kraepelinian group, particularly at dorsal levels. Significant correlations emerged between internal capsule size in normal controls and surrounding size of subcortical brain regions. These associations tended to be progressively weaker in the two patient groups. Taken together, these findings support the validity of the Kraepelinian/non-Kraepelinian distinction and provide further evidence for involvement of both anterior and posterior brain circuits in poor outcome.

Acknowledgements

I am grateful to many people whose guidance and support facilitated completion of this project and my doctoral studies. Joan Borod, Ph.D., my academic advisor and chair of my dissertation committee, provided unparalleled mentorship over the years. Her encouragement has been exceptionally kind and generous. Dr. Borod has been, and will continue to be, an inspirational scientific role model. I am also indebted to Nancy Foldi, Ph.D., who served as a member of my dissertation committee. Dr. Foldi's contribution to my academic training and personal growth has been multifactorial. As a clinician and as a scientist, she has taught me to formulate ideas and concepts from multiple perspectives. And, perhaps most importantly, she has provided unconditional personal support. As Director of the Neuroscience PET Laboratory at Mount Sinai School of Medicine, Monte Buchsbaum, M.D., generously provided laboratory support and countless hours of mentorship. Above all else, he is a scientist, and has instilled in me a passion for neuroscience and research. For these reasons, I am very grateful to him. Since I started my graduate studies, Lina Shihabuddin, M.D., has given me continuous support and opportunities to conduct psychiatric research. She has enthusiastically fostered my academic development through a combination of skilled supervision and promotion of autonomy. She provided careful and insightful input as a reader on my dissertation committee. Gwenn Smith, Ph.D., contributed thoughtful and thorough critique in her role as a reader on my dissertation committee.

Many other individuals were integrally involved with conceptualization, data collection, data and image analysis, and manuscript preparation. They include Olga Berwid, M.A., Rachel Bloom, B.A., Janah Boccio, C.S.W., Pauline Bockhoven, R.N., Jesse Brand, B.A., William Byne, M.D., Ph.D., King Wei Chu, Ph.D., Kenneth L. Davis, M.D.,

Joseph Friedman, M.D., Philip D. Harvey, Ph.D., Erin Hazlett, Ph.D., Mehmet Haznedar, M.D., Zlatin Ivanov, M.D., Megan McWade, B.A., Serge Mitelman, M.D., Randall Newmark, B.A., Jimcy Platholi, M.A., Cheuk Tang, Ph.D., and Tsechung Wei, Ph.D.

I am indebted to the 146 participants who graciously dedicated their time, energy, and brains to our efforts in better understanding schizophrenia. This research was supported, in part, by grants from the Veterans Administration (2571-005) and from the National Institutes of Health (MH60023, MH56489, and MH603845).

On a personal note, I am grateful to Molly Zimmerman, Ph.D., who held my hand through the completion of this project.

Most importantly, I would like to acknowledge that I could not have completed my doctoral studies without the absolute love and support from my parents, Jane and Paul, and, especially, my sister, Jen. They believed in me at times when I found it difficult to believe in myself, they made jokes when I wasn't laughing, and they laughed at my jokes when they weren't funny.

This dissertation is dedicated to the memory of my grandfather, Bernard Boruck, who taught me the value of formal education and patience.

Table of Contents

Tables

Figures

CHAPTER ONE

Introduction

The purpose of this series of studies was to examine characteristics of good-outcome (i.e., "non-Kraepelinian") and poor-outcome (i.e., "Kraepelinian") patients with schizophrenia with neuropsychological and structural magnetic resonance imaging techniques. Three studies were conducted.

The first study used a comprehensive neuropsychological battery, clinical data, and symptom severity ratings to predict functional group membership (Brickman et al., 2001; Brickman et al., 2002; Brickman et al., in preparation). While neurocognitive deficits have long been recognized as part of the presentation of schizophrenia (e.g., Mirsky, 1969; Silverman, 1972), their salience as central to disease etiology has drawn renewed attention. Neurocognitive deficits are increasingly recognized as core symptoms in schizophrenia and are intimately related to disease course and functional outcome (Green, 1996; Green, Kern, Braff, & Mintz, 2000). This study sought to determine whether neurocognitive functioning was predictive of diagnostic group membership using neuropsychological tests that have been linked to functional outcome in schizophrenia. Whether neuropsychological predictors of Kraepelinian versus non-Kraepelinian status were different from predictors of other common measures of functional outcome was determined to examine the validity of this classification system.

The second study utilized structural magnetic resonance imaging (MRI) and focused on neuromorphometric analysis of the thalamus and its cortical grey and white matter correlates (Brickman et al., in press). The thalamus has extensive and reciprocal connections to the striatum and cortex and its association nuclei are importantly involved in maintaining attention and modulation of sensory input. The disturbance of

these functions in schizophrenia, together with evidence from postmortem and neuroimaging studies of volume reduction and functional abnormalities, has implicated the thalamus as a nexus of defective circuits in schizophrenia (Jones, 1997). This study used comprehensive semi-automated analysis of the thalamus at five distinct axial levels to determine whether thalamic size varied as a function of diagnosis and functional outcome. Circuitry abnormalities were inferred by examining relationships between thalamus size *and* cortical grey and white matter volume in anterior and posterior cortex.

The third, also a structural MRI study, examined the size of the internal capsules and its relationship to cortical grey and white matter and symptom severity (Brickman, Ivanov, Shihabuddin, & Buchsbaum, 2003; Brickman et al., in preparation). Converging lines of evidence from genetic, magnetic resonance, diffusion tensor, and postmortem studies of schizophrenia have linked oligondendroglia and/or myelin-related abnormalities in the pathophysiology of schizophrenia (Davis et al., 2003). While some MRI studies have examined gross white matter volume (Cannon et al., 1998; Wright et al., 2000) and anisotropy (e.g., Buchsbaum et al., 1998) reduction in schizophrenia, neuromorphometric region-of-interest (ROI) analyses of the internal capsules have been limited. Understanding the morphological changes in the internal capsules is critical, as the area contains robust white matter fiber tracts connecting thalamus, striatum, and cortex. Further, determination of whether morphology of the internal capsules varied as a function of outcome in schizophrenia provides important insights into the relationship between subcortical-cortical circuitry abnormalities and functioning. For this study, a novel neuromorphometric ROI protocol for examining the size of the anterior internal capsules was developed. Differences among non-Kraepelinian patients, Kraepelinian

patients, and normal controls were determined and the relationship between internal capsule size *and* thalamic, striatal, and ventricular size was examined.

Hypotheses for the current studies were based on findings from the extant literature as well as preliminary imaging studies from our laboratory. While studies of neurocognition in schizophrenia have shown deficits in most domains (e.g., Bilder et al., 2000), poor performance on tasks of verbal memory, immediate memory, executive functioning, and attention are most predictive of poor functional outcome (Green et al., 2000). This profile has generally been confirmed in the one existing study of neurocognition specifically comparing Kraepelinian and non-Kraepelinian schizophrenia patients (Roy et al., 2003). Functional and structural MRI studies from our laboratory have implicated deficits in frontal areas in both Kraepelinian and non-Kraepelinian schizophrenia patients, but greater temporal and occipital deficits in Kraepelinian patients compared to both controls and non-Kraepelinian patients (Brickman et al., 2002; Buchsbaum et al., 2002; Mitelman, Shihabuddin, Brickman, Hazlett, & Buchsbaum, 2003; Shihabuddin et al., 2001). Taken together, these findings suggest that schizophrenia, as a diagnostic entity, is associated with anterior pathology, whereas the Kraepelinian subtype of schizophrenia is associated with *both* anterior pathology *and* posterior pathology. This pattern of pathology has been termed the *two-hit defective compensation model* of poor outcome (Mitelman et al., 2003).

The purpose of the current studies was to extend preliminary findings in Kraepelinian and non-Kraepelinian schizophrenia to include behavioral data, subcortical regions, and white matter morphometry. Primary hypotheses were based on the two-hit defective compensation model. For Study 1, it was hypothesized that neuropsychological tests associated with more posterior brain functioning would be

most predictive of group membership within the Kraepelinian diagnostic scheme. For Study 2, it was hypothesized that schizophrenia patients, as a group, would have reduced thalamus size compared to normal controls, but regions of the thalamus that are interconnected with posterior cortex would best distinguish Kraepelinian and non-Kraepelinian patients. For Study 3, it was hypothesized that both Kraepelinian and non-Kraepelinian patients would have reduced white matter in the anterior internal capsules, but areas of the anterior internal capsules containing fibers associated with more posterior regions would distinguish the two groups.

Literature Review

Diagnostic Classification in Schizophrenia

Historically, two different general patterns of the course of schizophrenia have been proposed. The first, consistent with Emil Kraepelin's (Kraepelin, 1904) description of "dementia praecox" suggests that schizophrenia is a progressive disease that results in a dementia-like syndrome. The second view maintains that schizophrenia follows a relatively stable, nondeclining course possibly as the result of a static lesion that occurs early in life (Bleuler, 1950). There is currently little debate that schizophrenia is a heterogeneous disorder (Buchanan & Carpenter, 1994; Harvey & Davidson, 2002; Tsuang & Faraone, 1995). As this heterogeneity is manifested as varying outcomes and symptom profiles, both positions could be valid (McGlashan & Hoffman, 2000), but applicable to different subgroups of patients; some patients could experience progressive deterioration (Friedman et al., 2001), whereas others could have a relatively stable course after the initial episode (Goldberg, Hyde, Kleinman, & Weinberger, 1993). Better understanding of valid subgroups of patients with schizophrenia is of critical importance in both elucidating the possible multiple etiologies of the disease as well as

in developing viable treatments targeted at the specific characteristics of different patients.

Several attempts have been made to classify the clinical heterogeneity of schizophrenia into valid subtypes (for review, see Roy, Merette, & Maziade, 2001). These approaches have generally focused on analysis of current symptom profiles. One system, for example, which categorizes patients as either "deficit" or "nondeficit," is based on the quality and severity of negative symptoms (Carpenter, Heinrichs, & Wagman, 1988). Deficit schizophrenia is defined by the presence of primary, enduring negative symptoms. Studies have demonstrated that this subtype of schizophrenia has a distinct symptom and neuropsychological profile (Buchanan, Kirkpatrick, Heinrichs, & Carpenter, 1990; Buchanan et al., 1994; Buchanan, Strauss, Breier, Kirkpatrick, Kirkpatrick, & Carpenter, 1997; Carpenter, Arango, Buchanan, & Kirkpatrick, 1999; Fenton & McGlashan, 1992), in part suggesting its validity as a subtype. Other authors have focused on the positive symptoms of schizophrenia, distinguishing between paranoid and non-paranoid patients (Tsuang & Winokur, 1974). Reliable differences in neuropsychological test performance have demonstrated that non-paranoid patients are more impaired than paranoid patients (Zalewski, Johnson-Selfridge, Ohriner, Zarrella, & Seltzer, 1998). Gur and colleagues (1994) classified schizophrenia patients as negative, paranoid, disorganized, Schneiderian, or unclassified and demonstrated neuroanatomical differences among groups; further research on neuropsychological domains (Hill, Ragland, Gur, & Gur, 2001) has supported this distinction.

A problem with many of these attempts to validly categorize schizophrenia patients is that they focus on cross-sectional symptom profiles, which do not necessarily stay stable over time (Deister & Marneros, 1993). To deal with this issue, Keefe and

colleagues (Keefe et al., 1987) proposed a classification system that is based on longitudinal analysis of the presence of severe and stable self-care deficits (Keefe et al., 1987). Specifically, the term "Kraepelinian" has been used to describe those schizophrenia patients with a very poor functional outcome, defined by five or more continuous years of dependency on others for life necessities accompanied by unremitting symptomatology. Kraepelinian patients are unable to independently maintain personal hygiene; they are unable to handle money or have jobs for the purpose of making money; they are dependent on others to prepare meals, and they are incapable of living alone (or with dependents). As Kraepelin had proposed early in the twentieth century, this group of patients may have a deteriorating course (Harvey et al., 1999) that often results in long-term institutionalization and profound functional deficits (Davidson et al., 1995). In contrast, non-Kraepelinian schizophrenia patients are reported to have better cross-sectional and longitudinal outcomes. Cognitive functioning is not part of the non-Kraepelinian/Kraepelinian distinction. The advantage of the Kraepelinian classification system is that it characterizes the course of the illness with a focus on longitudinal outcomes, as opposed to other classification systems (e.g., Andreasen & Olsen, 1982; Crow, 1980; Strauss, Carpenter, & Barko, 1974), which are based on current symptoms (Keefe et al., 1996). The current series of studies utilized the Kraepelinian diagnostic classification system to better understand the characteristics of the two subtypes.

Cognition in Schizophrenia

Neuropsychological functioning in schizophrenia. Neurocognitive deficits have been well documented in schizophrenia both early in the disease in younger patients (Brickman et al., in press a; Hoff et al., 1999; Kenny et al., 1997) and later in the disease in

older patients (e.g., Harvey et al., in press). Because of the severity of neurocognitive deficits, their consistency across the course of the disease, and their strong association with functional outcome (Green, 1996; Green et al., 2000), neurocognition is considered a central clinical feature of the disease and is now an important target of psycho-pharmacological intervention (Sharma & Antonova, 2003).

Although there has been variability in reported deficits across studies of schizophrenia patients, several consistent findings are suggestive of both global cognitive deficits as well as a specific schizophrenia-associated neuropsychological profile. In terms of global deficits, schizophrenia patients tend to score lower on estimates of intellectual functioning across domains (Bilder et al., 2000; Cantor-Graae, Warkentin, & Nilsson, 1995; Heinrichs & Zakzanis, 1998), and display a generalized neuropsychological deficit, approximately 1.5 standard deviations below the performance of normal volunteers (Bilder et al., 2000). In terms of a specific neuropsychological profile, most investigators have implicated deficits in attention (Bilder et al., 2000; Heaton et al., 1994; Townsend et al., 2001; for review, see Heinrichs & Zakzanis, 1998), executive functioning (Bilder et al., 2000; Heaton et al., 1994; Townsend, Malla, & Norman, 2001; Velligan, Ritch, Sui, DiCocco, & Huntzinger, 2002), and verbal (Hoff et al., 1999; Rempfer, Hamera, Brown, & Cromwell, 2003; Saykin et al., 1991) and spatial memory (Chey, Lee, Kim, Kwon, & Shin, 2002). Whether there is age-associated cognitive decline in schizophrenia remains uncertain, with some investigators reporting an age-related decline (Waddington & Yousseff, 1996), some reporting no change over time (Nopoulos, Flashman, Flaum, Arndt, & Andreasen, 1994), and others reporting improvement with age (Gold, Arndt, Nopoulos, O'Leary, & Andreasen, 1999). Discrepant findings in the literature are likely due to inclusion of schizophrenia patients

at varying levels of functioning. For example, Friedman and colleagues (2001) found that institutionalized patients, who met Kraepelinian criteria by virtue of their extended institutional stay and consistent psychotic symptoms, had dramatic overall decline in a 6-year follow-up period.

As neuroleptic exposure may inhibit cognitive decline, or even improve cognition (Lieberman et al., 2001), and most studies that examine neuropsychological functioning do so in medicated patients (Heinrichs & Zakzanis, 1998), it is difficult to assess the true cognitive profile of schizophrenia from the literature. To address this issue specifically, we conducted the first neuropsychological study of adolescents with psychosis prior to the onset of pharmacological treatment (Brickman et al., in press a). Patients' performance on a comprehensive neuropsychological battery was compared to that of age- and sex-matched normal controls. The patient group was overall more impaired than the normal comparison subjects, and largest effect sizes were observed on tasks of executive functioning, attention, and memory, suggesting that these areas of impairment are "core" features of schizophrenia.

Neuropsychological functioning in Kraepelinian and non-Kraepelinian schizophrenia. Several differences between Kraepelinian and non-Kraepelinian patients have been described. Kraepelinian patients have more severe negative symptoms and formal thought disorder (Keefe et al., 1987; Keefe et al., 1988; Keefe et al., 1991; Keefe et al., 1996), are less responsive to typical antipsychotic medication (Harvey et al., 1991), and are more likely to have family members with schizophrenia-spectrum disorders (Keefe et al., 1991). Although these clinical characteristics have been well defined, there remains a paucity of studies that have compared cognitive functioning between Kraepelinian and non-Kraepelinian patients. Cognitive functioning is not part of the

Kraepelinian criteria, despite the intrinsic relationship between cognitive and functional deficits (Green, 1996; Green et al., 2000). Harvey and colleagues (1998) found that geriatric institutionalized schizophrenia patients, whose functional status was severely impaired enough to meet criteria for Kraepelinian schizophrenia, performed more poorly on a variety of global and specific measures of cognitive functioning than patients with a lifetime history of ambulatory status, a finding replicated by Evans and colleagues (1999). Both of these studies examined patients in late life. However, there are few such studies in younger patients. It is well known that cognitive performance plays a valuable role in psychiatric research because it can increase understanding of the relationship among neurocognition, symptoms, and course (Keefe, 1995).

Only two studies have compared neuropsychological test performance between Kraepelinian and non-Kraepelinian patients specifically. The first, which examined age disorientation (i.e., a lack of knowledge of one's own age) in a group of patients with schizophrenia, demonstrated that a significant proportion of Kraepelinian patients but none of the non-Kraepelinian patients was disoriented to age (Tapp, Tandon, Scholten, & Dudley, 1993). As age disorientation serves as a reasonable marker for poor overall cognition (Liddle & Crow, 1984), this finding suggests that Kraepelinian patients have significantly worse gross intellectual functioning compared to non-Kraepelinian patients. The second, a pilot study using a limited neuropsychological battery, found that Kraepelinian patients performed significantly worse than non-Kraepelinian patients on a simple motor task and a measure of executive functioning, while performing similarly on tasks of reaction time, associative learning, and attention span (Roy et al., 2003). This study provided important preliminary data demonstrating specific areas of deficit in Kraepelinian patients, but small sample sizes (only 9 Kraepelinian patients

completed the neuropsychological battery) and the fact that limited cognitive domains were assessed suggest that a larger-scale study with a more comprehensive battery is necessary to more clearly elucidate cognitive differences between the two groups.

Structural MRI Findings in Schizophrenia

Cortical regions. Since the publication of the first MRI study of schizophrenia in 1984 (Smith et al., 1984), there have been approximately 200 similar efforts. These studies have yielded somewhat mixed results, with almost more brain regions implicated in schizophrenia than not. Two recent meta-analyses suggest an approximate 2%-4% grey matter volume reduction in schizophrenia patients compared to normal controls (Lawrie & Abukmeil, 1998; Wright et al., 2000). In terms of regional specificity, a recent comprehensive review of the MRI literature by Shenton and colleagues (2001) noted that the most consistent reported cortical abnormalities involve temporal lobe structures, particularly the superior temporal gyrus; frontal lobe regions, particularly prefrontal cortex; and parietal lobe. By far, researchers have focused on the frontal and temporal lobes as primary cortical areas involved in the pathophysiology of schizophrenia (Davidson & Heinrichs, 2003).

Even though findings in these regions have been replicated often, there is still a lack of consistency throughout the published literature. For example, abnormalities, defined as volume or size reduction in the frontal lobes have been reported in only about 50% to 60% of schizophrenia cases (Henn & Braun, 1999; Raz & Raz, 1990; Shenton et al., 2001); however, strong associations are often found between volume of the frontal lobes and schizophrenia-associated symptomatology, even in negative studies of frontal volume reduction (Baare et al., 1999; Henn & Braun, 1999; Wible et al., 1995). Furthermore, frontal lobe dysfunction is often cited as the most salient correlate or

predictor of the schizophrenia diagnosis (Davidson & Heinrichs, 2003), which is consistent with the view that schizophrenia is best characterized by "hypofrontality" (Buchsbaum et al., 1982; Buchsbaum, 1990).

Cortical temporal lobe findings are also commonly found in schizophrenia. Overall temporal lobe reduction has been demonstrated in 55% to 61% of studies (Shenton, Wible, & McCarley, 1997; Shenton et al., 2001). The superior temporal gyrus has been the most consistently reported subregion of volume reduction in schizophrenia (Flaum et al., 1995; Shenton et al., 1992; Sullivan, Mathalon, Lim, Marsh, & Pfefferbaum, 1998; see Shenton et al., 2001 for review), and morphological abnormalities have been shown to be related to severity of schizophrenia symptomatology (e.g., Barta, Pearlson, Powers, Richards, & Tune, 1990). Much like findings in the frontal lobe, however, reports of temporal lobe abnormalities have been somewhat equivocal. In fact, a recent meta-analysis suggests that temporal lobe volume reduction distinguishes only about 25% of schizophrenia patients from normal controls (Davidson & Heinrichs, 2003), although the majority of studies do report group differences (Shenton et al., 2001).

Compared to the frontal and temporal lobes, the parietal and occipital lobes have been understudied. According to the recent review by Shenton and colleagues (2001) only 15 structural MRI studies in schizophrenia have examined the parietal lobes specifically, with 9 of them demonstrating volume reduction. Similarly, Shenton et al. (2001) describe only 9 studies including areas of the occipital lobes, with 4 reporting a reduction in size. Considering the strong neuroanatomical interconnections between parietal and occipital cortices and temporal lobe (Mishkin & Ungeleider, 1982) and their corresponding cognitive processes (e.g., Mesulam, 1998), further study of these structures is clearly warranted.

Subcortical regions: The first (Johnstone, Crow, Frith, Husband, & Kreel, 1976) and most consistent abnormality noted on structural neuroimaging studies of schizophrenia is enlargement of the lateral ventricles (Shenton et al., 2001). Most investigators believe that enlargement of the ventricles is secondary to reduced size of surrounding brain tissue. There is less agreement about which regions are responsible for enlargement of the ventricles. Furthermore, the impact of ventricular enlargement on surrounding subcortical structures has not been considered. It is possible, for example, that ventricular enlargement occurs without associated cortical or subcortical pathology, such as what is seen in normal pressure hydrocephalus. In this scenario, ventricular enlargement could impact the shape or size of surrounding structures via increased pressure. Given the proximity of the striatum and thalamus to the ventricles, and their involvement in circuitry abnormalities thought to be implicated in the pathophysiology of the disease, much attention has been focused on these regions.

The striatum, composed of the caudate nucleus and putamen, is robustly innervated by cortical projections and has strong influences on thalamic nuclei, which, in turn, project back to cortical regions (for more comprehensive review, see Brickman et al., 2003). Via cortical-striatal-thalamic and midbrain-striatal-cortical circuitry, the striatum is implicated in a number of cognitive and sensorimotor processes (Rauch & Savage, 1997). Interestingly, striatal volume in schizophrenia has generally found to be increased, particularly in those patients who have been chronically treated with neuroleptic medications (Hokama et al., 1995). On the other hand, never-medicated patients tend to have smaller striatal regions than controls (Shihabuddin et al., 1998; Shihabuddin et al., 2001a). These findings suggest a physiological response to neuroleptic treatment. Increased striatal size after neuroleptic treatment could be

indicative of post-synaptic dopaminergic dendritic expansion in response to the dopamingergic antagonism of neuroleptic treatment.

The thalamus has extensive and reciprocal connections to the striatum and cortex, and its association nuclei, including the medial dorsal nucleus and pulvinar, are involved in maintaining attention and modulation of sensory input. The disturbance of these functions in schizophrenia, together with neuroimaging and postmortem studies demonstrating volume reduction, has implicated the thalamus as a nexus of defective circuits in schizophrenia (Jones, 1997). Both postmortem studies (reviewed in Byne et al., 2001; Byne et al., 2002) and MRI studies (see meta-analysis by Konick & Friedman, 2001) of the thalamus in schizophrenia have generally found reduced volume, but this effect has been variable, of small effect size, and not seen in all studies (Bridle et al., 2002; Deicken, Eliaz, Chosiad, Feiwell, & Rogers, 2002). In postmortem (Byne et al., 2002; Highley, Walker, Crow, Esiri, & Harrison, 2003; Young, Manaye, Liang, Hicks, & German, 2000) and MRI studies where specific nuclei were individually analyzed, the medial dorsal nucleus and pulvinar have appeared to be more reduced in volume than other regions (Byne et al., 2001; Byne et al., 2002; Kemether et al., 2003). Functional neuroimaging studies have corroborated these findings (see Hazlett et al., 2004). Although total thalamic reduction has been found in schizophrenia in some studies (Andreasen et al., 1994; Gur et al., 1998), it has not been found in all (Arciniegas et al., 1999; Deicken et al., 2002; Portas et al., 1998).

White matter. There has been a recent focus on defective white matter as central to the pathophysiology of schizophrenia, following a culmination of genetic, imaging, and postmortem evidence of oligondendroglia or myelin-related abnormalities (Davis et al., 2003). The presence of gross white matter pathology in schizophrenia would help

account for findings of volume reduction in several specific nuclei (Shenton et al., 2001). That is, studies that have demonstrated reductions in specific nuclei (e.g., thalamus, caudate, and putamen) have generally done so in isolation without consideration of interconnecting white matter.

Structural MRI studies that have examined white matter volume, however, have been somewhat equivocal. White matter volume reduction in schizophrenia may be a small effect; a recent meta-analysis demonstrated only a 1% total white matter volume loss compared to controls (Wright et al., 2000). Furthermore, the presence of white matter defects in schizophrenia may be restricted to specific brain regions. Investigations of white matter in frontal regions (Breier et al., 1992; Buchanan, Vladar, Barta, & Pearlson, 1998; Sanfilipo et al., 2000; Sigmundsson et al., 2001) and temporal areas (Cannon et al., 1998; Foong et al., 2001) have been more consistent in their findings of schizophrenia-related volume reduction.

Development of newer MRI sequences and analytic techniques has increased the ability for more detailed examination of white matter. Diffusion tensor imaging, which allows for the assessment of white matter tract cohesion or integrity (i.e., anisotropy), has been used to show schizophrenia-related decreased anisotropy, particularly in frontal regions (Buchsbaum et al., 1998; Lim et al., 1999; Minami et al., 2003). Furthermore, higher Tesla magnets and the ability to acquire multiplanar images with very thin slice thickness allows for greater anatomical specificity, more detailed regional analyses, and less operator error. When coupled with new statistical approaches for MRI data analysis, such as voxel-based morphometry, these advances in technology have provided more evidence for white matter pathology. Paillere-Martinot and

colleagues (2001), for example, demonstrated reductions in frontal lobe volume and a fairly robust association between frontal white matter volume and symptom severity.

A problem with several studies of white matter abnormalities is that they have examined gross regional areas, without measurement of specific pathways that are implicated in schizophrenia-associated circuitry abnormalities. This limitation is likely due to the inherent difficulty in the quantification of white matter given its diffuse representation throughout the entire brain. Although few white matter pathways have discrete anatomical borders, the anterior limb of the internal capsule is uniquely delimited by subcortical nuclei that can be used for reliable anatomical landmarks in manual tracing approaches. The anterior limb of the internal capsule contains descending motor and ascending sensory fibers interconnecting brain regions implicated in the pathophysiology of schizophrenia, including neocortex, striatum, thalamus, and pons. Disruption of this fiber bundle can result in cognitive deficit with a "subcortical" profile, which is similar to the cognitive deficits seen in schizophrenia (Chukwudelunzu, Meschia, Graff-Radford, & Lucas, 2001). Furthermore, the internal capsule contains a heterogeneous set of neurons, including cholinergic and noncholinergic projections, which may mediate sensory and behavioral functioning often affected in schizophrenia (Zaborszky, Pang, Somogyi, Nadasdy, & Kallo, 1999).

The anterior limb of the internal capsule contains frontothalamic and thalamofrontal pathways, the corticopontine pathways, and a lesser number of caudate/pallidum fibers (Axer, Lippitz, & von Keyserlingk, 1999; Axer & Keyserlingk, 2000). The thalamocortical fibers appear most concentrated in the anterior tip of the internal capsule filling the space between anterior tip of the caudate nucleus and putamen, while the posterior section of the anterior limb of the internal capsule has

primarily corticopontine fibers (Axer & Keyserlingk, 2000). Reduction in the size of the internal capsules in patients with schizophrenia would be consistent with diminished coritocothalamic and corticostriatal connectivity. Manual tracings of the anterior limb of internal capsules on coronal MRI slices in 53 patients with schizophrenia and 48 controls revealed bilateral decrease in volume (Zhou et al., 2003). Volume decreases in the were also observed with voxel-based morphometry (Hulshoff Pol et al., 2004; Suzuzki et al., 2002; Zhou et al., 2003). One study using voxel-based morphometry did not find anterior limb volume differences but did report a significant correlation between the severity of negative symptoms and right internal capsule volume (Paillere-Martinot et al., 2001). A study of 39 patients and estimates from voxel based morphometry showed significant correlations between right posterior internal capsule volume and illness duration but contrasts with normal volunteers were not available (Vekakoulis et al., 2002).

Multi-planar manual tracing of the internal capsule can provide better regional specificity than approaches that consider voxel-wide or full volume comparisons. By tracing the internal capsules at various slices in the dorsal-to-ventral plane, contrasts with other brain regions at various slice levels can be made to more comprehensively examine interrerlationships among brain regions. Furthermore, multi-planar tracing allows for examination of shape of the internal capsules as well as overall size. For example, the lateral ventricles appear at more dorsal levels of the internal capsules, but not at ventral levels. Expansion of the lateral ventricles could put pressure on adjacent internal capsule fibers, thus narrowing the fiber tract at dorsal levels or pushing them in the ventral direction. This scenario would not necessarily cause a total volume reduction of the internal capsules, but it might create significant shape abnormalities.

Progressive change and outcome. Few structural MRI studies have examined whether there is schizophrenia-associated measurable regional change in specific brain regions over time. Longitudinal studies of progressive brain change have generally shown a reduction of grey matter volume. For example, Cahn and colleagues (2002) demonstrated a total brain volume loss of 1.2% over a 2-year follow-up period in a group of first-break patients with schizophrenia. In another longitudinal study of adult men with schizophrenia, Mathalon, Sullivan, Lim, and Pfefferbaum (2001) showed a schizophrenia-associated accelerated shrinkage in frontal and temporal lobe grey matter following a 4-year follow-up period. Hulshoff Pol and colleagues (2001) demonstrated that older schizophrenia patients had decreased density in the amygdale compared to older, matched normal controls and younger patients with schizophrenia, providing some cross-sectional evidence for regional tissue loss in schizophrenia.

Whether increased structural change is associated with poorer functional outcome in schizophrenia is also an area that has limited attention. In one study (van Haren et al., 2003) grey matter volume at a baseline MRI scan was not significantly associated with functional outcome or symptom severity after a 2-year interval. However, Cahn and colleagues (2002) found that decreases in cortical grey matter volume after a 1-year interval were associated with poorer functional outcome, defined as dependency on others, after a 2-year interval. Similarly, Matholon and colleagues (2001) reported that higher rates of atrophy over a 4-year period were associated with more time spent in a psychiatric hospital.

Conclusions. Structural MRI studies in schizophrenia reveal volume reduction in several regions throughout the brain (Shenton et al., 2001). While no consistent pattern of abnormalities has emerged from the extant literature, evidence of frontal lobe,

temporal lobe, thalamic, striatal, and internal capsule abnormalities implicates a dysfunctional circuit involving these regions. However, these findings have been equivocal; some studies show reductions in these areas, while others have not. Equivocal findings could be due to a number of factors. First, many studies that have examined morphometry have done so in relatively gross anatomical regions. Inclusion of specific cortical regions, such as examination of Brodmann areas, or subcortical regions, such as measurement of varying levels of caudate nucleus, may increase sensitivity. Second, methodological differences among imaging laboratories could lead to subtle, but significant, differences in findings. For example, fully automatic versus semi-automated or manual approaches could provide measurement error that obscures significant group differences. Finally, the considerable variability in structural findings in schizophrenia might also reflect etiological heterogeneity or a sequential developmental change with illness progression. Regional volume reduction could vary as a function of disease severity or of schizophrenia subtype diagnosis, and sampling from differing subgroups of patients across studies could account for discrepancies in findings. Distinguishing patients with schizophrenia according to outcome via the Kraepelinian classification scheme may be one strategy to address the problem of etiological heterogeneity.

Preliminary Studies

Overview

Recent efforts in our laboratory have focused on comprehensive neuro-morphometric analyses of Kraepelinian and non-Kraepelinian schizophrenia, following an earlier report of progressive lateral ventricular enlargement over five years in the former but not the latter group (Davis et al., 1998). The primary focus thus far has been

to characterize brain differences between the two groups and normal comparison subjects. A large cohort of schizophrenia patients was recruited from outpatient and long-term inpatient departments and all subjects are followed prospectively for longitudinal analyses. Baseline, cross-sectional analyses on a subset of patients and the entire sample, described below, have focused on Brodmann area analyses (Mitelman, Shihabuddin, Brickman, Hazlett, & Buchsbaum, 2003), cingulate gyrus (Mitelman, Shihabuddin, Brickman, Hazlett, & Buchsbaum, in press), ventricular volume (Shihabuddin et al., in preparation), striatum (Buchsbaum et al., 2003), and anisotropy (Shihabuddin et al., 2001). These structural MRI studies provide preliminary evidence for reliable differences between the two subgroups of schizophrenia patients, in part suggesting the validity of the diagnostic scheme. These studies are also the first systematic MRI studies of Kraepelinian and non-Kraepelinian schizophrenia and, therefore, provide important background data for the current efforts on the thalamus and the anterior limb of the internal capsules. While no preliminary studies from our laboratory have emerged for the neuropsychological study of the two subtypes, the structural MRI data have provided important insight into differences between the two groups in terms of brain functioning.

Assessment of Cortical Brodmann Area Gray and White Matter Distribution in non-Kraepelinian and Kraepelinian Schizophrenia (Mitelman et al., 2003).

High resolution MRI scans were acquired on 37 patients with schizophrenia and 37 age- and sex-matched normal controls. Schizophrenia patients were divided into Kraepelinian (n=13) and non-Kraepelinian (n=24) subgroups based on the objective criteria put forth by Keefe and colleagues (1987). Magnetic resonance images sectioned in the coronal orientation were segmented into grey matter, white matter, and

cerebrospinal fluid (CSF) for each of 39 cortical Brodmann areas in right and left cerebral hemispheres. Contrasts comparing all schizophrenia patients together compared to normal controls and comparing non-Kraepelinian and Kraepelinian patients were made for specific cortical regions. When grey, white, and CSF relative volume in frontal (Brodmann areas 44, 45, 46), temporal (Brodmann areas 20, 21, 22), and occipital (Brodmann areas 17, 18, 19) lobes were compared between all schizophrenia patients and normal controls, schizophrenia patients had significantly reduced grey and white matter, particularly in temporal regions (see Figure 1, left panel). When Kraepelinian and non-Kraepelinian patients were compared to each other with a similar analysis, the Kraepelinian patients had significantly reduced grey and white matter volumes, and increased CSF space in temporal and occipital regions compared to the non-Kraepelinian patients (see Figure 1, right panel).

In an effort to explore pattern differences between schizophrenia patients and normal comparison subjects and between Kraepelinian and non-Kraepelinian patients, we conducted t-tests comparing volume of each Brodmann area between groups. As can be seen in Figure 2 (top panel), schizophrenia patients, as a group, had significantly smaller anterior areas, particularly in the dorsal lateral prefrontal cortex, compared to normal controls. When Kraepelinian patients were compared to non-Kraepelinian patients, the former had significantly smaller areas of the posterior cortex, particularly temporal lobe and occipital lobe (see Figure 2, bottom panel). When each schizophrenia subtype was compared to the normal control group, the exact same pattern emerged: non-Kraepelinian patients had significantly reduced frontal areas compared to controls (see Figure 3, top panel) whereas Kraepelinian patients had significantly reduced posterior cortical areas (see Figure 3, bottom panel).

Findings are consistent with several MRI studies that have demonstrated schizophrenia-associated frontal and temporal lobe grey matter volume reduction, especially in the dorsal lateral prefrontal cortex and superior temporal gyrus, respectively (Shenton et al., 2001). Further, the study demonstrated more of a "posterior" profile associated with Kraepelinian, or poor-outcome, patients, and is consistent with a recent positron emissions tomography study that showed hypometabolism in posterior cortical regions in Kraepelinian patients (Buchsbaum et al., 2002). Thus, poor outcome appears to be the result of having two or more affected regions in both the frontal and temporal lobes.

Volume of the Cingulate and Outcome in Schizophrenia (Mitelman et al., in press).

After demonstration of a possible anterior-posterior gradient difference in cortical Brodmann areas between Kraepelinian and non-Kraepelinian patients (Mitelman et al., 2003), we examined whether the same pattern was evident in the cingulate gyrus. The cingulate has been implicated in schizophrenia (Suzuki et al., 2002) and cognitive processes mediated by the structure, such as spatial working memory and conflict monitoring (Carter et al., 1998), have been shown to be predictive of functional outcome (Green et al., 2000). Parallel to our cortical findings, schizophrenia patients, as a whole, had reduction in anterior cingulate volumes, compared to the normal comparison subjects. However, Kraepelinian patients had significantly reduced anterior and posterior cingulate volume reduction. The results are consistent with the two-hit hypothesis, implicating both anterior and posterior brain areas in poor outcome, but only anterior deficits in good outcome.

Volume of the Ventricles and Cortical Volume Correlates in Kraepelinian and non-Kraepelinian Schizophrenia (Shihabuddin et al., in preparation).

To replicate findings from an earlier CT study of Kraepelinian and non-Kraepelinian schizophrenia (Davis et al., 1998), the lateral ventricular system was examined in the entire cohort of study participants. The cohort comprised the total study sample, including 106 schizophrenia patients (54 Kraepelinian patients and 52 non-Kraepelinian patients) and 42 age- and sex-matched normal controls. To measure the ventricles, we traced each axial slice from the most ventral region to the most dorsal region. The lateral ventricles began at the highest slice with ventricular space visible and extended downward until the ventricular space divided into the anterior and temporal regions. Ventricles were manually traced on each continuous slice, with the aid of a Sobel-gradient filter, as illustrated in Figure 4. Values for right and left anterior horn, temporal horn, and superior ventricles were obtained.

As displayed in Figure 5, the lateral ventricles were largest in the Kraepelinian patients and smallest in the normal control subjects, with non-Kraepelinian patients intermediate. The effect was most pronounced for the temporal horns of the lateral ventricles. However, ventricular enlargement was not systematically related to regional shrinkage in surrounding cortical Brodmann areas. The findings replicate earlier observations of increased ventricles in Kraepelinian patients (Davis et al., 1998), but the impact, or cause, of the ventricular enlargement is less clear. Because no systematic relationship between ventricular size and cortical volume was found, several possibilities exist. First, ventricular enlargement could occur in the absence of cortical changes. Second, the relationship between ventricular size and size of other brain regions could be restricted to specific subcortical nuclei or regions. Third, lateral ventricular size could be an endophenotype of schizophrenia (Gottesman & Gould,

2003); that is, ventricular size increase could be the primary manifestation of the Kraepelinian etiology.

Caudate and Putamen Volumes in Non-Kraepelinian and Kraepelinian Patients with Schizophrenia (Buchsbaum et al., 2003).

Striatal volume has been reported to be increased in unmedicated schizophrenia patients (McCarley et al., 1999; Shihabuddin et al., 1998) and increased in schizophrenia patients following chronic treatment with antipsychotic neuroleptics (Hokama et al., 1995). The observed volume increase is most likely a physiological response to the dopaminergic antagonistic effects of neuroleptic medications (Chakos, Lieberman, & Bilder, 1994), possibly reflective of post-synaptic dendritic expansion following dopaminergic upregulation (see Brickman et al., 2003 for discussion). Differences in striatal volume between demographically-matched Kraepelinian and non-Kraepelinian patients could be reflective of pathophysiological variation between the two subtypes. To test this possibility, we examined caudate and putamen volume differences among the 24 non-Kraepelinian patients, 13 Kraepelinian patients, and 37 normal participants described above.

The most dorsal and most ventral axial brain slices containing caudate and putamen were determined separately and five equidistant slices were chosen for manual tracing in the right and left hemispheres. Non-Kraepelinian patients had significantly larger putamens than Kraepelinian patients and normal controls, particularly at more dorsal levels. Kraepelinian patients and normal controls had similar putamen size, except at the most dorsal levels, where the former group was smaller. This interaction is displayed in Figure 6. Size of the caudate nucleus was similar among the three groups.

The findings from the study suggest an association between drug responsiveness and striatal enlargement and the possibility that the widely observed striatal enlargement in medicated patients is associated with therapeutic improvement rather than merely being a nonspecific effect of dopamine blockade. Furthermore, the findings raise the possibility that Kraepelinian patients have a unique etiology; these patients may have differing underlying pathophysiology that is unresponsive to medications used to treat schizophrenia, thus leading to poor functional outcome.

Diffusion Tensor Imaging in Kraepelinian and non-Kraepelinian Schizophrenia (Shihabuddin et al., 2001).

As described above, diffusion tensor imaging allows for the assessment of white matter tract coherence, or anisotropy. Diffusion tensor studies of schizophrenia have demonstrated disrupted anisotropy, particularly in anterior white matter bundles (e.g., Buchsbaum et al., 1998). The purpose of this study was to examine whole brain anisotropy in Kraepelinian and non-Kraepelinian schizophrenia patients. Diffusion tensor images were obtained in conjunction with standard structural MR sequences in the 24 non-Kraepelinian, 13 Kraepelinian, and 37 matched normal controls described above.

Consistent with Brodmann area and cingulate gyrus findings, schizophrenia patients as a group were distinguished from normal controls by diminished anisotropy in frontal regions, particularly the cingulum bundle (see Figure 7). However, Kraepelinian patients had more significantly reduced anisotropy in more posterior regions, particularly posterior areas of the temporal lobe (see Figure 8). The findings provide more evidence for circuitry abnormalities in schizophrenia and for more posterior circuitry abnormalities related to poor functional outcome.

Conclusions

Several important conclusions can be drawn from these preliminary studies of non-Kraepelinian and Kraepelinian schizophrenia. First, taken together with earlier reports (e.g., Buchsbaum et al., 2002; Davis et al., 1998; Keefe et al., 1996), reliable structural brain differences between the two schizophrenia subtypes further supports the validity of the classification system. Second, non-Kraepelinian schizophrenia is associated with anterior brain abnormalities, consistent with the classic conceptualization of schizophrenia as a frontal lobe disorder (Buchsbaum et al., 1982; Buchsbaum et al., 1990), whereas Kraepelinian schizophrenia appears to be associated with *both* deficits in anterior *and* in posterior cerebral regions. Third, a lack of putamen enlargement in Kraepelinian patients, despite chronic treatment with neuroleptic antipsychotic medications, could be reflective of pathophysiological differences and/or unique etiology. Fourth, striatal, frontal, and temporal deficits, together with reduction in white matter anisotropy, in Kraepelinian schizophrenia suggest circuitry abnormalities. Finally, as ventricular enlargement was not associated with shrinkage in surrounding cortical areas, the finding may indicate that enlargement of the ventricles is endophenotypic of schizophrenia.

These preliminary studies provide a solid rationale for the current series of studies. Little work has been done with the clinical manifestations of non-Kraepelinian and Kraepelinian schizophrenia. Findings from the extant literature (e.g., Green, 1996; Green et al., 2000) suggest that measures of verbal learning are predictive of poorer functional outcome in schizophrenia. In light of our findings of greater posterior, particularly temporal, deficits in Kraepelinian patients, neuropsychological measures mediated by these regions may be the best predictors of subtype status. Furthermore,

our studies are consistent with the possibility of differential circuitry abnormalities underlying non-Kraepelinian and Kraepelinian schizophrenia. As the thalamus is a central gatekeeper between incoming sensory information and intracerebral communication (Jones, 1997), it is a primary candidate for a nexus of defective circuit. Finally, the anterior limb of the internal capsule contains robust fibers connecting cortex, thalamus, and striatum, and thus represents another important area potentially central to schizophrenia-related circuitry abnormalities. The anterior limb of the internal capsule is also proximal to the lateral ventricles; if ventricular expansion is endophenotypic, its enlargement may disrupt this circuitry in a process similar to normal pressure hydrocephalus.

Hypotheses

Study 1. Neuropsychological Predictors of Non-Kraepelinian and Kraepelinian Status

The primary purpose of this study was to determine neuropsychological differences between non-Kraepelinian and Kraepelinian patients with schizophrenia. The existing literature suggests more severe neuropsychological functioning in patients with poor functional outcome, with particular impairment in tasks mediated by frontal and temporal lobes (Green, 1996; Green et al., 2000). Further, our preliminary studies are consistent with these findings and implicate a two-hit model for poor outcome, with both anterior and posterior deficits noted in the Kraepelinian subtype. Based on these findings, it was hypothesized that Kraepelinian patients would evidence a more severe neuropsychological profile than non-Kraepelinian patients. The largest effects were predicted to be seen in tasks of verbal learning and executive functioning, domains mediated by temporal and frontal lobes, respectively. Neurocognitive measures in these domains were hypothesized to be the best predictors of Kraepelinian status.

There were two secondary goals for the study. First, the study sought to determine whether neurocognitive measures predicted Kraepelinian status when considered together with measures of psychiatric symptom severity. This analysis was important in establishing whether neuropsychological deficits accounted for a unique proportion of variance above-and-beyond the severity of psychiatric symptoms. It was predicted that neurocognitive measures would significantly predict Kraepelinian status when considered together with symptom severity ratings, thus suggesting that neuropsychological deficits are a unique component of the Kraepelinian classification system.

Second, the study sought to determine whether neuropsychological predictors of Kraepelinian status differed from predictors of other measures of more specific aspects of outcome (e.g., occupational history) subsumed under the classification scheme. The analysis addressed the critical question of whether the Kraepelinian/non-Kraepelinian distinction reflects a unique functional construct or whether it is simply a surrogate for other measures of functional outcome. While several correlates of Kraepelinian status have been previously described, no study has employed this approach for testing its validity.

Study 2. Thalamus Size in Non-Kraepelinian and Kraepelinian Schizophrenia

Rather than examining total volume of the thalamus, this study focused on a detailed slice-by-slice analysis from dorsal to ventral levels to determine regional effects. It was hypothesized that both schizophrenia groups would have reduced thalamus size at more dorsal levels, which contain the mediodorsal nucleus and has greater interconnections with anterior regions. Further, Kraepelinian patients were predicted to have reduced thalamus size compared to non-Kraepelinian patients and normal controls

at more ventral levels, which contains the pulvinar nucleus and has greater temporal lobe interconnectivity.

To examine the possibility of circuitry abnormalities, the relationship between the sizes of dorsal and ventral levels of the thalamus *and* size of the frontal and temporal lobes was examined. It was predicted that ventral levels of the thalamus would correspond with temporal lobe volume in the Kraepelinian patient group, suggesting that the two regions covary and are involved with a faulty posterior circuit.

Exploratory analyses were conducted to examine the effects of hemisphere, and the relationship between thalamic size and measures of psychopathology and neuroleptic treatment exposure.

Study 3. Size of the Internal Capsules in Non-Kraepelinian and Kraepelinian Schizophrenia

Similar to the approach with the thalamus size, this study focused on multi-slice tracings of the anterior limb of the internal capsule. Primary hypotheses were that there would be internal capsule volume reduction in all schizophrenia patients compared to controls, suggesting circuitry abnormalities involving cortex, striatum, and thalamus. Furthermore, Kraepelinian patients are expected to have even greater volume reduction than non-Kraepelinian patients and normal controls. To test circuitry abnormalities specifically, the relationship between the size of the anterior limb of the internal capsule at each dorsal-to-ventral slice and the size of the caudate, putamen, thalamus, and ventricles were examined. Significant relationships between the anterior limb of the internal capsule and surrounding subcortical nuclei would be consistent with a hypothesis of a primary schizophrenia-related circuit abnormality. Alternatively, size of the anterior limb of the internal capsule could be primarily related to size of the

surrounding lateral ventricles. Thus, Kraepelinian patients, who have larger lateral ventricles, could have smaller dorsal internal capsules (i.e., levels at which the ventricular system exists) compared to non-Kraepelinian patients and normal controls.

Exploratory analyses were conducted to examine the effects of hemisphere, and the relationship between internal capsule size *and* measures of psychopathology and neuroleptic treatment exposure.

CHAPTER TWO

Methods

Subjects

Overview. Participants in the current studies are part of a larger effort that examines longitudinal brain changes in Kraepelinian and non-Kraepelinian schizophrenia. The parent study is a five-year follow-up experiment that acquires MR images at baseline and then again after a five-year period. The project is currently in follow-up period, and work conducted to date has focused on cross-sectional analyses of baseline data. As the primary focus of the parent study is on brain morphometry, neuropsychological data were only collected on a subset of participants (described in greater detail below) and with a brief, but focused, battery. Thus, the current two neuroimaging studies focus on the entire sample, and the neuropsychological study focuses on a subset of participants. Inclusion and exclusion criteria, however, across studies were the same and will be described only once here.

Inclusion and exclusion criteria for schizophrenia patients. All schizophrenia patients met DSM-IV (American Psychiatric Association, 1994) diagnostic criteria for schizophrenia or schizoaffective disorder. Diagnosis was determined by a structured clinical interview with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen, Flaum, & Arndt, 1992). Diagnostic interviews were administered by a trained graduate-level research assistant or co-investigator and each patient received a consensus diagnosis with at least one senior clinician. Administration of the CASH was only performed by individuals who had demonstrated rater reliability by attending formal training sessions and group diagnosis conferences.

Schizophrenia patients were recruited from outpatient and inpatient departments at Mount Sinai School of Medicine and the Bronx VA Medical Center and from long-term inpatient units at Pilgrim State Psychiatric Hospital. Patients between ages 18 and 85 were included. Patients were included regardless of their history of neuroleptic exposure.

Patients were excluded if they had a significant history of medical or neurological disorder thought to interfere with brain functioning (e.g., epilepsy, head trauma, brain tumor, significant cardiac disease), determined by patient interview and medical chart review. Patients were also excluded if they had a comorbid DSM-IV Axis I disorder, including past or current history of substance or alcohol abuse and major depressive disorder, determined by the CASH interview, or history of loss of consciousness for greater than five minutes. Each participant was screened and excluded if they had contraindications to an MRI scan (i.e., metal implants, cochlear implants, pacemakers, or history of claustrophobia). Assessment of urine osmolality was conducted on the day of MR image acquisition and subjects were excluded if values were abnormal. History of electroconvulsive therapy was exclusionary.

Determination of non-Kraepelinian and Kraepelinian status. Following objective criteria put forth by Keefe and colleagues (1987), Kraepelinian status was determined by clinical interview and review of available medical records. Specifically, Kraepelinian patients were defined as those who met the following criteria for at least the five years prior to study contact: 1) continuous hospitalization, or, if living outside the hospital, complete dependence on others for food, clothing, and shelter; 2) no useful work or employment; and 3) no evidence of symptom remission. All other schizophrenia patients were considered non-Kraepelinian. After formal diagnostic interview, a

preliminary assignment of Kraepelinian status was made by a graduate-level research assistant and a consensus assignment occurred after discussion with at least one senior member of the research team.

Inclusion and exclusion criteria for normal controls. Normal control subjects underwent similar screening procedures as the schizophrenia patients. These participants were recruited by word-of-mouth and by IRB-approved advertisement. A graduate research assistant administered a modified version of the CASH, and participants were excluded if they met criteria for any Axis I psychopathological disorder, including past or current history of substance or alcohol abuse. Participants were similarly excluded if they had a history of significant medical or neurological illness or history of loss of consciousness for greater than five minutes. Subjects were excluded if they had contraindications to an MRI scan (i.e., metal implants, cochlear implants, pacemakers, or history of claustrophobia).

Study 1 participants. Forty-nine patients meeting criteria for schizophrenia and three patients meeting criteria for schizoaffective disorder participated in this study. There were 26 non-Kraepelinian and 26 Kraepelinian patients. Demographic and clinical characteristics of the patient sample are displayed in Table 1. The two groups were matched on age ($t(50)=1.23$, $p=0.22$), sex distribution ($\chi^2=0.50$, $p=0.48$), and duration of illness ($t(49)=1.70$, $p=0.10$). Kraepelinian patients, however, had significantly less education than non-Kraepelinian patients ($t(50)=2.57$, $p=0.01$); thus, analyses were conducted with number of years of education as a covariate.

Studies 2 and 3 participants. The schizophrenia patient group was made up of 106 patients (95 patients with schizophrenia, 11 patients with schizoaffective disorder), and there were 42 matched normal control subjects. Demographic and clinical data

were collected at the time of MR image acquisition; these are displayed in Table 2. Schizophrenia patients and normal controls were similar in age (t (146)=0.46, p=0.643) and sex distribution ($\chi^2(1)=3.04$, p=0.080). Non-Kraepelinian and Kraepelinian were similar to each other in age (t (104)=1.79, p=0.077) and sex distribution ($\chi^2(1)=0.022$, p=0.883). Schizophrenia patients were assessed with the Positive and Negative Syndrome Scales (PANSS; Kay, Fiszbein, & Opler, 1987), and Kraepelinian patients had more severe positive symptom, negative symptom, and general subscale scores (all Fs>15.00, p<0.0001), consistent with their more severe psychopathology. For the schizophrenia patients, interview and clinical chart reviews were conducted to determine age of neuroleptic exposure and medication history over the three-year period prior to scan acquisition. To examine the effects of neuroleptic exposure, we classified patient treatment at the time of MRI scan and for the predominant pattern over the three-year period prior to the scan as off-medication, typical neuroleptics, atypical neuroleptics, or both typical and atypical neuroleptics. Kraepelinian patients began neuroleptic treatment significantly earlier than non-Kraepelinian patients (t(82)=2.02, p=0.006). The distribution of type of neuroleptic exposure was similar between the two groups at the time of scan ($\chi^2(3)=4.36$, p=0.225) and for the majority of time over the three-year period prior to the scan ($\chi^2(3)=4.14$, p=0.247). Of the patients not taking antipsychotic at the time of scan, only 2, both non-Kraepelinian, were drug naïve.

Procedures: Study 1

Rationale. Because the focus of the parent study was on acquisition and analysis of MR images, only a brief neuropsychological battery was employed for the current study. However, care was taken to select a battery that maximized the range of

cognitive domains represented and that assessed those domains that are thought to be involved with functional outcome in schizophrenia (e.g., verbal memory and executive functioning). In addition to the neuropsychological tests, the severity of psychiatric symptomatology was assessed, and information pertaining to several other functional outcome features was collected. Patients were evaluated in one testing session, which took approximately an hour to complete. Assessments were completed by a graduate level research assistant, who was trained and supervised by a senior clinical neuropsychologist. The research assistant was also reliable conducting semi-structured interviews of psychiatric symptomatology; reliability was ensured by participating in regular consensus reliability sessions.

Battery. Psychiatric symptomatology for each patient was assessed with the PANSS (Kay et al., 1987). This 30-item scale consists of 7 items measuring positive symptoms, 7 items measuring negative symptoms, and 16 items measuring general psychopathology. The dependent measures are the total scores on the positive and negative subscales. Previous research by our group with this measure in Kraepelinian patients yielded an inter-class correlation of 0.89 for the total score of the PANSS (Davidson et al., 1995).

In addition to classifying patients as Kraepelinian or non-Kraepelinian, information pertaining to several other functional outcome features was collected. This information included years of education, marital status (i.e., ever married versus never married), occupational status (i.e., never employed, currently unemployed by previously employed, currently employed), current residence status (i.e., independently or with spouse equivalent, with parent or relative, group home, institutions), and the

number of previous psychiatric hospitalizations. These data were collected by a graduate research assistant and verified by a review of available medical records.

The California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) has the unique advantage of assessing several cognitive domains with one test. It is primarily used to assess verbal learning and memory; however, task strategy, organization, and error analysis provides measures of "higher order" executive functioning. The CVLT is a commonly used instrument that involves repeated presentation of a word list that consists of 16 items comprising four conceptual categories. The 16-item list (list A) is presented in a fixed order over five trials, with each trial followed by free recall for the list. A second word list (list B) with two of the same conceptual categories and two different ones is then presented and the subject is asked to recall the items from that list. Subjects are then asked to free recall items from the first list, first without and then with semantic cues. After a 20-minute delay, there is a second free-recall and semantic cue trial. Finally, subjects are administered a forced-choice recognition trial. There are several possible dependent measures, which are computed automatically with a software package. For the purposes of the current study, all possible dependent measures were used. These included performance on list A learning trial 1, performance on list A learning trial 5, total list A learning over 5 trials, total learning on list B, total score at short and long delayed free and cued recall of list A, recognition hits, semantic cluster ratio, serial cluster ratio, intrusive errors on free recall and cued recall trials, total intrusive errors, and a measure of perseverative responses.

Gross language functioning was assessed with the category fluency test (see Brickman et al., submitted, for discussion). Participants were instructed to generate exemplars of animals within a 60-second time period (Goodglass & Kaplan, 1983).

The Trailmaking Test (TMT; Amy Individual Test Battery, 1944) was used as a gross measure of attention and executive functioning. The TMT has two parts. Part A, which requires subjects to connect, in order, 25 encircled numbers spread randomly about a white piece of paper as quickly as possible, measures visual scanning, speed, and attention. Part B, in which subjects are required to connect 25 alternating numbers and letters as quickly as possible, is thought to tap into mental flexibility with a motor component or concept alternation, considered to be an aspect of executive functioning. If subjects make an error during performance of either Part A or Part B, they are corrected by the examiner. Total time in seconds for Part A and total time for Part B are the two dependent variables derived from this examination.

Data analysis. Group differences in outcome measures, including marital status, occupational status, and current residency status were compared with Pearson Chi-squared analysis. The mean number of psychiatric hospitalizations was compared between the two groups with t-tests.

For analysis of symptom severity and neuropsychological test performance, Kraepelinian and non-Kraepelinian patients were compared with one multivariate analysis of covariance (MANCOVA), controlling for years of education, which was significantly different between the two groups. Dependent measures included PANSS positive and negative scores, all CVLT measures, number of unique animals named, and time on the TMT parts A and B. Follow-up multivariate one-way corrected analyses of variance (ANOVA) were conducted for the PANSS and neuropsychological battery.

A discriminant function analysis was used to determine the relative importance of the cognitive dependent measures for discrimination of Kraepelinian and non-Kraepelinian patients. This analysis examines whether cognitive performance measures,

aspects of the illness that are not part of the intrinsic definition of Kraepelinian status, but are related to outcome, discriminate these two patient groups. The cognitive variables that were significantly different across the two group in the MANCOVA were entered into a discriminant function analysis with the entry criterion set at $p<0.05$. Canonical correlations and positive and negative predictive power was calculated. Both simultaneous and stepwise entry procedures were used.

Similarly, neuropsychological measures and clinical variables on which the two patient groups differed were entered together in a discriminant functions analysis to classify Kraepelinian status.

To determine whether Kraepelinian status represents a unique outcome measure, discriminant function analyses were used with all of the patients and all of the cognitive measures to predict occupational status and current residency status. These functional status variables were chosen because they are common measures of patient outcome in schizophrenia and they are subsumed under the Kraepelinian classification scheme. If Kraepelinian status is indeed a unique construct, its neuropsychological predictors would differ from predictors of other measures of functional outcome.

MRI Procedures (Studies 2 and 3)

Image acquisition. The 1.5 T Signa 5x system (GE Medical Systems, Milwaukee, WI) with a 3D-SPGR sequence (TR=24 ms, TE=5 ms, flip angle=40° and slice thickness=1.22 mm, matrix size 256 x 256, total slices=128) was used for T_1-weighted image acquisition. MR images were adjusted along the anterior commissure – posterior commissure (AC-PC) axis using semiautomatic procedures. All participants were scanned on the same MRI machine with the identical protocol. Each MR image was

screened by a neuroradiologist, and subjects with significant brain pathology (e.g., evidence of stroke) were excluded from analyses.

Sobel-gradient filtration. For manual tracings of all subcortical nuclei and lateral ventricles, a Sobel-gradient filter is applied to the raw MR image. The filter maximizes contrast points between matter types (e.g., between grey and white matter) and ensures accurate and reliable tracings of the regions of interest (e.g., Brickman et al., 2003). Subcortical regions of interest are traced by manually depositing points on the enhanced edge with a semi-automated 3 x 3 local pixel maximum search. Specific procedures and examples are described in greater detail below.

Study 2 Procedures

Manual tracing of the thalamus. Thalamus tracing took place in the axial orientation. The top and bottom of the thalamus were determined as the most dorsal axial slice showing a visible grey patch and the most ventral extent of the entire structure, respectively. The distance between the two slices was divided by six to produce five equally spaced slices considered for analysis, as has been done previously with caudate and putamen (Buchsbaum et al., 2003). After application of the Sobel-gradient filter, the thalamus was manually traced at each of the five levels in each hemisphere by depositing outlining points around the structure (see Figure 9) at each of the five slices. Figure 10 displays a 3-dimensional representation of the five dorsal to ventral tracings. The size of the thalamus was determined by automatic summation of the pixels contained within each outlined border. Interrater reliability for manual tracing of the thalamus has been established in a report by Byne and colleagues (2001; intraclass correlation coefficient [ICC] = 0.83).

Brodmann area measurements and quantification of tissue type. Brodmann area localization is based on an unpublished coronal atlas provided by Perry (unpublished). The atlas is composed of 33 axial Brodmann area maps determined by microscopic examination of a single hemisphere of a postmortem brain. Coronal images, perpendicular to the AC-PC line, were examined; the most anterior slice (i.e., first slice containing cortical ribbon) and most posterior slice (i.e., last slice containing cortical ribbon) were identified; and 33 equidistant slices were selected for analysis. For temporal lobes, the temporal pole and the most posterior extent of the sylvian fissure were chosen as the most anterior and posterior regions, respectively, and the structure was divided into 13 equally spaced slices. Figure 11 displays a mid-cerebral Brodmann area map superimposed on a 3-dimensional rendering of the brain. The brain edge was obtained on the approximately circular 33 nontemporal and 26 (13 in each hemisphere) temporal slices by depositing points visually on the tips of the gyri and then fitting a spline curve to the points. Each slice was then divided into 10 midline sectors and 20 radial sectors in each hemisphere.

For grey matter, white matter, and CSF segmentation and quantification, within-brain-edge histograms of axial MRI values were visually examined, and thresholds for each matter type were determined by using cut-off points. All subjects had points of rarity separating each matter type in each matter type. Grey matter, white matter, and CSF values were determined by automatic summation of pixels corresponding to each matter's threshold value in each of the cortical Brodmann areas. Four methods used to validate this approach are described in detail in Mitelman et al. (2003). Briefly, ICCs were calculated by comparing two independent tracers assessment of grey matter, white matter, and CSF; interrater reliability was high (0.98, 0.99, and 0.92, respectively).

Second, a correlation coefficient of 0.87 was obtained when comparing visually-counted grey matter volume to automatically-determined grey matter volume. Third, grey matter, white matter, and CSF volume was compared between right and left hemispheres; ICCs were 0.85, 0.74, and 0.86, respectively. Finally, a subset of scans from participants who had two MRIs at 4 to 6 week intervals was examined for test-retest reliability using thresholds obtained from the first scan only. This conservative approach yielded ICC values of 0.88, 0.75, and 0.77 for gray matter, white matter, and CSF volume, respectively.

For the purposes of the current study, we determined absolute and relative size of the frontal and temporal lobe grey and white matter. For frontal lobe, we combined grey and white pixels separately for Brodmann areas 44, 45, and 46. For temporal lobe, we combined grey and white matter pixels separately for Brodmann areas 20, 21, and 22. Cortical size was corrected for whole brain volume by taking the ratio of each region to whole brain volume (e.g., frontal lobe white matter/whole brain volume).

Data analysis. Repeated-measures ANOVAs were used to examine the size of the thalamus. As total brain size differed at a trend level ($p=0.067$) between schizophrenia patients and normal controls, both absolute and relative thalamic size were considered for analysis. Absolute size was computed in cubic millimeters and relative size as the ratio of area of ROI/total brain size. Total brain size was calculated by summing the area of 61 contiguous coronal edges. For these analyses, Diagnostic group (2: schizophrenia versus normal control or non-Kraepelinian versus Kraepelinian) was a between-subjects variable, while Hemisphere (2: left, right) and Slice (5: most ventral to most dorsal) were within-subjects variables. Follow-up simple interactions and pairwise post hoc tests were used to identify the greatest source of variance for

significant interactions involving Diagnosis. Pearson product moment correlational analyses were conducted between relative thalamic size at each slice level (collapsed across hemispheres) and relative frontal lobe and temporal lobe grey and white matter volumes. Exploratory analyses between dorsal and ventral thalamic size and sex, age at which the patient was first treated, duration of neuroleptic treatment, and PANSS positive, negative, and general scores in all schizophrenia patients grouped together were conducted.

Study 3 Procedures

Manual tracing of the anterior limb of the internal capsules. The left and right anterior internal capsules were manually traced in the axial plane on five dorsal-to-ventral equidistant levels. The five slices were determined based on anatomy of the striatum, following Buchsbaum and colleagues (2003). Briefly, the most ventral and most dorsal slices containing the putamen were selected. The most ventral aspect was defined as the slice in which the caudate and putamen were entirely merged. The most dorsal slice was defined as that in which the putamen was no longer visible. The number of slices between the most dorsal and most ventral slices was divided by 6 to yield five equally spaced slices for tracing. The internal capsule was traced on the five slices corresponding to the five equidistant spaced slices of putamen.

The tracing protocol was developed after consultation with a neuroanatomist, expert in cerebral white matter, with the intent of maximizing consistent measurements across subjects while capturing fibers restricted to the anterior limb of the internal capsule region. Four manually-inserted landmarks were used to create the "corners" of a polygon containing the fibers of the internal capsule. For each hemisphere, a landmark was placed on the most lateral anterior part of the caudate nucleus to define

the anterior medial corner of the internal capsules. A landmark was placed on the most medial anterior part of the putamen to define the anterior lateral corner of the internal capsule. For the more posterior medial and lateral corners, a landmark was placed on the most posterior part of the caudate nucleus, and one was placed on the most medial aspect of the putamen, respectively. An automatic boundary-finding method based on the Sobel-gradient filter, allowed for maximization of grey/white matter contrast for accurate placement of the landmarks on the borders between the striatum and internal capsules. Figure 12 displays an example of placement of the landmarks on the five equidistant slices.

An automatic computer program developed by M.S. Buchsbaum, M.D., was used to compute the area of the internal capsule at each slice, by counting pixels with the polygon formed by the four landmarks. A three-dimensional reconstruction of the internal capsule is displayed in Figure 13.

Manual tracing of the striatum and lateral ventricles. The top, most dorsal, and bottom, most ventral, levels of the caudate and putamen were selected separately for each structure, as described above. Five equidistant slices of the striatum were chosen for manual tracing in the right and left hemisphere. Manual tracing procedures for the striatum were identical to the procedures employed for thalamus tracings. Intraclass correlation coefficients of 10 subject traced by two independent raters were 0.92 and 0.98 for the caudate and putamen, respectively. The lateral ventricles were traced as described in Shihabuddin et al. (in preparation) and above, in the Preliminary Studies section. Two independent tracers outlined the lateral ventricles in eight subjects; the ICC for size was 0.98.

Data analysis. We first calculated a summary volume of the ventral three and dorsal two slice areas multiplied by slice thickness to yield absolute volumes in cubic millimeters for the in the left and right hemispheres. Data were entered into a repeated-measures ANOVA with Group (3: non-Kraepelinian, Kraepelinian, Normal Control) as a between-subjects factor and Level (2: ventral, dorsal) and Hemisphere (2: left, right) as repeated measures. The analyses were run with and without total brain volume as a covariate. Follow-up simple interactions and pairwise post hoc tests were used to identify the greatest source of variance for significant interactions involving Diagnosis.

Pearson product moment correlation coefficients were calculated to examine the relationship between left and right dorsal and ventral internal capsule size *and* the size of the lateral ventricles, caudate, putamen, and thalamus.

Exploratory analyses between dorsal and ventral size *and* sex, age at which the patient was first treated, duration of neuroleptic treatment, and PANSS positive, negative, and general scores, in all schizophrenia patients grouped together were conducted.

CHAPTER THREE

Results

Study 1

Distribution of outcome measures for the two patient groups are displayed in Table 3. There were no significant differences in marital status ($\chi^2(2)= 2.07$, $p = 0.15$) or employment history ($\chi^2(2)= 4.47$, $p = 0.12$) between the non-Kraepelinian and Kraepelinian patients. Thus, even non-Kraepelinian patients were likely to have minimal histories of adequate social or occupational functioning. As expected, the Kraepelinian patients, on average, had significantly more psychiatric hospital admissions ($t(48) = 2.77$, $p = 0.008$) and were more likely to live in residencies with greater supervision ($\chi^2(4) = 19.02$, $p < 0.001$) than non-Kraepelinian patients.

Fifty percent of the Kraepelinian patients resided in an inpatient (institutional) setting, while all of the non-Kraepelinian patients were outpatients. First, to assess whether differences between Kraepelinian and non-Kraepelinian patients were due to differences in current residency, Kraepelinian patients were compared across residency status (i.e., inpatient versus outpatient) on all neuropsychological measures and the PANSS. The overall MANOVA was not significant (Wilks' Lambda = 0.101, $F(19, 6) = 2.80$, $p = 0.10$). Furthermore, inpatient and outpatient Kraepelinian patients did not differ in age ($t(24) = 0.216$, $p = 0.83$), years of education ($t(24) = -0.512$, $p = 0.61$), or duration of illness ($t(23) = -0.485$, $p = 0.63$). Therefore, for all subsequent analyses the inpatient and outpatient Kraepelinian patients were examined as a single group.

The overall MANCOVA comparing non-Kraepelinian and Kraepelinian patients on the neuropsychological and symptom severity measures was statistically significant (Wilks' Lambda = 0.34, $F(19, 30) = 3.01$, $p = 0.003$). Multivariate corrected tests of

between-subjects effects indicated that Kraepelinian patients had several aspects of their functioning that were significantly ($p<0.05$) more impaired than non-Kraepelinian patients. Kraepelinian patients had more severe positive and negative symptoms and scored significantly lower than non-Kraepelinian patients on most neuropsychological measures, including CVLT list A learning trial 1, list A learning trial 5, total list A learning over 5 trials, total learning on list B, intrusive errors on free recall and cued recall trials, total intrusive errors, and TMT part B. Kraepelinian patients performed better than non-Kraepelinian patients on category fluency. Table 4 displays scores and multivariate one-way corrected analyses of variance for the PANSS and neuropsychological battery.

When neuropsychological variables that were significantly different between the groups were entered into a discriminant function analysis simultaneously, 40% of the variance in group membership was accounted for (canonical correlation = 0.63) and 79% of the patients were correctly classified. For this analysis, positive predictive power (e.g., the percentage of individuals classified as Kraepelinian who in fact were Kraepelinian) was 78%, and negative predictive power (e.g., the percentage of individuals classified as non-Kraepelinian who in fact were non-Kraepelinian) was 80%. When the discriminant function analysis was repeated with a stepwise entry procedure to determine the order of importance for the predictive variables discriminating the two groups a two-step function emerged. CVLT recall intrusions entered at the first step and CVLT list A trial 5 learning entered at the second step.

When neuropsychological measures and clinical variables on which the two patient groups differed were entered together in a discriminant function analysis to classify Kraepelinian status, simultaneous entry accounted for 70% of the variance

(canonical correlation=0.83), correctly classifying 96% of the patients. Positive predictive power and negative predictive power were 100% and 92%, respectively. When the analysis was rerun using a stepwise entry method, PANSS negative subscale scores, CVLT recall intrusions, current residency status, and PANSS positive subscale scores, in order, entered into the equation, accounted for 64% of the variance (canonical correlation=0.80).

For occupational status, which was dichotomized into *never employed* versus *ever employed*, 48% (canonical correlation = 0.69) of the variance was accounted for by the neuropsychological measures, with 90% of the patients correctly classified. No neuropsychological variables qualified for the analysis using a stepwise entry method.

For residency status, which was dichotomized into *living independently* (i.e., alone or with family members) versus *living dependently* (i.e., group home or institution), 50% (canonical correlation = 0.71) of the variance was correctly accounted for by the neuropsychological measures, and 90% of the patients were correctly classified. When stepwise entry method was used, CVLT short delay free recall and CVLT short delay cued recall, respectively, entered the model significantly.

Study 2

Relative thalamic size. When schizophrenia patients were compared to normal controls, there were no significant interactions or a main effect involving Diagnostic Group.

When non-Kraepelinian and Kraepelinian patients were compared, there was an interaction between Diagnostic Group and Slice Level ($F(4, 416) = 7.377$, $p=0.00001$), indicating a double-dissociation pattern: at the two most ventral levels, Kraepelinian patients had smaller thalami than non-Kraepelinian patients, while at the two most

dorsal levels, Kraepelinian patients had larger thalami than non-Kraepelinian patients. Post hoc analyses between the two patient groups did not reach statistical significance. Kraepelinian patients had smaller right but similar sized left thalami than non-Kraepelinian patients (Diagnostic Group by Hemisphere interaction, $F(1, 104) = 11.785$, $p=0.00086$). No other significant effects involving Diagnostic Group were statistically significant.

Absolute thalamic size. When schizophrenia patients were compared to normal controls, the patient group had smaller thalami at the two most ventral levels and larger thalami at the two most dorsal levels than normal controls (Diagnostic Group by Slice interaction, $F(4, 584) = 3.47$, $p = 0.0082$; see Figure 14).

When non-Kraepelinian and Kraepelinian patients were compared, Kraepelinian patients had significantly smaller thalami than non-Kraepelinian patients (main effect of Diagnostic Group, $F(1, 104) = 6.22$, $p = 0.014$), particularly at the three most ventral levels (Diagnostic Group by Slice Level interaction, $F(1, 104) = 12.13$, $p = 0.0007$; see Figure 15). Neuroleptic treatment at the time of scan (i.e., none, typical, atypical, or both) did not significantly affect thalamic size (main effect of Neuroleptic Status, $F(3, 78) = 0.46$, $p = 0.70$). Similarly, predominant neuroleptic for the three-year period prior to scan acquisition had no significant effects (main effect of Neuroleptic Status, $F(3, 78) = 0.33$, $p = 0.81$; Diagnostic Group by Neuroleptic Status, $F(3, 78) = 2.08$, $p = 0.11$).

When the three groups (Kraepelinian, non-Kraepelinian, and normal controls) were included in the same analysis, there was a significant Diagnostic Group by Slice interaction ($F(8, 580) = 7.32$, $p < 0.0001$). As can be seen in Figure 16, the most robust thalamic reductions were in ventral slices in Kraepelinian patients compared to non-Kraepelinian patients and normal controls. Dorsal differences were not as robust;

Kraepelinian patients had similar dorsal aspects of thalamus as normal controls, whereas non-Kraepelinian patients had reduction compared to the other two groups.

Clinical correlates of thalamic volume. For ventral thalamus, significant correlations were obtained with PANSS positive ($r(77) = -0.25$, $p<0.05$), PANSS general ($r(77) = -0.24$, $p<0.05$). For dorsal thalamus, there was only a significant correlation found with PANSS positive scores ($r(77) = -0.22$, $p<0.05$). There were no significant correlations with age, sex, or duration of treatment. When considered separately, correlations between dorsal thalamus volume and PANSS positive scores ($r(43) = -0.34$, $p<0.05$) in the non-Kraepelinian group and between dorsal thalamus volume and PANSS negative scores ($r(36) = 0.33$, $p<0.05$) in the Kraepelinian patients reached statistical significance. Other comparisons were not statistically significant, although the effect sizes were similar to the overall group correlations.

As the largest group differences in thalamus size were seen in right ventral thalamus, we explored correlations between dorsal and ventral thalamus on the right side and the clinical variables described above in the Kraepelinian patients only. There was a significant positive association between right ventral volume and PANSS negative scores ($r(36) = 0.34$, $p<0.05$). Further, larger right ventral thalamus was associated with a later onset of treatment ($r(36) = 0.33$, $p<0.05$) and with a shorter duration of treatment ($r(36) = -0.33$, $p<0.05$). Correlations between right dorsal thalamus and clinical measures did not reach statistical significance.

There were no significant associations between dorsal or ventral thalamus volume and type of neuroleptic exposure at the time of scan or for the majority of time over the three-year period prior scan acquisition for either schizophrenia group alone or when considered together.

Correlations with other brain regions. There was a tendency for larger frontal grey matter to be associated with larger dorsal thalamic areas while larger temporal grey matter was associated with larger thalamic areas, at least for slices 2-4 (see Table 4).

Study 3.

Relative internal capsule size. With total brain volume as a covariate, neither the main effect of Diagnostic Group ($F(1, 145) = 0.458$, $p = 0.50$) nor the Diagnostic Group by Level interaction ($F(1, 145) = 2.37$, $p = 0.12$) reached statistical significance when the schizophrenia patients were considered together and compared to normal controls. Similarly, when the Kraepelinian and non-Kraepelinian patients were contrasted, neither the main effect of Diagnostic Group ($F(1, 103) = 0.036$, $p = 0.85$) nor the Diagnostic Group by Level interaction ($F(1, 103) = 3.11$, $p = 0.080$) were statistically significant. Total brain volume entered significantly into both models ($F(1, 145) = 19.45$, $p = 0.000020$ and $F(1, 103) = 18.26$, $p = 0.000043$, respectively).

However, when the three groups were considered together, the dorsal internal capsule was smaller in Kraepelinian patients than in non-Kraepelinian patients and normal controls, but larger than the other two groups at the ventral level (significant Diagnostic Group by Level interaction, $F(2, 144) = 3.15$, $p = 0.046$; see Figure 17). Brain volume entered the statistical model as a significant covariate ($F(1, 144) = 17.90$, $p = 0.000042$). These findings suggest subtle shape differences in the internal capsule among the three groups. To explore this possibility further, absolute size of the internal capsule across the five dorsal-to-ventral levels as a function of diagnostic group was examined.

Absolute internal capsule size. For this analysis, a Diagnostic Group (2: schizophrenia, normal control) by Hemisphere (2: L,R) by Slice Level (5: ventral to dorsal) repeated-measures ANOVA was run. Again, the main effect of Diagnostic

Group ($F(1, 146) = 2.21$, $p = 0.140$), the Diagnostic Group by Slice Level interaction ($F(4, 584) = 1.14$, $p = 0.337$), the Diagnostic Group by Hemisphere interaction ($F(1, 146) = 3.15$, $p = 0.078$), or the three-way interaction ($F(4, 584) = 1.93$, $p = 0.103$) were not statistically significant.

When non-Kraepelinian patients were contrasted with Kraepelinian patients, Kraepelinian patients had significantly smaller internal capsules than non-Kraepelinian patients (main effect of Diagnostic Group, $F(1, 104) = 9.59$, $p = 0.0025$); this main effect was modified by a significant Diagnostic Group by Slice Level interaction ($F(4, 416) = 3.235$, $p = 0.0124$), which indicated that internal capsule reduction in the Kraepelinian group was most pronounced at the three most dorsal levels (see Figure 18). Follow-up analyses confirmed that the two groups differed significantly at the two most dorsal levels ($p = 0.047$ and $p = 0.043$, respectively).

When the three groups were entered into the ANOVA together, there was a significant main effect of Diagnostic Group ($F(2, 145) = 6.25$, $p = 0.0024$) and a significant Diagnostic Group by Slice Level interaction ($F(8, 580) = 2.200$, $p = 0.026$; see Figure 19). Follow-up analyses for the significant main effect of Diagnostic Group revealed that Kraepelinian patients had smaller internal capsules than non-Kraepelinian patients ($p = 0.0018$) and normal controls ($p = 0.0053$), but non-Kraepelinian patients and normal controls were similar to each other ($p = 0.862$). Follow-up analyses for the significant interaction demonstrated that Kraepelinian patients had smaller internal capsules than non-Kraepelinian patients at the two most dorsal levels (as above) and at the most dorsal level ($p = 0.019$) when compared to normal controls. Non-Kraepelinian patients and normal controls were similar ($p > 0.05$) at all five levels.

Clinical correlates of internal capsule volume. Relative (to whole brain volume) internal capsule size did not significantly correlate ($p>0.05$) with age, age at first neuroleptic exposure, type of neuroleptic at time of scan or for the three year period prior to scan acquisition, PANSS scores, or sex when all of the schizophrenia patients were considered together. When the two schizophrenia patient groups were considered separately, there was a significant negative association between age at scan and internal capsule size at the most dorsal level ($r(24) = -0.43$, $p<0.05$) in the Kraepelinian group. In the non-Kraepelinian group, male subjects tended to have larger relative internal capsules in the middle slice ($r(35) = 0.47$, $p<0.05$) and there was a significant positive association between the size of the most ventral slice of the internal capsule and age of commencement of neuroleptic treatment (a correlate of age of onset).

As differences between groups tended to vary as a function of ventral-to-dorsal slice level, ratio scores of the three most ventral slices to the two most dorsal slices were calculated for comparisons with the clinical variables. When the two schizophrenia patient groups were combined, the only significant association to emerge was a positive one between the ratio score and age of commencement of neuroleptic treatment ($r(84) = 0.28$, $p < 0.05$). Correlation coefficients between the ventral/dorsal ratio scores and the clinical measures did not reach statistical significance for either of the two patient groups when analyzed separately.

Correlations with other brain regions. Correlation coefficients were examined between average size of the ventral and dorsal levels of the internal capsules and average size of subcortical nuclei, lateral ventricles, and cortical regions. Subcortical nuclei included thalamus, caudate and putamen; average values (collapsed across hemisphere) were calculated for each of the five ventral to dorsal slices for each nucleus.

Correlations were conducted, controlling for whole brain volume. Relationships were examined for normal controls, all schizophrenia patients together, and each of the schizophrenia subtypes separately.

For the thalamus (see Table 6), significant positive associations emerged between dorsal internal capsule and the most ventral and the most dorsal thalamus size in normal controls. In the entire schizophrenia sample, ventral internal capsule size was significantly positively associated with the second most dorsal level (slice 4) of the thalamus. In non-Kraepelinian patients, this pattern emerged for the two most dorsal levels of thalamus. However, in the Kraepelinian patient group, there were no significant associations between internal capsule size and thalamus size; qualitative examination of the effect sizes in this group revealed coefficients close to zero.

For the caudate nucleus (see Table 7), significant positive associations were observed between ventral internal capsule and the second most ventral level (slice 2) and second most dorsal level (slice 4) and between the dorsal internal capsule and second most ventral level (slice 2) in the normal control group. In the schizophrenia group, there was a significant positive association between ventral internal capsule and the middle caudate slice, a pattern that was similar in the Kraepelinian group, but not in the non-Kraepelinian group. Of note, however, the two correlation coefficients for that association did not significantly differ ($p=0.59$) between the two schizophrenia patient groups with Fisher's Z test.

For the putamen (see Table 8), several significant associations emerged. First, ventral internal capsule size was positively correlated with the second most ventral level of putamen (slice 2) in normal controls. A negative association emerged between the dorsal internal capsule and the most ventral level of putamen, but the associations with

the next two levels (slices 2 and 3) were positive. In the schizophrenia group, both the ventral and dorsal internal capsule was positively associated with the middle putamen level (slice 3). For the non-Kraepelinian group, there was a significant positive association between the dorsal internal capsule and the second most ventral level (slice 2), whereas in the Kraepelinian group, there was a positive association between ventral internal capsule and the middle putamen slice.

Several significant negative associations emerged for the ventricles (see Table 9). In normal controls, there were significant correlations between both dorsal and ventral internal capsules and anterior horn, temporal horn, and lateral aspects of the ventricles. In the combined schizophrenia group, only the association between dorsal internal capsule and the size of the anterior horn was statistically significant. In the non-Kraepelinian group, the dorsal internal capsule was associated with anterior horn and lateral ventricular size. No significant associations emerged in the Kraepelinian group.

There were no significant correlations between ventral or dorsal internal capsule and frontal or temporal grey and white matter size in any of the study groups (see Table 10).

CHAPTER FOUR

Discussion

Study 1.

Three important findings emerged from the current study. First, Kraepelinian patients demonstrated a unique and more severe neuropsychological profile than non-Kraepelinian patients. Second, the addition of neuropsychological predictors to measures of symptom severity resulted in close to 100% accuracy in classification of Kraepelinian status. Finally, neuropsychological and clinical predictors of Kraepelinian status utilized in this study were different from predictors of more traditional outcome measures subsumed under the classification system. Taken together, these findings support the validity of the Kraepelinian/non-Kraepelinian distinction and highlight the unique contribution of neuropsychological functioning to this classification system.

Both subtypes of schizophrenia patients performed significantly worse on all neuropsychological measures than would be expected by healthy individuals. Kraepelinian patients exhibited greater impairment on measures of episodic learning and memory, as well as executive functioning compared to non-Kraepelinian patients. Specifically, they performed worse on most indices of the CVLT, which assesses verbal encoding, retrieval, recognition, and the executive aspects of strategy formation (Lezak, 1994). The largest effect sizes on the CVLT for differences between the groups were seen on measures of intrusions, learning over multiple trials, and short delay free recall. These findings suggest that Kraepelinian patients have particular impairment in areas of inhibition or filtration of relevant stored information, encoding of new material, and retrieval strategies. That cued memory and recognition memory measures were not significantly different between the two groups suggests similarly affected memory

storage systems. Additionally, Kraepelinian patients were more impaired on part B of the Trailmaking test, which examines cognitive abilities such as visual scanning, motor speed and agility, attention (Lezak, 1994), and aspects of executive functioning (Spreen & Strauss, 1998). The two groups did not differ on part A of the task, suggesting similarly affected visual motor tracking and sustained attention. Thus, the differences on part B are most likely attributable to more severe executive functioning in the Kraepelinian group.

Interestingly, Kraepelinian patients performed better on the task of category fluency when educational status was considered as a covariate. This finding was most likely due to the strong influence of education on verbal fluency performance (e.g., Brickman et al., submitted), as Kraepelinian patients performed worse on this task when scores were not education-corrected. Further, differences between the Kraepelinian and non-Kraepelinian patients were not due to residency status, as institutionalized Kraepelinian patients in this study did not significantly differ from non-Kraepelinian patients on neuropsychological, symptom or demographic measures.

The findings that cognitive deficits on the part of Kraepelinian patients were not detected on every measure suggests that the differences between the two samples were not due to some generalized performance deficit or to noncognitive factors, such as poor motivation or test anxiety. Instead, they are consistent with the idea of specific brain abnormalities in the Kraepelinian group. These data support the hypothesis of greater frontal and temporal lobe abnormalities, which subserve functioning in the cognitive domains of executive functioning and memory, respectively. Indeed, recent structural neuroimaging studies in schizophrenia have suggested that the size of frontal lobe areas, particularly the dorsolateral prefrontal cortex, correlate significantly with tasks of

executive functioning (Gur et al., 2000; Seidman et al., 1994; Szeszko et al., 2000; see Antonova, Sharma, Morris, & Kumari, in press, for review). Further, the neuropsychological pattern seen in the Kraepelinian patients is similar to the profile observed in subcortical dementias, such as Huntington's disease (Paulsen et al., 1995). This profile is characterized by worse performance on measures of free recall than on measures of recognition or cued memory.

In terms of clinical and demographic differences, Kraepelinian patients had significantly worse positive and negative symptomatology than non-Kraepelinian patients. This finding is in contrast to earlier studies (Keefe et al., 1987; Keefe et al., 1988), which reported worse negative, but not positive, symptomatology in Kraepelinian patients. Inconsistencies with earlier studies are most likely due to the fact that all subjects in the previous studies (Keefe et al., 1987; Keefe et al., 1988) were inpatients at the time of assessment; hospitalization of non-Kraepelinian patients was most likely due to acute positive symptoms rather than an exacerbation of negative symptoms. Further, Kraepelinian patients had significantly less education than non-Kraepelinian patients, but similar ages of onset, which was indexed by the age of the first identifiable acute psychotic episode. Thus, it is possible that Kraepelinian patients discontinued formal education prior to their first episode as a result of some prodromal process already operative prior to meeting formal diagnostic criteria for the illness. As would be expected by the nature of the classification system, Kraepelinian patients were more likely to be inpatients and had significantly more psychiatric admissions than non-Kraepelinian patients.

When considered separately, cognitive variables were able to correctly classify almost 80% of the patients. Stepwise analyses revealed that reduced initial list learning

and errors of intrusion on the CVLT were the most powerfully predictive neurocognitive discriminators. Again, this finding supports the hypothesis of more impaired frontal and temporal lobe systems in Kraepelinian patients by demonstrating that cognitive processes mediated by these systems are the most salient predictors of Kraepelinian status. Further, neurocognitive profile analysis is not part of the Kraepelinian versus non-Kraepelinian diagnostic criteria, but is clearly central to functional outcome.

Demographic and symptom severity ratings were slightly better predictors of Kraepelinian status than cognitive performance, correctly classifying 85% of the patients. However, it is important to note that several of the variables in these analyses were subsumed under the definition of Kraepelinian status. For example, occupational status, residency status, and PANSS scores overlap with employment, maintenance of independent living, and remission Kraepelinian criteria (Keefe et al., 1987). Despite being compared to classification accuracy of variables that were part of the criterion for Kraepelinian status, cognitive functioning still produced high levels of correct classification of patients. While these findings suggest that overall severity of illness is the most salient predictor of overall functional status, they also highlight the important covariate of neurocognitive functioning. The dichotomous classification of Kraepelinian versus non-Kraepelinian outcome may be most useful in accounting for the great heterogeneity seen in functional status of schizophrenia patients. Whether the two patient groups have differing functional course over time, which would provide stronger evidence for differing etiologies, remains to be determined with well-controlled longitudinal studies.

This study replicates the findings of Roy and colleagues (2003) who reported significant differences in neuropsychological test performance between Kraepelinian

and non-Kraepelinian patients. Identical to these investigators, we found that 79% of the participants can be correctly classified as Kraepelinian or non-Kraepelinian based on significant neuropsychological variables. We extend these findings to demonstrate that with the addition of clinical measures of psychopathology, even greater diagnostic classification accuracy can be achieved. The findings are also consistent with Green's reviews (Green, 1996; Green et al., 2000) that have implicated neurocognition in the prediction of functional outcome in schizophrenia and add to our existing knowledge of difference between Kraepelinian and non-Kraepelinian patients. Given that Kraepelinian patients have a different course (Davis et al., 1998; Friedman et al., 2001), are significantly less responsive to treatment (Harvey et al., 1991), and have a more severe cognitive deficit profile than non-Kraepelinian patients, the possibility exists that a proportion of schizophrenia is due to an etiology marked by neurodegeneration.

There are some limitations in the study that require discussion. The current study supports the idea that neurocognitive functioning can predict, or account for, a significant amount of variance in functional outcome at one time point. However, it did not address the question of whether neurocognitive deficits can predict future poor functional outcome. These initial cross-sectional data will provide important baseline data for future longitudinal analyses on the same cohort to address this issue. Further, although the current study employed neropsychological measures that have not been previously used to study Kraepelinian and non-Kraepelinian patients specifically, the battery was still limited in its scope. For example, although the Trailmaking test provides a useful estimate of executive function, the Wisconsin Card Sorting Task (Heaton, 1981) is a more common, and perhaps sensitive and specific, test of executive functioning in schizophrenia (Green et al., 2000). The battery did not include a formal

test of sustained attention and working memory, functions which have also provided useful data in schizophrenia functional outcomes research (Green et al., 2000); future work in this area should clearly include measures in these important neurocognitive domains. Similarly, it did not include an assessment of gross or fine motor skill. Another limitation of the current study is the relatively small sample size. However, the findings of the study were statistically robust. That is, the effect size of the MANCOVA examining symptom and cognitive differences between the groups was large by most standards (d=0.63). Finally, information regarding intercurrent illness was limited for the current cohort and possible confounding influences of this factor was not examined. Of note, however, is that most of the Kraepelinian patients were residents in long-stay facilities. As such, their nutritional and health status were closely monitored and their poorer outcome was therefore less likely to be attributable to secondary health factors. Individuals with unstable medical conditions or neurological disease thought to interfere with brain functioning were not included in the study. Furthermore, the potential contribution of anticholinergic or psychotropic treatment was not considered. It is unlikely that Kraepelinian patients differed from non-Kraepelinian patients in terms of anticholinergic treatment or that differences in medication could account for the large effect size differences in neuropsychological test performance. Future efforts in examining neuropsychological functioning in these two groups of patients should clearly consider the effects of medication.

Future research should focus on analysis of longitudinal change of neuropsychological test performance to assess whether there is indeed a deteriorating course in Kraepelinian patients, but not non-Kraepelinian patients. Our data suggest that many of the Kraepelinian patients who were fully dependent on others for the past

5 years had better functioning previously, as indexed by a history of previous employment that is no different from the non-Kraepelinian patients. These data may suggest functional decline after the onset of illness. Several longitudinal studies have found no evidence for significant changes in cognitive test scores in largely ambulatory patients, often (Gold et al., 1999; Hoff et al., 1999), but not always (Heaton et al., 2001), early in the course of their illness. Kraepelinian patients (i.e., those expected to decline) are most likely underrepresented in those studies and studies that have focused on ambulatory patients. One recent longitudinal study included only schizophrenia patients who would have met Kraepelinian criteria and found a dramatic drop in global cognition over a 6-year follow-up period beginning at around age 70 (Friedman et al., 2001). These findings suggest that Kraepelinian patients may show a deteriorating cognitive course, detectable in relatively brief (6-year) follow-ups only in later life. That study, however, cannot address the question of whether more subtle longitudinal cognitive changes in poor-outcome schizophrenia occur earlier in life and whether these potential changes would predict the sudden and rapid decline in global cognition during the later years. Indeed, the cohort of Kraepelinian patients, with non-Kraepelinian patients as a control group, in the current study is being followed longitudinally to answer such questions.

Study 2

Because of marked attentional and sensory-perceptual disturbances characteristic of schizophrenia, the thalamus has been implicated as a central structure in its underlying pathophysiology. This theory is in line with the conceptual role of the thalamus as a gatekeeper of information flow to and from relevant areas of the cortex (Jones, 1997). However, as several lines of investigation have implicated other brain

regions, including frontal lobe (e.g., Buchsbaum et al., 1982; Goldman-Rakic & Selemon, 1997; Ingvar, 1974), temporal lobe (e.g., Shenton et al., 2001), and striatum (e.g., Shihabuddin et al., 1998; Shihabuddin et al., 2001), it is most likely that the thalamus is but one of several structures implicated in dysfunctional schizophrenia-associated subcortical-cortical circuitry. In fact, the interconnection among the implicated regions suggests that the function of one must be considered together with the function of the others.

Some studies have shown reduction in size in the thalamus in schizophrenia patients compared to matched normal control comparison subjects (Andreasen et al., 1994; Gur et al., 1998), whereas others (Arcineagas et al., 1999; Deicken et al., 2002; Hazlett et al., 1999; Portas et al., 1998) have not. The results from the current study found that schizophrenia patients do not have overall reduced absolute or relative thalamic size compared to normal comparison subjects (i.e., no main effect of Diagnostic Group). Reported negative findings of thalamic size reduction in schizophrenia could be due to specific level or nucleus dysfunction, which is not evident when the entire thalamus is considered as a whole. That is, there may be insufficient power and insufficient sensitivity to detect a small expected effect when only a single thalamic level or whole thalamus is traced (Konick & Friedman, 2000). This idea was supported by our finding of a significant Diagnostic Group by Slice Level interaction, which showed that schizophrenia patients do have reduced thalamic size at more ventral levels of thalamus.

The reduction of more ventral aspects of the thalamus implicated thalamo-temporal dysfunction. Indeed, correlational analyses demonstrated an association of larger frontal grey matter with larger dorsal thalamic areas while larger temporal grey matter was associated with more ventral thalamic areas, consistent with significant

differences in the extent of reciprocal interconnections between the two areas. The assessment of the volume in the thalamus and the cortex was done two entirely independent ways and on geometrically different (axial and coronal) slices and, thus, could not be related to a tracer bias or to systematic signal intensity differences along an axis.

An alternative explanation of the finding of reduced ventral aspects of thalamus in Kraepelinian patients and in all patients compared to controls is the possibility of thalamic *shape* differences among the groups. Schizophrenia patients as a group had slightly larger thalami at more dorsal levels than normal volunteers and the effect appeared to be mostly driven by Kraepelinian patients. Thus, there is the possibility of nucleus reorganization, such that more ventral aspects of thalamus had shifted dorsally in Kraepelinian patients. This type of abnormal thalamic organization is consistent with the idea of faulty neurodevelopment in specific brain regions (Innocenti, Ansermet, & Parnas, 2003) that might be specific to Kraepelinian patients. When the three groups were considered together, most of the group differences were accounted for by dramatic reduction in ventral portions of the thalamus in the Kraepelinian patients and differences in dorsal thalamus among the three groups were not as robust. Therefore, a more likely explanation of the findings is that the loss of volume in Kraepelinian patients appears to result in reduced tissue mass in the ventral portion of the thalamus.

Kraepelinian patients had significantly smaller absolute and relative ventral aspects of the thalamus than non-Kraepelinian patients. These findings are consistent with the hypothesis of greater posterior circuitry abnormalities in Kraepelinian patients because ventral aspects of thalamus contain mostly pulvinar nucleus, which has strong reciprocal interconnection with the temporal lobe. Further, these findings complement

our previous report on a subset of these patients (Mitelman et al., 2003), which demonstrated smaller temporal lobe areas in the Kraepelinian cohort and, again, suggested trophic effects related to outcome.

The results of the current study are consistent with in vivo and postmortem data from our laboratory suggesting volume and neuronal loss restricted to the medial pulvinar (Byne et al., 2001; Byne et al., 2002; Kemether et al., 2003). These data are also in line with the ventral lateral posterior nucleus volume decreases reported by Danos and colleagues (2002), and our results might actually reflect both pulvinar and ventral lateral posterior nucleus volume loss. It should be noted that in MRI studies from our laboratory where both medial dorsal and pulvinar were traced, whole thalamic volume was not significantly reduced nor was whole thalamic volume minus medial dorsal and pulvinar volume (Byne et al., 2001). Whole thalamic volume measures are probably only an indirect indicator of more marked association nuclei and regional loss.

The findings of greater right hemisphere volume reduction in Kraepelinian patients are consistent with the recent report of greater right hemisphere than left hemisphere volume reduction in inpatient schizophrenia patients (Sullivan, Rosenbloom, Serventi, Deshmukh, & Pfefferbaum, 2003). The right posterior region, generally consisting of the pulvinar, was also confirmed as smaller in an earlier study from our laboratory (Buchsbaum et al., 1996). Using voxel-based morphometry, Hulshoff Pol and colleagues (2001) found focal grey matter density decreases in the medial dorsal region (Talairach -3, -19, 5), and these were larger in the right hemisphere. However, recent volumetric voxel-basd morphometry found left hemisphere and dorsal decreases not extending into the pulvinar or the right hemisphere (Ananth et al., 2002). The findings from the current study also raise the question of whether poor outcome is

more associated with bilateral pathology, instead of the unilateral left hemisphere pathology often reported in studies of schizophrenia groups in general (e.g., Crow, 2000). Indeed, schizophrenia patients with predominantly negative symptoms, particularly flat affect, have been reported to have similar impairments to patients with right hemisphere damage on affective measures of expression and perception (Borod et al., 1989; Borod et al., 1990) and on cognitive tasks mediated by the right hemisphere (Borod, Martin, Alpert, Brozgold, & Welkowitz, 1993). Of note, increased negative symptoms are associated with poor functional outcome (Tamminga, Buchanan, & Gold, 1998), thus providing greater evidence of right hemisphere involvement in Kraepelinian patients.

Findings of smaller thalami in patients taking atypical neuroleptics (Sullivan et al., 2003) were not replicated. Shifts from earlier treatment with conventional neuroleptics, noncompliance in outpatients, and differences in duration of treatment make replication of chronic medication effects difficult. Issues of nonresponsiveness to typical drugs further confound these analyses. A significant relationship between type of neuroleptic treatment at the time of scan or type during the 3-year period prior to scanning and dorsal or ventral thalamic volume was not found in either patient group. This finding is somewhat inconsistent with other reports of a significant positive association between antipsychotic treatment response and volumetric expansion of the thalamus (Strungas, Christensen, Holcomb, & Garver, 2003). However, unlike in previous studies (Strungas et al., 2003), patients in the current study had been chronically treated with neuroleptics and were symptomatically stable. Follow-up studies of never-previously medicated patients are necessary to resolve this question.

Finally, some interesting correlates of thalamic size emerged from the current study. Thalamic size was positively associated with measures of positive psychopathology in dorsal and ventral areas and with general psychopathology in ventral levels. The finding has been reported by other investigators (Portas et al., 1998), and is consistent with notion of thalamus as central to sensory-gating and information flow to cortex (Jones, 1997). The finding of a significant positive association between dorsal and ventral thalamic size in Kraepelinian patients and severity of negative symptoms was somewhat idiosyncratic and requires further exploration. Significant associations between increased thalamic volume and both shorter duration of illness and older age of onset in the Kraepelinian group only provide some preliminary evidence of thalamic degeneration.

Taken together with other recent reports, these data provide further evidence of thalamic volumetric deficits in schizophrenia and suggest that poor outcome may be associated with more ventral thalamic volume loss. They suggest that variability in the reports of thalamic volume loss may be related to the volume loss restricted to pulvinar, medial dorsal, and ventrolateral posterior regions. Detailed examination of thalamic nuclei in larger samples of patients will be helpful in relating thalamic volume loss to patterns of disease outcome and regional cortical change.

Study 3

The findings from this study provide tentative support for internal capsule size reduction in schizophrenia. These abnormalities may be restricted to dorsal levels of the internal capsule in poor functioning patients and are associated with age. Significant correlations emerged, particularly between the internal capsule size in normal controls and the surrounding size of subcortical brain regions. However, these associations

tended to become weaker with progressive decline in functional outcome. Taken together, these findings are suggestive of internal capsule abnormalities in Kraepelinian patients, which may reflect a neurodegenerative process and disrupted cortical-subcortical circuitry.

Analyses of relative and absolute internal capsule size revealed several important findings. First, schizophrenia patients, when considered together, did not significantly differ from normal control comparison subjects. Relative internal capsule size also did not significantly differ between non-Kraepelinian patients and normal controls. However, Kraepelinian patients had smaller relative dorsal internal capsules and larger relative ventral internal capsules than both non-Kraepelinian patients and normal controls. These findings suggested subtle shape abnormalities in the Kraepelinian group; that is, abnormal fiber distribution in the internal capsules could have accounted for smaller relative dorsal size and larger relative ventral size. To explore this possibility further, comprehensive analyses of the five slice dorsal-to-ventral absolute size were conducted. These analyses confirmed that Kraepelinian patients had smaller internal capsule size (i.e., main effect of Diagnostic Group), which was most prominent at dorsal levels (i.e., Diagnostic Group by Slice Level interaction), than both non-Kraepelinian patients and normal controls. Non-Kraepelinian patients and normal controls did not significantly differ from each other.

Only one published study, to our knowledge, has taken an *a priori*, region-of-interest approach to examining the internal capsules in schizophrenia (Zhou et al., 2003). In that study, the authors used manual tracing and confirmatory analysis with voxel-based morphometry to demonstrate that total bilateral anterior limb volume was decreased in schizophrenia patients compared to matched controls. Findings from the

current study are somewhat consistent with this report; reduced internal capsule size was found, but restricted to poor outcome patients. Discrepancies between the two studies could be due to subject characteristics. Specifically, the functional status (e.g., inpatient, outpatient, institutionalized) or disease severity of the patient sample in the Zhou et al. (2003) paper was not reported. Thus, their sample could have been composed of particularly poor functioning patients. Unlike Zhou and colleagues (2003), the current study did not find greater right than left side asymmetry in the patient group relative to controls. Two other studies using voxel-based morphometry have reported significant anterior limb internal capsule reduction in schizophrenia patients compared to controls (Hulshoff Pol et al., 2004; Suzuki et al., 2002). Voxel-based morphometry studies are inherently exploratory because they rarely test *a priori* hypotheses. Instead, they provide important information after voxel-by-voxel comparisons are made. Thus, the two positive findings of internal capsule decreases in schizophrenia with this method should be interpreted cautiously given that most studies using voxel-based morphometry have failed to report similar differences.

The anterior limb of the internal capsules contains mostly thalamocortical, corticothalamic, corticopontine, and caudatopallidal fibers (Axer et al., 1999; Axer & von Keyserlingk, 2000; Parent, 1996). Furthermore, because the internal capsules comprise a portion the larger corona radiata, which has wide spread cerebral distribution, fibers in the internal capsule are at least indirectly involved with projections to and from most cortical regions (Parent, 1996). In terms of the specific pathways comprising the region, the anterior thalamic peduncle forms a large portion of the anterior limb, connecting anterior and medial nuclei of the thalamus with the cingulate gyrus and with dorsolateral and medial aspects of the frontal lobe, as has been demonstrated with

polarized light and confocal scanning laser microscopy (Axer & von Keyserlingk, 2000). Fibers extending between caudate nucleus and globus pallidus are also found in the anterior limb (Axer & von Keyserlingk, 2000; Axer et al., 1999), particularly at dorsal levels of the pallidum (Hazrati & Parent, 1992). Finally, frontopontine fibers, which were well described in classic postmortem studies of individuals with leucotomy (Meyer, 1949), have been shown to occupy approximately 37% of anterior limb volume (Axer et al., 1999). Consistent with the systematic distribution of the corona radiata throughout the brain, fibers coursing through the anterior limb of the internal capsule are topographically organized (Parent, 1996), particularly in the anterior-posterior direction (Axer et al., 1999). However, several of the fiber bundles intertwine with one another and are distinguishable by their slope of projection, rather than their discrete boundaries (Axer & von Keyserlingk, 2000).

Consideration of the pathways contained within the anterior limb of the internal capsules suggests particular frontothalamic, thalamofrontal, and intrastriatal abnormalities in poor-outcome patients. Findings from our recent examination of the thalamus (Brickman et al., in press; Study 2) indeed demonstrated thalamic volume reduction in the same cohort of Kraepelinian patients compared to non-Kraepelinian patients and normal controls. Furthermore, the results are consistent with a study on a subsample of the included participants (Buchsbaum et al., 2003), which suggested striatal abnormalities in Kraepelinian patients. Results may be viewed as supportive of the "two hit" hypothesis by demonstrating reduction in anterior brain circuitry and in circuitry that is indirectly related to more posterior limbic circuits via the anterior nucleus of the thalamus (Parent, 1996) in the Kraepelinian patient group.

Correlation coefficients examining the relationship between internal capsule size and the size of surrounding cortical and subcortical regions provide some further insight into the nature of the internal capsule size reduction seen in the Kraepelinian patients. By far, the most consistent associations were between ventral and dorsal internal capsule size and all aspects of the lateral ventricles; larger ventricles were associated with smaller internal capsules in normal controls. This normal relationship suggests that enlargement of the ventricles contributes to reduction in size of the internal capsule, potentially as a secondary effect of atrophy or increased ventricular pressure. However, this association was not as consistent in the non-Kraepelinian patients and non-existent in the Kraepelinian patients. The markedly enlarged ventricles (Davis et al., 1998; Shihabuddin et al., in preparation) and reduced internal capsule size in the Kraepelinian patients may therefore be the result of independent pathophysiological processes. This finding lends support to the idea that ventricular enlargement in Kraepelinian patients is endophenotypic and does not cause secondary surrounding structural reduction in Kraepelinian patients.

Consistent with the report by Zhou and colleagues (2003), significant positive associations were found between ventral and dorsal internal capsule size and some levels of the caudate in the normal comparison subjects, but these associations were less consistent in either of the patient groups. Dorsal internal capsule sizes were not related at all to caudate size at any level in either of the schizophrenia groups when considered separately or alone. Given that the caudate nucleus forms the medial border of the internal capsules, the findings of a normal association between the two structures is not surprising. However, the lack of association in the schizophrenia patients, particularly the Kraepelinian group, suggests that internal capsule size reduction is independent of

variability in the caudate. Our findings are not consistent with those of Hulshoff Pol and colleagues (2004), who reported negative associations between internal capsule and caudate density, attributing the finding to normal brain maturation. A somewhat similar pattern emerged with associations with the putamen. Significant correlations were strongest in normal controls, but still present in both schizophrenia groups. Given that slices for analysis of the internal capsule were chosen based on putamen morphology, and that the internal capsule borders the lenticular nucleus, these associations are not unexpected.

Although some significant positive associations were found between ventral and dorsal aspects of the internal capsule and levels of the thalamus in all three groups, they were less consistent than expected. Dorsal internal capsule was associated with dorsal and ventral thalamic size in normals, whereas ventral aspects of the internal capsule were associated with dorsal slices of the thalamus in non-Kraepelinian patients. Kraepelinian patients evidenced no significant relationships. The findings tentatively suggest a greater disruption in circuitry as a function of worsening functional outcome, but do not support the idea that one structure affects the other. Similarly, there was a lack of significant associations between internal capsule size and cortical grey or white matter volume in any of the groups.

Few previous studies have examined the relationship between internal capsule morphometry and clinical or demographic variables in schizophrenia patients. The current study found a significant negative association between age at the time of scan and dorsal internal capsule size in the Kraepelinian group, but not in the non-Kraepelinian patients. The finding speaks to the possibility that Kraepelinian patients, who exhibited dorsal internal capsule size reduction, have a progressive,

neurodegenerative course. It is also somewhat consistent with a report by Velakoulis and colleagues (2002), who found a negative association between right internal capsule volume and illness duration in a group of schizophrenia patients. Similar to Hulshoff Pol and colleagues (2004), the current study found little relationship between internal capsule size and exposure to neuroleptic treatment and only a modest effect of sex on internal capsule size.

There are some limitations to the current study. The anterior limb of the internal capsules contains fibers that are part of the corona radiata, a much larger, diffusely distributed cortical-subcortical white matter system. A benefit to studying morphometry of the internal capsules is that it is largely contained within surrounding subcortical structures, facilitating reliable boundary demarcation. However, positive findings in the internal capsule are likely to be representative of much more diffuse white matter changes and, given the intertwining fiber bundles and the anterior-posterior topography contained within the structure (Axer & von Keyserlingk, 2001), it is difficult to draw conclusions about specific pathways, particularly when considering the internal capsules in the dorsal-ventral direction. Studies using diffusion tensor, an MRI sequence that provides information about the coherence and directionality of white matter fibers, would complement morphometric efforts and help better characterize white matter abnormalities in good and poor outcome patients. Indeed, in the first study using diffusion tensor in schizophrenia patients, Buchsbaum and colleagues (1998) demonstrated anisotropic reductions in areas of the anterior limb of the internal capsule. Further, preliminary diffusion tensor analyses with a subset of patients from the current cohort (Shihabuddin et al., 2001) showed schizophrenia-associated anterior

anisotropic reduction, but greater reduction in posterior regions in Kraepelinian patients.

In conclusion, internal capsule size reduction in this study was restricted to Kraepelinian patients at dorsal levels, and appeared to be somewhat related to age. The findings suggest neurodegeneration in this poor outcome group. Internal capsule size appeared to be most related to ventricular size in normal controls, but this relationship was less strong in non-Kraepelinian patients and nonexistent in Kraepelinian patients. Disruption of fibers coursing through the internal capsule in Kraepelinian patients may be reflective of myelin-related/oligodendroglial abnormalities or neurodevelopmental maturational problems. Findings from the study are less supportive of trophic effects.

Conclusions

The current series of studies gives further support to the Kraepelinian/non-Kraepelinian classification system by extending findings into clinical and new neuromorphometric domains. Kraepelinian patients evidenced more severe neurocognitive profiles than non-Kraepelinian patients and reduction of thalamic and internal capsule regions compared to non-Kraepelinian and demographically-similar normal controls. Importantly, though Kraepelinian patients were more psychiatrically symptomatic, results from the current series of studies and from earlier efforts suggest that neuropathological differences in this group of patients are not global; global differences would suggest that Kraepelinian patients are simply "more ill" but otherwise similar to non-Kraepelinian patients. Rather, complex interactions involving diagnostic group demonstrated that both the *profile* of neurocognitive deficits and of brain abnormalities distinguish the two groups. Cognitive domain and brain regional specificity implicates unique patterns of pathology and raise the question of whether

Kraepelinian patients and non-Kraepelinian do indeed have distinct etiological underpinnings. Our study of greater expansion of the striatum in non-Kraepelinian patients than in Kraepelinian patients (Buchsbaum et al., 2003) provides some early evidence of pathophysiological differences between the two groups.

Implicit in the Kraepelinian/non-Kraepelinian classification is the idea that the former has a neurodegenerative course and the latter remains relatively more stable. The current series of studies provides important baseline, cross-sectional data that suggest more severe neuropathology in the Kraepelinian group, but are less informative regarding a potential neurodegenerative course. The findings of worse neurocognitive functioning and smaller brain regions, particularly those that negatively correlate with age in the Kraepelinian group only, are suggestive of a more severe disease progression in Kraepelinian patients, but do not provide the longitudinal analyses required to demonstrate decline. However, in the context of the preliminary studies and earlier studies with Kraepelinian and non-Kraepelinian patients, there is accumulating data that are consistent with degeneration. Longitudinal studies that have followed Kraepelinian patients over time have demonstrated enlargement of the lateral ventricles on CT scan (Davis et al., 1998) and marked decline in gross cognitive functioning, particularly in later life (Friedman et al., 2001). These studies have not been replicated with higher resolution MRI or more sensitive neuropsychological tests in younger patients, respectively. Patients and controls in the current series of studies are being followed longitudinally to examine potential decline.

Data from the current series of studies provide support for the "two-hit" hypothesis of poor functional outcome, which postulates that Kraepelinian status is due to particular dysfunction in anterior *and* posterior brain circuitry. Indeed, earlier and

preliminary findings have demonstrated greater frontal and temporal grey matter deficits (Mitelman et al., 2003), larger temporal horns (Davis et al., 1998; Shihabuddin et al., in press), smaller posterior aspects of the cingulate gyrus (Mitelman et al., in press), and reduced posterior anisotropy (Shihabuddin et al., 2001) in Kraepelinian patients compared to non-Kraepelinian patients and controls. The current findings are consistent with these results: performance on neuropsychological tests mediated by frontal and temporal lobes was more severe in Kraepelinian patients and best distinguished between the two patient groups; ventral areas of the thalamus, which have strong interconnectivity with posterior brain regions, were smallest in Kraepelinian patients; and reduction in dorsal areas of the internal capsule in Kraepelinian patients implicates thalamocortical and corticothalamic dysfunction and posterior limbic circuits via the anterior nucleus of the thalamus.

Efforts to characterize schizophrenia patients by functional status may be one powerful approach to account for the tremendous amount of heterogeneity seen in the presentation and course of the illness. Discrepant findings in the literature may be largely due to sample characteristics. Kraepelinian patients may be overrepresented in postmortem studies, which often acquire brains from formalized relationships with long-term institutions, and underrepresented in many neuropsychological and neuroimaging studies, which tend to include cooperative patients, amenable to participation. Although all patients met criteria for schizophrenia, in the current series of studies, the non-Kraepelinian patients were much more representative of samples included in clinical research, whereas special efforts were made to recruit and retain the lower functioning Kraepelinian patients. In neuropsychological and neuroimaging

studies of schizophrenia, little attention is paid to functional status; thus, it is often difficult to evaluate the interaction of functional outcome and brain abnormalities.

The primary limitation of the current series of studies is in the Kraepelinian classification system itself. Several attempts have been made to reduce the clinical heterogeneity of schizophrenia by categorizing patients into more homogenous subtypes; however, all classification systems are somewhat problematic because no consistent etiological factors have been identified in schizophrenia or in any of the subtypes. The Kraepelinian classification system is theoretically-based, but data supporting the idea that the two subtypes actually represent two different diseases are still needed. In a similar vein, the classification system treats functional outcome, an ostensibly continuous construct, as a dichotomous variable. While there is no question that Kraepelinian patients represent an extreme form of poor functional outcome, there may be greater variability within the non-Kraepelinian patients. Nonetheless, consistent and reliable differences between Kraepelinian and non-Kraepelinian patients, together with recent evidence that the former group is characterized by clinical and neuroanatomical degeneration, lends support to the value of the classification.

In a similar vein, a proportion of the non-Kraepelinian patients in the current series of studies can presumably "convert" to meet Kraepelinian status in the future. If Kraepelinian schizophrenia is characterized by degeneration, some of these patients may clinically present as non-Kraepelinian earlier on in the course of their disease. Similarly, patients who have been ill for less than five years would not meet Kraepelinian status by definition. In the current series of studies, five non-Kraepelinian patients had been ill for less than five years. Longitudinal studies with these subtypes are essential to examine true conversion rates.

Further limitations of these studies include a lack of consideration of other schizophrenia-associated symptoms and medications. Specifically, fine motor abnormalities and the relationship between extrapyramidal motor symptoms and morphometry were not examined. Similarly, examination of the influence of anticholinergic and antidepressant treatment was not included in this series of studies. It should be noted that patients were excluded if they met criteria for another Axis I psychiatric disorder, including major depressive disorder. It *is* possible, however, that Kraepelinian patients were more medicated than non-Kraepelinian patients given their more severe symptomatological profile, and this issue should clearly be addressed in future studies. The potential role of white matter hyperintensities on neuropsychological functioning and/or measurements of specific brain regions were not considered, as only T1-weighted MR images were acquired. However, it is unlikely that severity of vascular white matter pathology varied systematically as a function of diagnostic group, especially as all participants were medically screened.

Future Directions

Future directions in the study of non-Kraepelinian and Kraepelinian schizophrenia fall into three general categories: 1) statistical/analytic approaches; 2) methodological approaches; and 3) consideration of functional outcome as a continuous variable.

In terms of statistical and analytic approaches, neuromorphometric data have been collected on a large sample of Kraepelinian and non-Kraepelinian patients, as well as demographically similar normal controls. Structural data are available for grey matter, white matter, and CSF volumes in all the cortical Brodmann areas; ventricular volume; striatal size; thalamic sizes; cingulate volume; and diffusion tensor

characteristics. Considering the large amount of data and that reliable differences have been demonstrated in several of these areas, a cross-sectional path analysis using neuromorphometric data to predict group membership would be an ideal approach to identifying the relative importance of each region. Path analysis provides a statistical model that may parallel underlying anatomical circuitry. For example, temporal lobe grey matter volume may predict thalamic volume, which in turn may predict internal capsule volume and anisotropy, and ultimately reliably predict group membership.

A second analytic approach focuses on a longitudinal study design. While the current series of studies provides valuable cross-sectional data, demonstration of decline in neuropsychological functioning and neuromorphometric change in the Kraepelinian group but not the non-Kraepelinian group would provide the most powerful evidence of the validity of the classification system. Indeed, the current cohort is being assessed at a five-year interval to examine the possibility of such change. Longitudinal analysis will focus both on *a priori* hypothesis testing and exploratory approaches. For the former, non-Kraepelinian, Kraepelinian patients, and normal controls will be compared longitudinally. For the latter, individuals will be rank ordered by severity of longitudinal change, and factor analysis will characterize the cohort into discrete groups. Ideally, the two approaches will yield similar findings, with Kraepelinian patients evidencing decline, non-Kraepelinian declining less, and normal controls remaining relatively stable.

Finally, the relationship between neuropsychological functioning and brain neuromorphometry should be considered in future studies. Although only a subset of participants received neuropsychological evaluation at baseline, important comparisons between brain structure size and performance on specific neuropsychological tasks can

be made. Whether the relationship between brain structure and neurocognition differs as a function of group membership would provide critical information pertaining to brain organization and clinical manifestations in schizophrenia. Furthermore, longitudinal analysis of neuropsychological functioning and tests of whether changes in specific brain regions mediate changes in neuropsychological test performance would provide another powerful approach understanding characteristics of Kraepelinian and non-Kraepelinian schizophrenia patients.

In terms of methodological approaches, future structural neuroimaging work should focus on more detailed parcellation of the thalamic nuclei. In the current studies, whole thalamic size was analyzed at 5 dorsal-to-ventral levels. New protocols have been developed (Byne et al., 2001; Hazlett et al., 2004; Kemether et al., 2003) that allow for morphometric analysis of individual thalamic nuclei, which may yield more specific information about circuitry abnormalities. In a similar vein, large scale diffusion tensor imaging studies in conjunction with region-of-interest neuromorphometric approaches would provide a more direct measurement of subcortical-cortical circuitry. Other imaging techniques, such as functional MRI and magnetic transfer imaging, as well as postmortem and genetic approaches would provide a comprehensive assessment of Kraepelinian and non-Kraepelinian differences and perhaps shed light on etiological differences between the two groups.

Finally, as discussed above, the Kraepelinian classification system is a valuable approach to dichotomously categorizing schizophrenia patients according to functional outcome. However, more detailed analyses between neurocognition and neuromorphometry *and* continuous measures of functioning (e.g., Harvey, Davidson,

Mueser, Parrella, & White, 1997; Jaeger, Berns, & Czobor, 2003) may provide more specific data regarding the relationship between brain systems and functional outcome.

Tables and Figures

Figure 1. Left panel: Relative tissue volume differences between schizophrenia patients and normal controls. A significant Diagnostic Group by Region by Brodmann Area by Hemisphere interaction ($F(4, 288)=2.81$, $p<0.03$) demonstrated that schizophrenia patients had significantly reduced grey and white matter volume particularly in the left hemisphere temporal and occipital lobes. Bars represent difference scores between normal controls and schizophrenia patients. Right panel: relative tissue volume differences between Kraepelinian and non-Kraepelinian patients. A significant Group by Region by Tissue Type interaction ($F(4, 140)=2.59$, $p<0.04$) indicated that Kraepelinian patients had reduced white and grey matter volume, and increased CSF volume, compared to non-Kraepelinian patients, particularly in the temporal and occipital lobes.

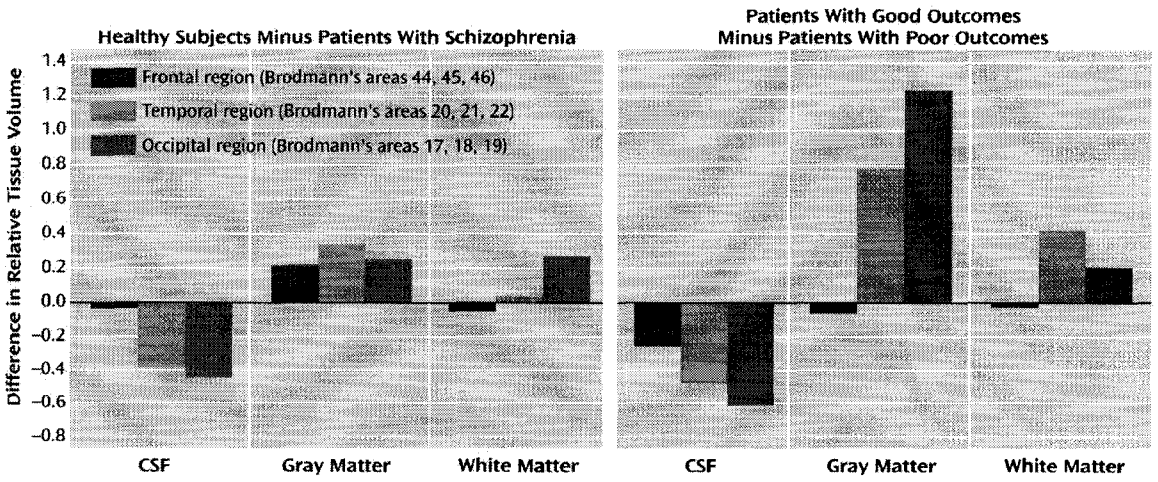

Figure 2. Top panel: Volume comparisons of individual Brodmann areas (averaged across right and left hemispheres) between all schizophrenia patients and normal control subjects. The colors represent p-values for t-tests between groups. Areas in which the patients had smaller volumes than normal controls are shown in blue and purple; areas in which the patient group had larger volumes are shown in yellow and red. Bottom panel: Volume comparisons of individual Brodmann areas (averaged across right and let hemispheres) between non-Kraepelinian and Kraepelinian patients. Areas in which the Kraepelinian patients had smaller volumes than non-Kraepelinian patients are darker; areas in which Kraepelinian patients had larger volumes are lighter.

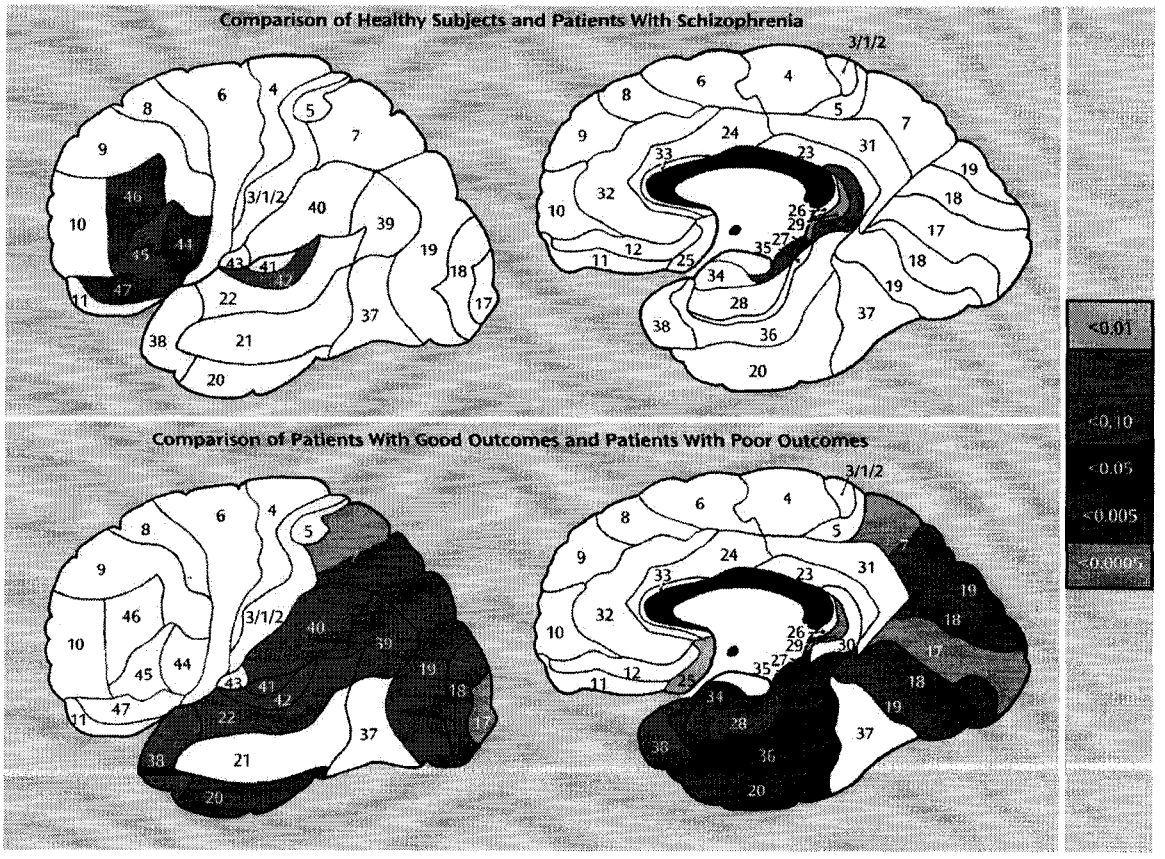

Figure 3. Volume comparisons of individual Brodmann areas (averaged across right and left hemispheres) between non-Kraepelinian patients and normal controls (top panel) and between Kraepelinian patients and normal controls (bottom panel). Areas in which the patient group had smaller volumes than the normal controls are dark; areas in which normal controls had smaller volumes are lighter.

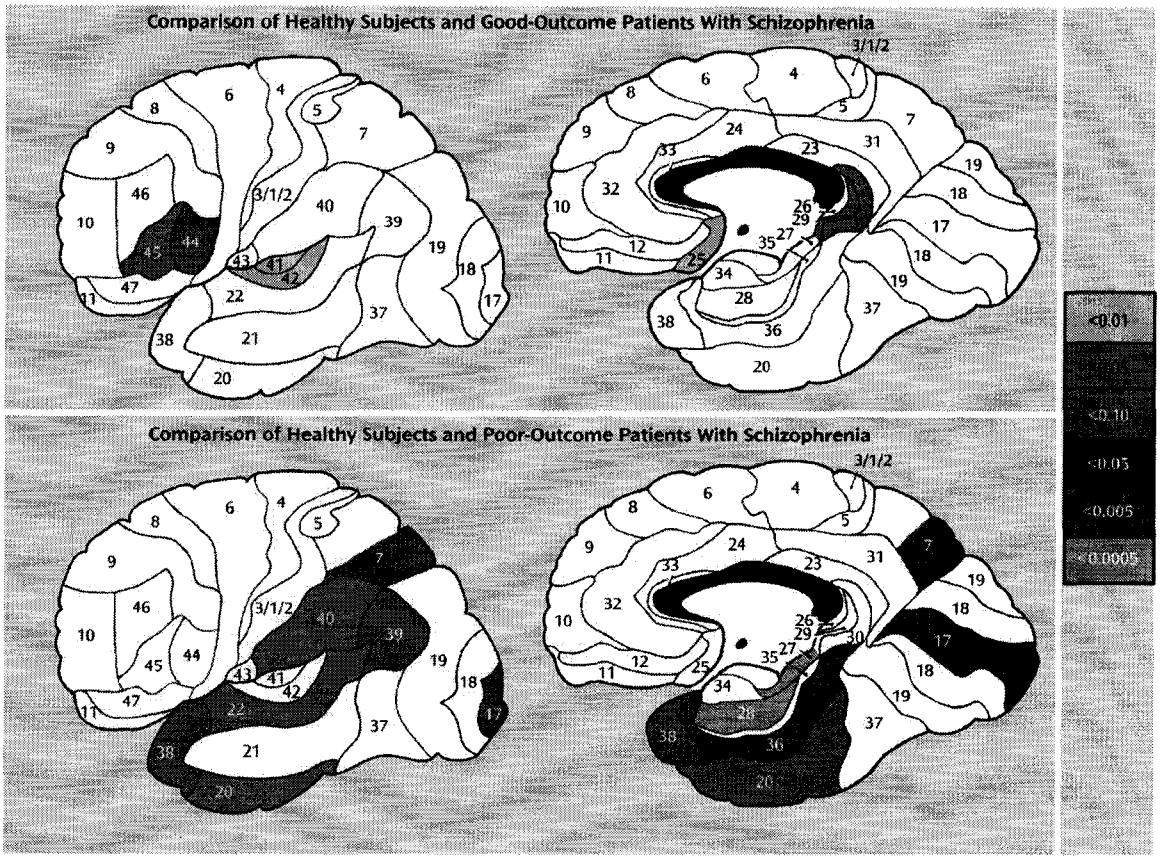

Figure 4. Upper left panel: A filter based on the Sobel gradient maximized differentiation between CSF and parenchymal matter, thus providing an edge for manual tracing with high reliability. Upper right panel: The same traced ventricular region without the Sobel-gradient filter.

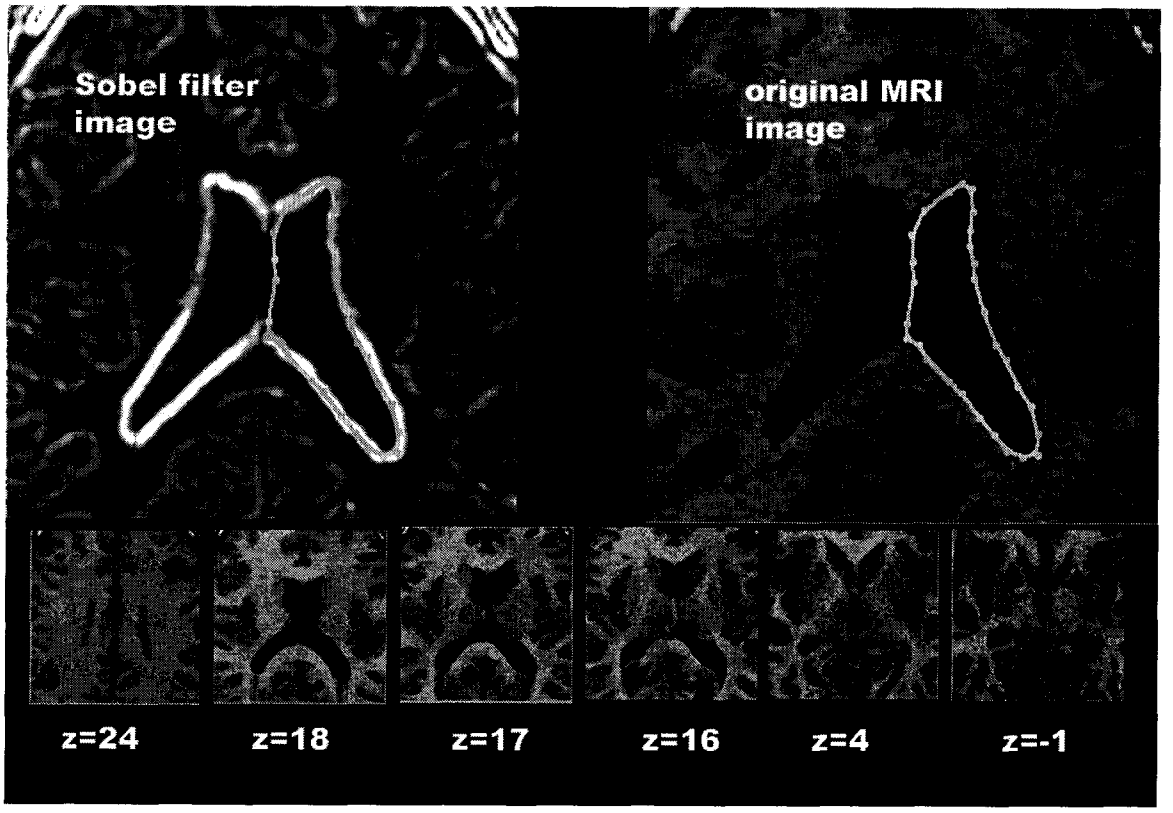

Figure 5. Ventricular volume in non-Kraepelinian (good outcome) patients, Kraepelinian (poor outcome) patients, and normal controls. Largest differences were found in temporal horns and lateral ventricles, with the largest effect seen in the left temporal horn of Kraepelinian patients.

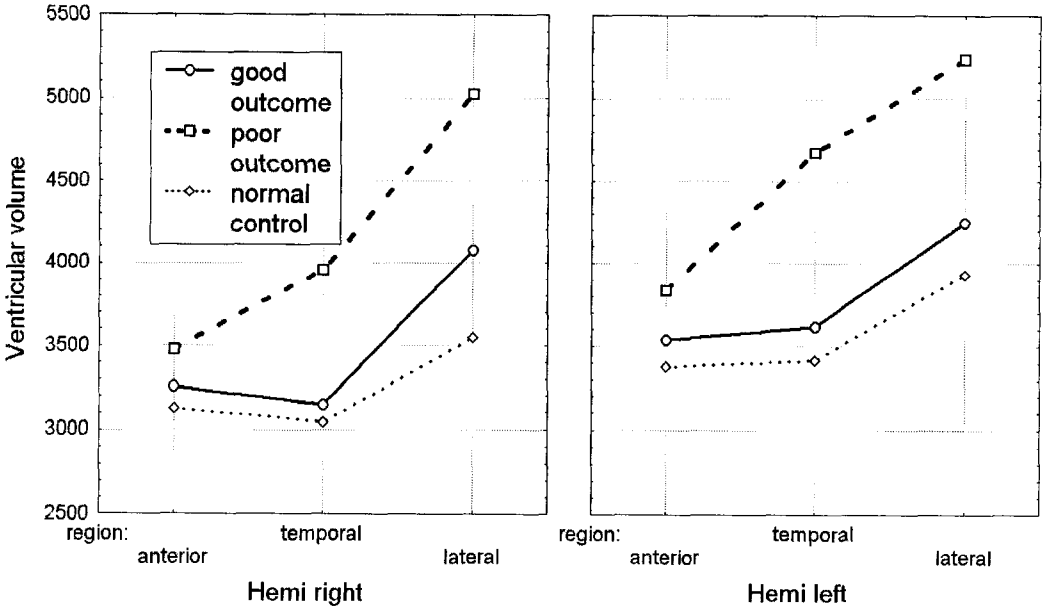

Figure 6. Relative putamen size in non-Kraepelinian patients, Kraepelinian patients, and normal controls. Non-Kraepelinian patients had significantly larger putamens than the other two groups, particularly at more dorsal levels. Kraepelinian patients were similar to normal controls at all levels, but the most dorsal, where their putamens were smaller.

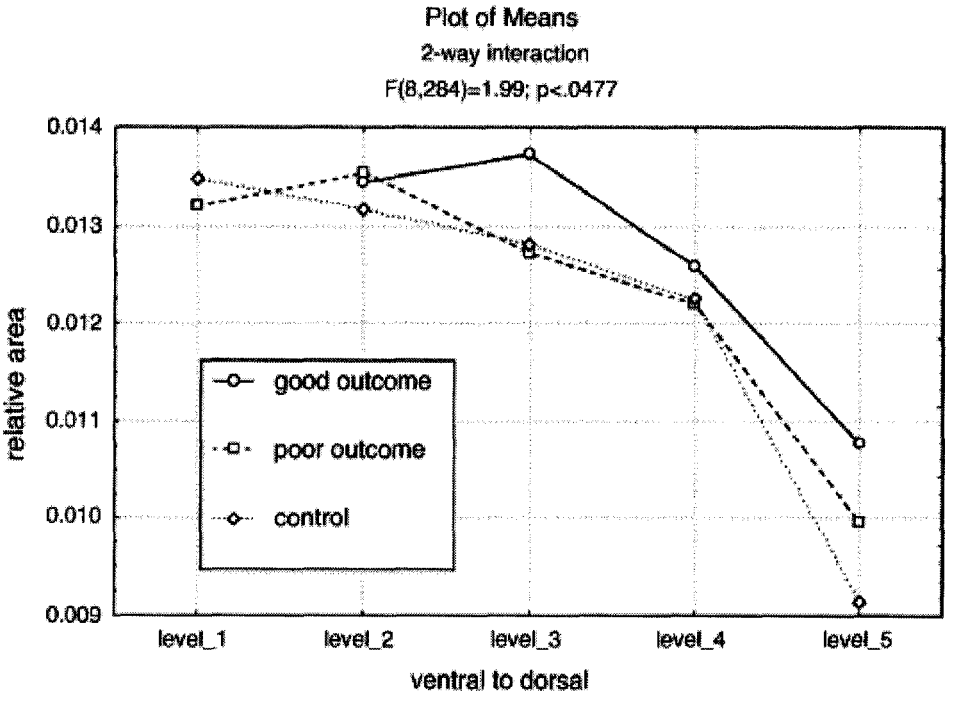

Figure 7. Statistical parametric maps comparing schizophrenia patients as a whole to matched normal comparison subjects with diffusion tensor imaging. Greater anisotropy deficits were measured in the schizophrenia regions, particularly clustered in the anterior regions, corresponding to the cingulum bundle of the corpus callosum.

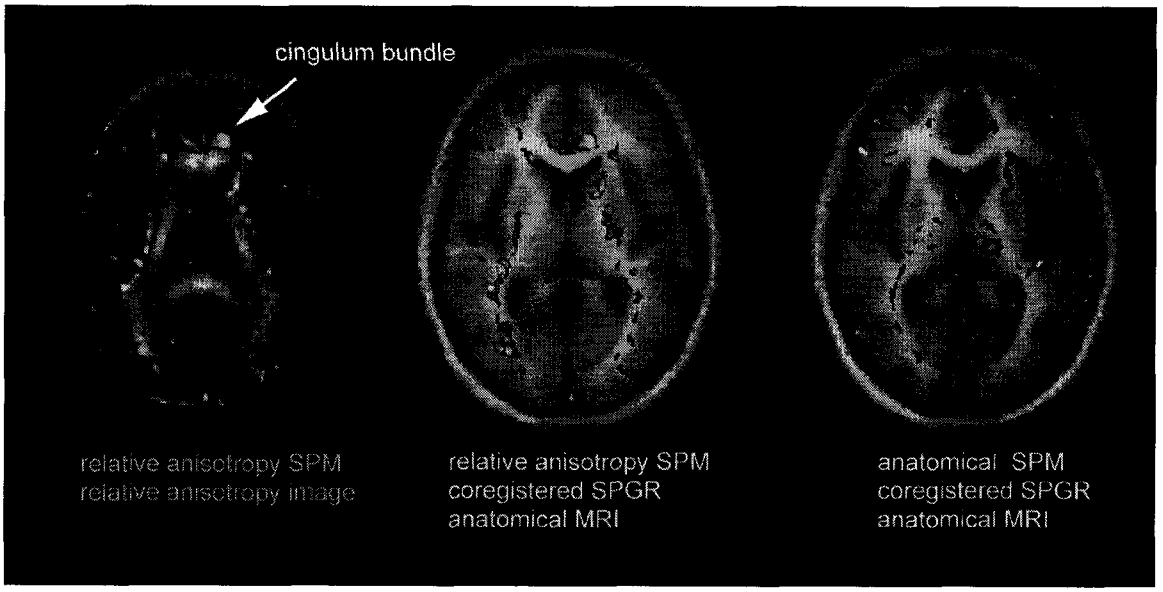

Figure 8. Statistical parametric maps comparing Kraepelinian patients to non-Kraepelinian patients with diffusion tensor imaging. Greater anisotropy deficits were noted in posterior regions of the temporal lobe in the Kraepelinian group.

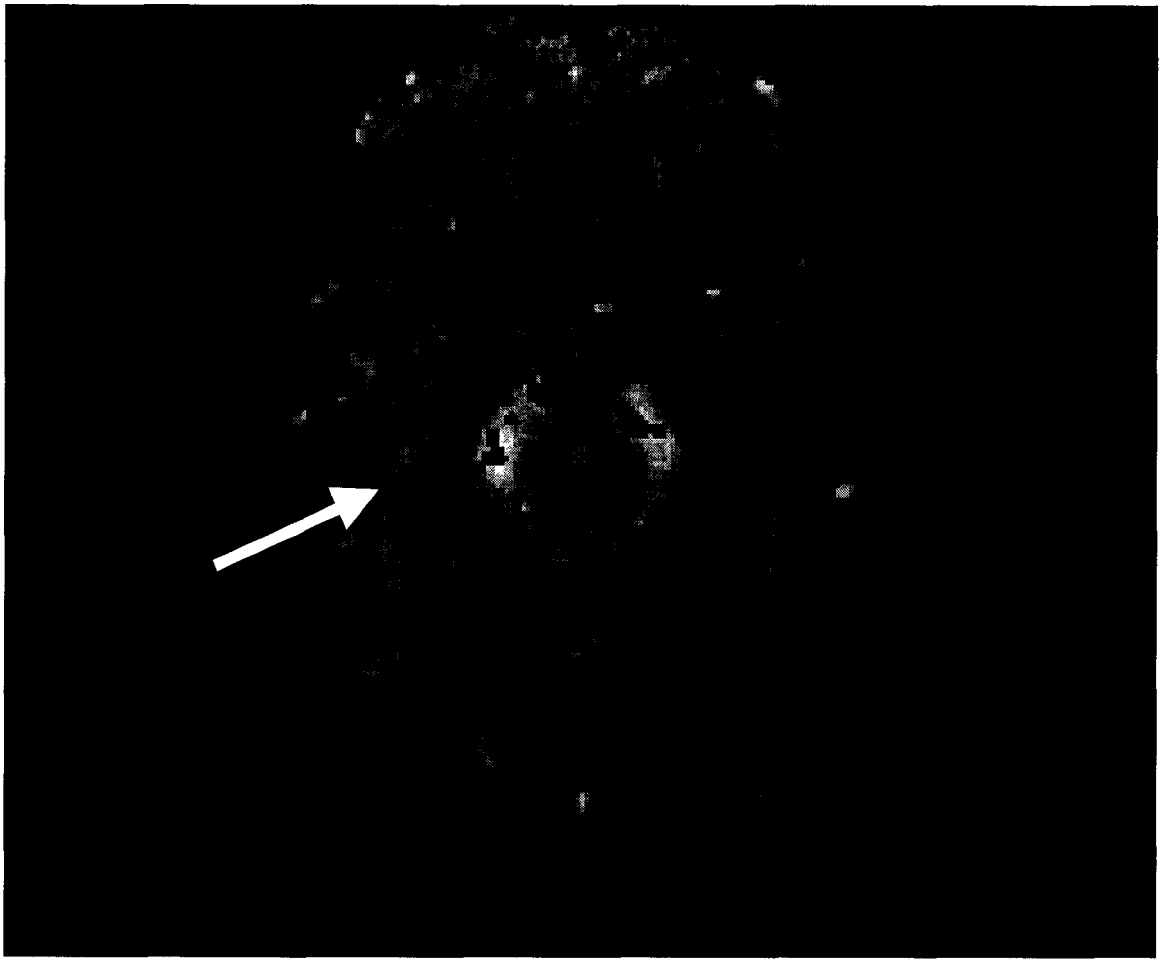

Table 1. Demographic and clinical characteristics of the patient sample for Study 1.

	Non-Kraepelinian patients (n=26)	Kraepelinian patients (n=26)
Gender, %female	23	15
Age, mean years (SD)	44.61 (10.13)	48.74 (13.74)
Education, mean years (SD)	12.96 (1.51)	11.73 (1.89)
Duration of illness, mean years (SD)	19.80 (11.80)	25.73 (13.13)

Table 2. Demographic and clinical characteristics of the schizophrenia patients and normal controls in Studies 2 and 3.

Variable		Normal Controls (n=42)	Schizophrenia Patients (n=106)		
			Total	Non-Kraepelinian (n=52)	Kraepelinian (n=54)
Age (M ± SD)		44.1 ± 14.5	43.0 ± 12.1	40.9 ± 12.6	45.1 ± 11.5
% women		33.3%	19.8%	19.2%	20.4%
Age neuroleptic onset (M ± SD)			25.0 ± 9.0	26.7 ± 6.9	22.8 ± 10.7
PANSS positive (M ± SD)			18.9 ± 6.6	16.1 ± 4.9	21.7 ± 6.9
PANSS negative (M ± SD)			18.9 ± 7.7	16.2 ± 5.4	21.6 ± 8.6
PANSS general (M ± SD)			37.1 ± 9.8	32.2 ± 7.7	41.8 ± 9.3
Neuroleptic exposure at scan date					
	% none		12.8	15.2	10.0
	% typical		2.6	32.6	17.5
	% atypical		43.0	39.1	47.5
	% both typical & atypical		18.6	13.0	25.0
Neuroleptic exposure for majority of 3-year period prior to scan					
	% none		29.4	28.3	30.0
	% typical		24.4	32.6	15.0
	% atypical		29.1	26.1	32.5
	% both typical & atypical		17.4	13.0	22.5

Figure 9. Left panel: MRI of the thalamus with midline. Right: Sobel gradient filter applied to the same image. Manual tracings of the thalamus were made by depositing points around the structure as displayed.

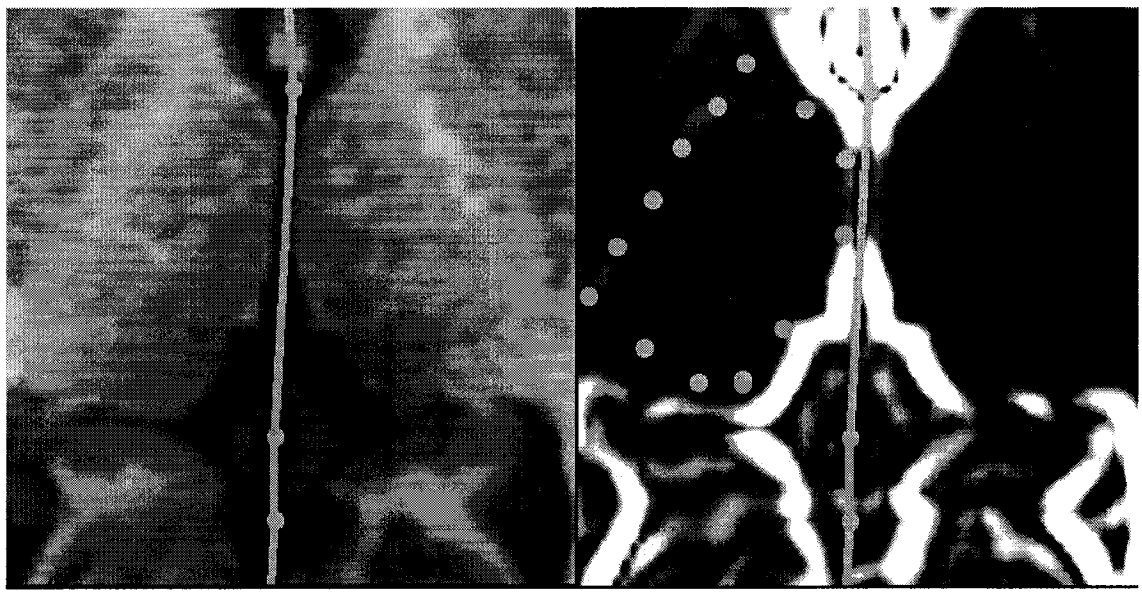

Figure 10. Upper panel: The five slices of thalamus are displayed in 3-dimensional form with the color corresponding to MRI intensity values. Lower panel: Pixel locations included in outline for most ventral and most dorsal of the five slices with Talairach directions and dimensions marked.

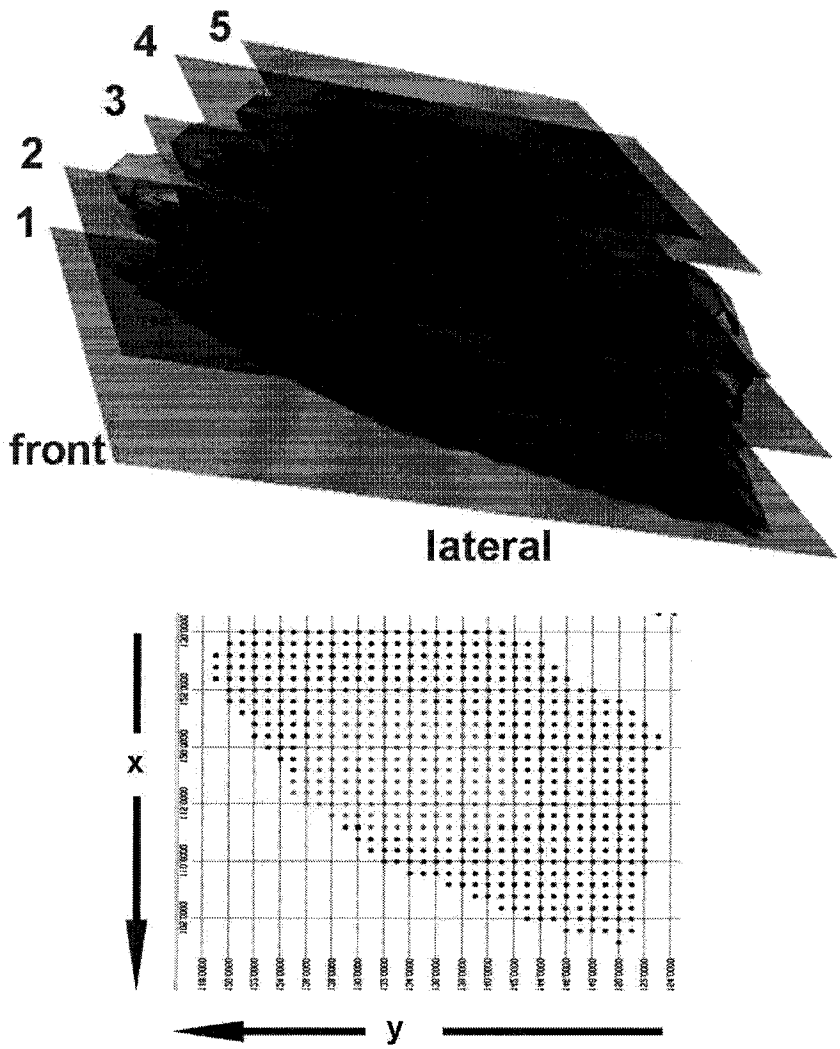

Figure 11. A mid-cerebral slice of the Perry Brodmann area atlas (right panel) superimposed on a 3-dimensional rendering of the brain (left panel). The central section of the brain and the temporal lobes are outlined.

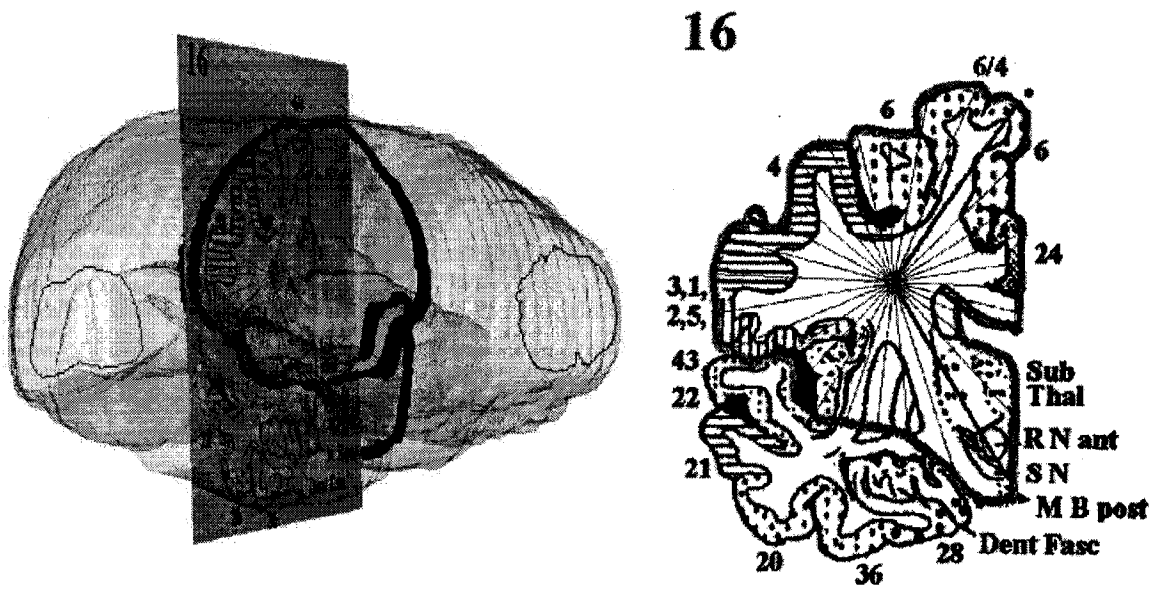

Figure 12. Manual landmarking of the anterior limb of the internal capsules on the five ventral to dorsal slices. Landmarks are shown in white. Left images are with the Sobel-gradient filter applied, and right images are raw.

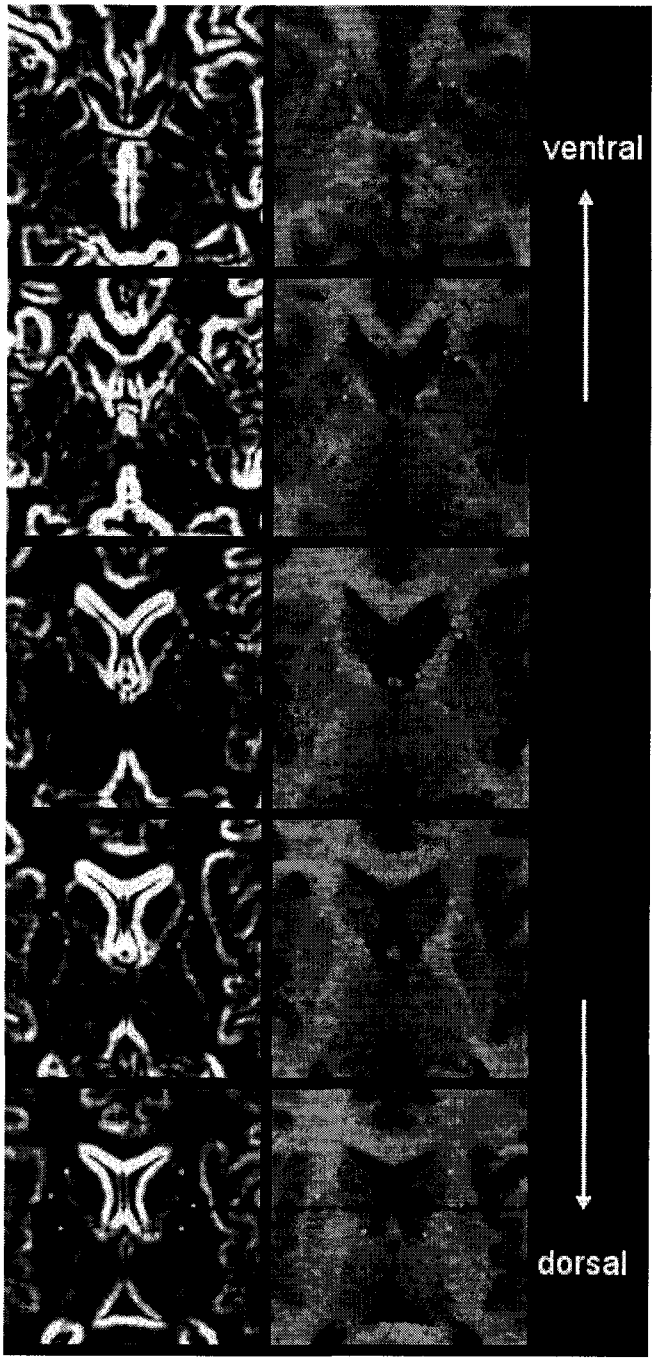

Figure 13. Three-dimensional reconstruction of the anterior limb of the internal capsules. The 3-dimensional reconstruction is illustrated as it bisects a mid-cerebral axial slice. Orthogonal coronal and sagittal slices are displayed for reference.

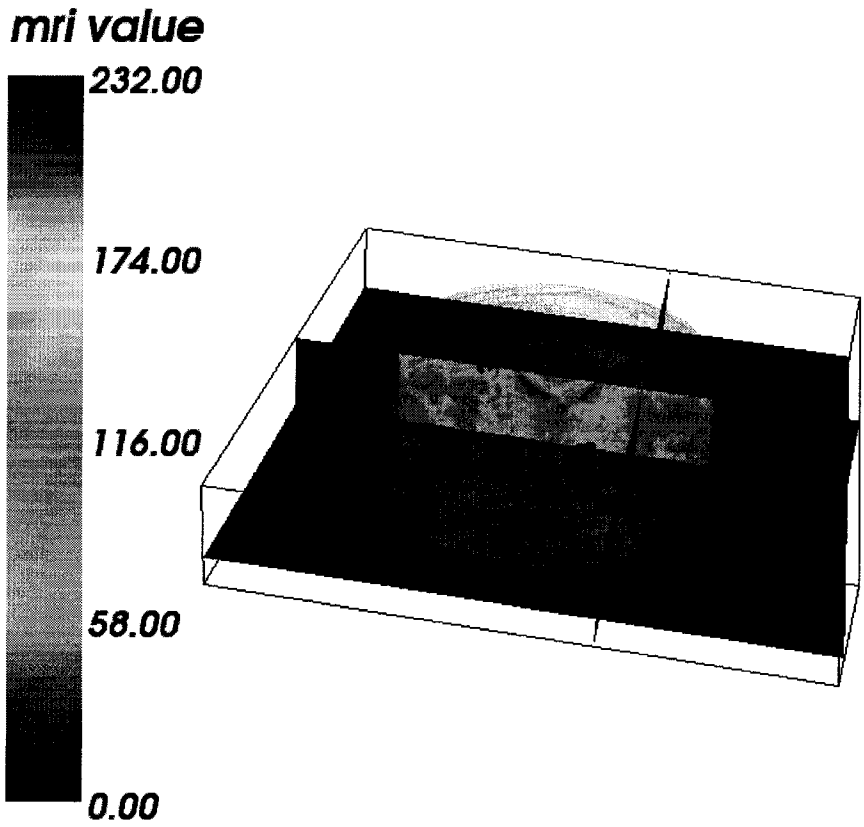

Table 3. Functional outcome measures for Kraepelinian and non-Kraepelinian patients in Study 1.

Outcome Variable		Non-Kraepelinian (n=26)	Kraepelinian (n=26)
Marital Status	%never married	54	73
	% ever married	46	27
Occupation Status	% never employed	4	23
	% currently unemployed but past employment	80	69
	% currently employed	15	8
Current Residency Status	% living alone or with spouse equivalent	61	23
	% living with parent or relative	35	19
	% living in group home	4	8
	% living in institution	0	50
Number of Psychiatric Hospitalizations	Mean (SD)	2.44 (2.26)	4.68 (3.36)

Table 4. Scores and multivariate one-way corrected analyses of variance for the PANSS and neuropsychological battery.

Variable	Non-Kraepelinian (n=26)		Kraepelinian (n=26)			
	M	SD	M	SD	F (2,48)	P
PANSS						
Positive	14.46	5.61	20.64	5.51	8.60	0.001
Negative	16.75	5.51	23.62	5.40	16.30	<0.001
CVLT						
List A Trial 1	5.42	2.40	3.87	2.35	4.87	0.01
List A Trial 5	9.63	3.47	7.05	3.42	5.01	0.01
List A Total Learning	39.20	14.89	29.58	14.58	3.98	0.03
List B	4.30	2.14	3.40	2.09	4.07	0.02
List A short-delay free	7.58	4.03	5.05	3.93	3.08	0.06
List A short-delay cued	8.64	4.33	6.54	4.23	1.44	0.25
List A long-delay free	8.49	4.18	5.80	4.08	3.06	0.06
List A long-delay cued	8.64	4.33	6.54	4.23	1.80	0.18
Semantic cluster ratio	1.68	0.92	1.22	0.92	1.88	0.16
Serial cluster ratio	2.14	2.04	2.33	1.99	0.06	0.94
Free recall intrusions	1.78	5.25	6.95	5.15	6.13	0.004
Cued recall intrusions	0.97	3.72	5.18	3.67	8.82	0.001
Total intrusions	2.75	8.21	12.13	8.06	8.52	0.001
Recognition hits	12.55	3.77	13.01	3.72	0.18	0.84
Perseverations	7.34	9.18	5.83	8.97	0.54	0.59
Category Fluency						
Animals	13.83	5.46	14.24	5.35	3.46	0.04
Trailmaking						
Trails A	40.92	43.44	69.27	42.58	2.87	0.07
Trails B	120.87	86.02	196.63	84.23	5.62	0.006

Figure 14. Absolute thalamus slice volume in patients with schizophrenia and normal controls.

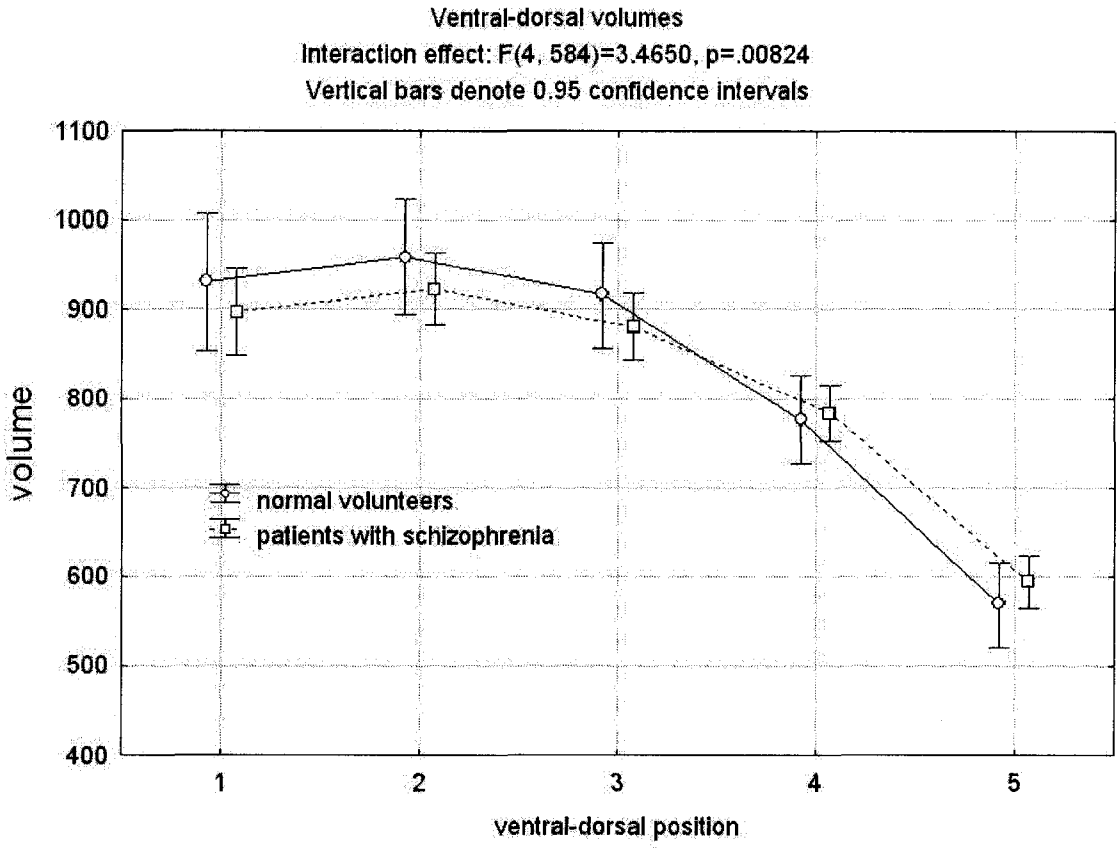

Figure 15. Absolute thalamus slice volumes in non-Kraepelinian and Kraepelinian patients.

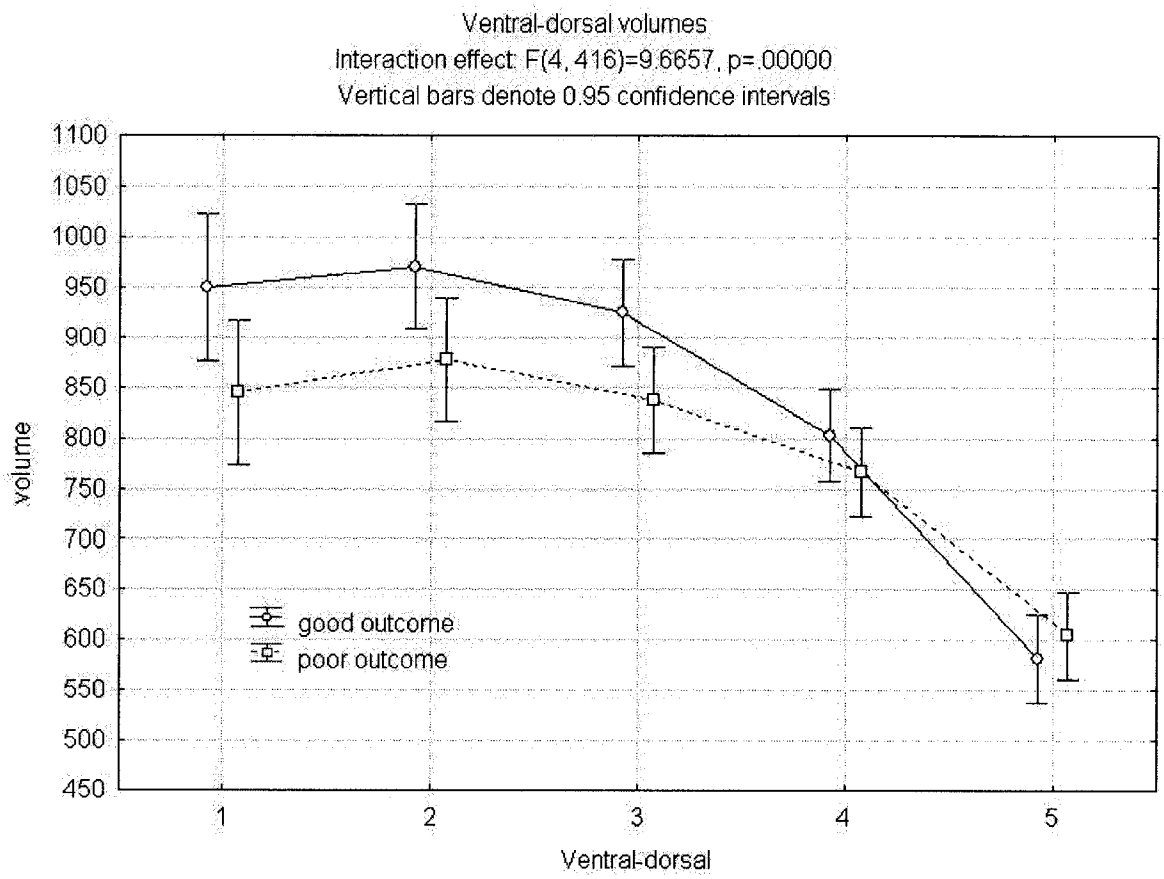

Figure 16. Absolute thalamus slice volumes in both schizophrenia patient groups and normal controls together.

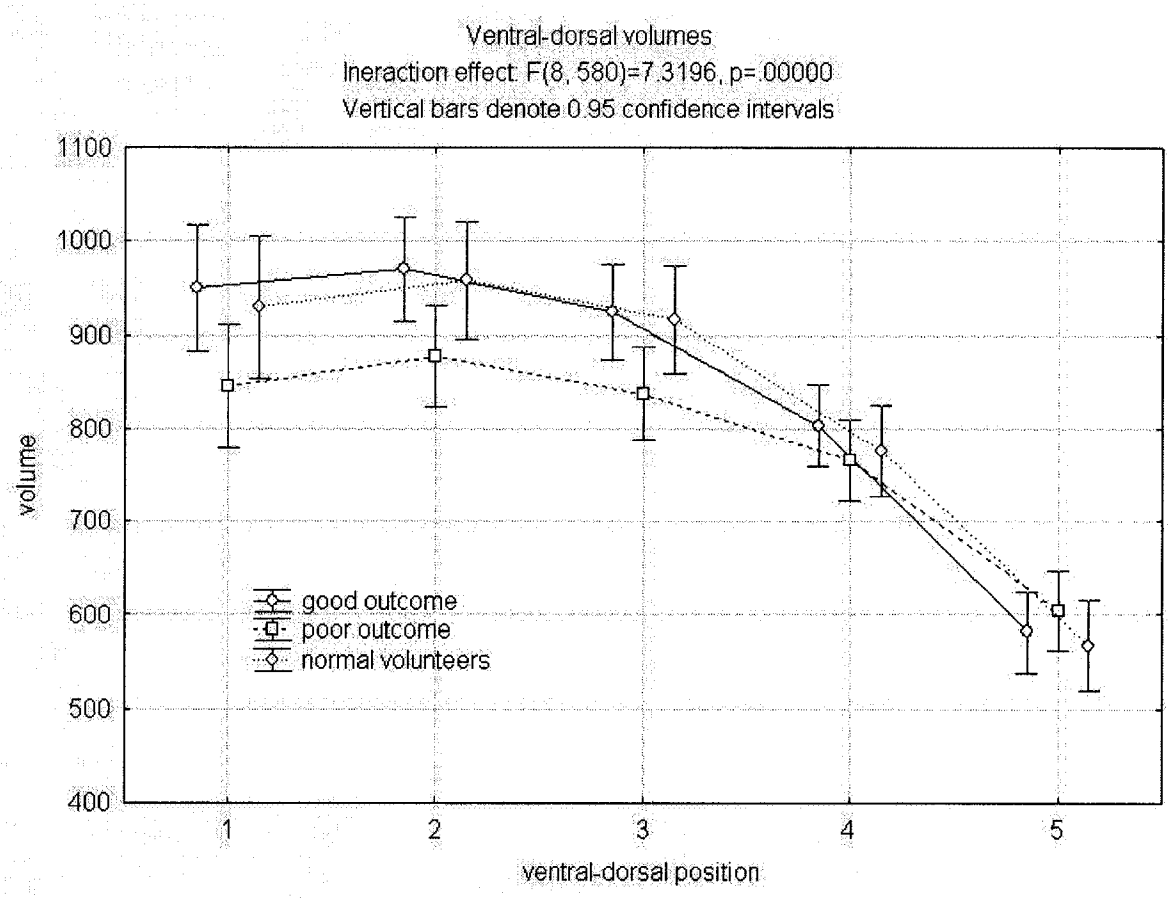

Table 5. Correlation coefficients between relative thalamic size at each level, collapsed across hemisphere, and sum of frontal and temporal grey and white matter in all schizophrenia patients, Kraepelinian patients, and poor outcome patients. Significant ($p<0.05$) associations are indicated with an asterisk (*).

Patient Group	Thalamus Slice	Sum relative frontal white	Sum relative frontal grey	Sum relative temporal white	Sum relative temporal grey
All Schizophrenia patients	Slice 1 (ventral)	-0.14	0.03	-0.08	0.18
	Slice 2	-0.08	0.16	-0.09	0.20*
	Slice 3	-0.15	0.21*	-0.15	0.26*
	Slice 4	-0.13	0.25*	-0.15	0.26*
	Slice 5 (dorsal)	-0.01	0.21*	-0.06	0.17
Good outcome patients only	Slice 1 (ventral)	-0.18	-0.26	0.01	0.13
	Slice 2	-0.05	-0.15	0.05	0.16
	Slice 3	-0.17	-0.09	0.01	0.22
	Slice 4	-0.10	-0.03	-0.02	0.16
	Slice 5 (dorsal)	-0.14	-0.10	0.06	0.12
Poor outcome patients only	Slice 1 (ventral)	-0.12	0.19	-0.16	0.20
	Slice 2	-0.12	0.32*	-0.19	0.23
	Slice 3	-0.16	0.37*	-0.28*	0.32*
	Slice 4	-0.19	0.39*	-0.27*	0.32*
	Slice 5 (dorsal)	-0.00	0.35*	-0.19	0.20

Figure 17. Internal capsule slice volumes, with whole brain volume as a covariate, in non-Kraepelinian patients, Kraepelinian patients, and normal controls.

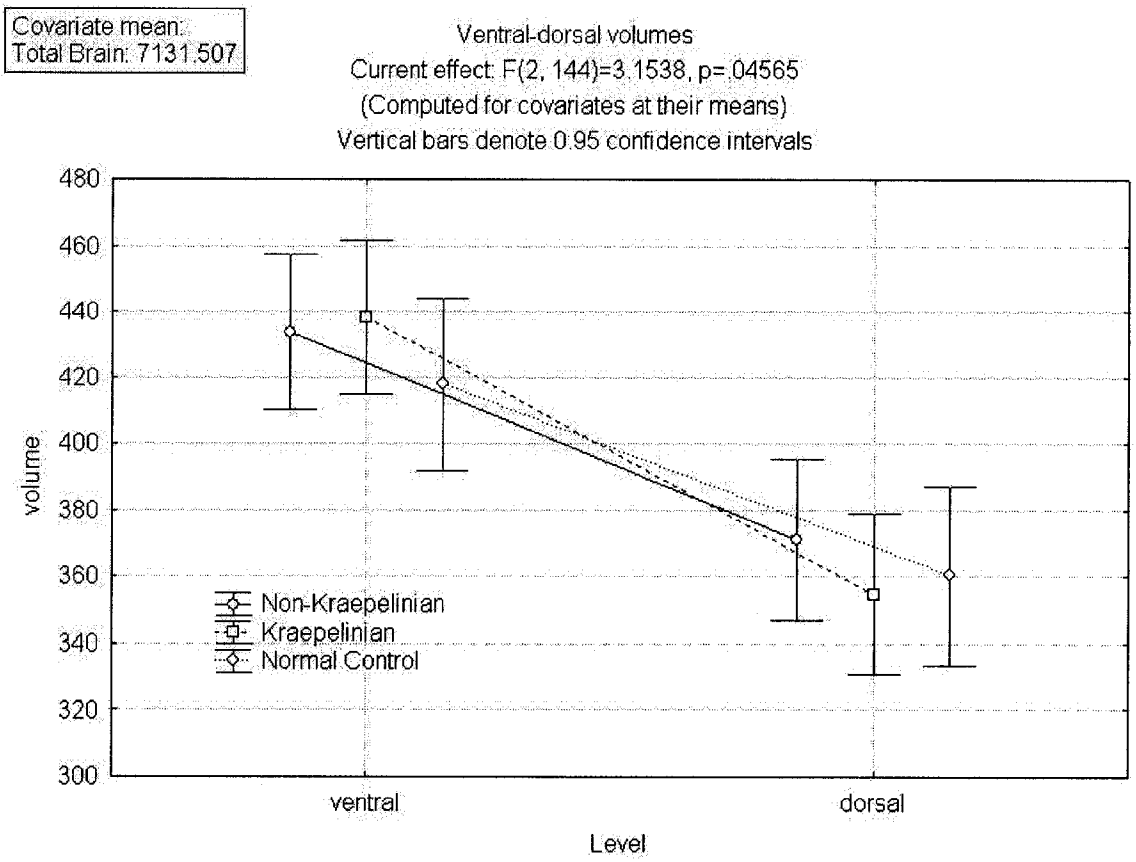

Figure 18. Absolute size of the internal capsules across dorsal to ventral levels in Kraepelinian and non-Kraepelinian patients.

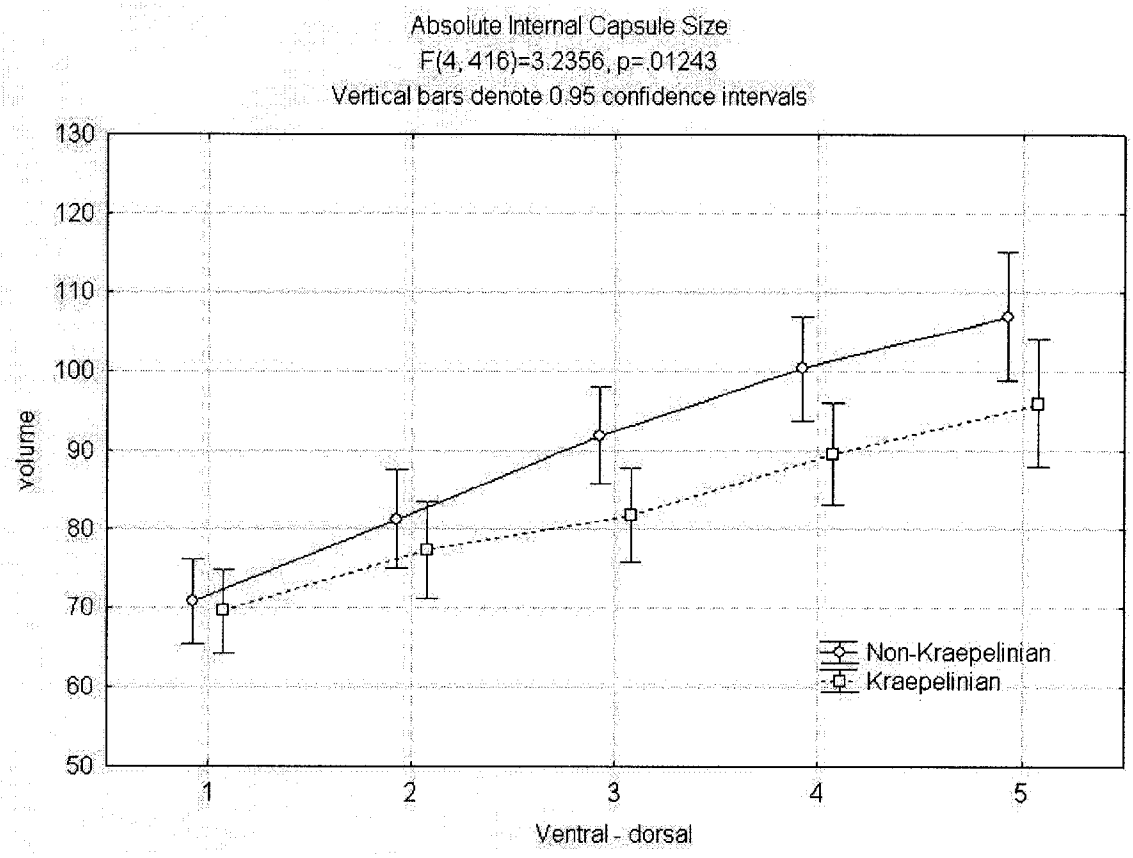

Figure 19. Absolute size of the internal capsules across dorsal to ventral levels in Kraepelinian patients, non-Kraepelinian patients, and normal controls.

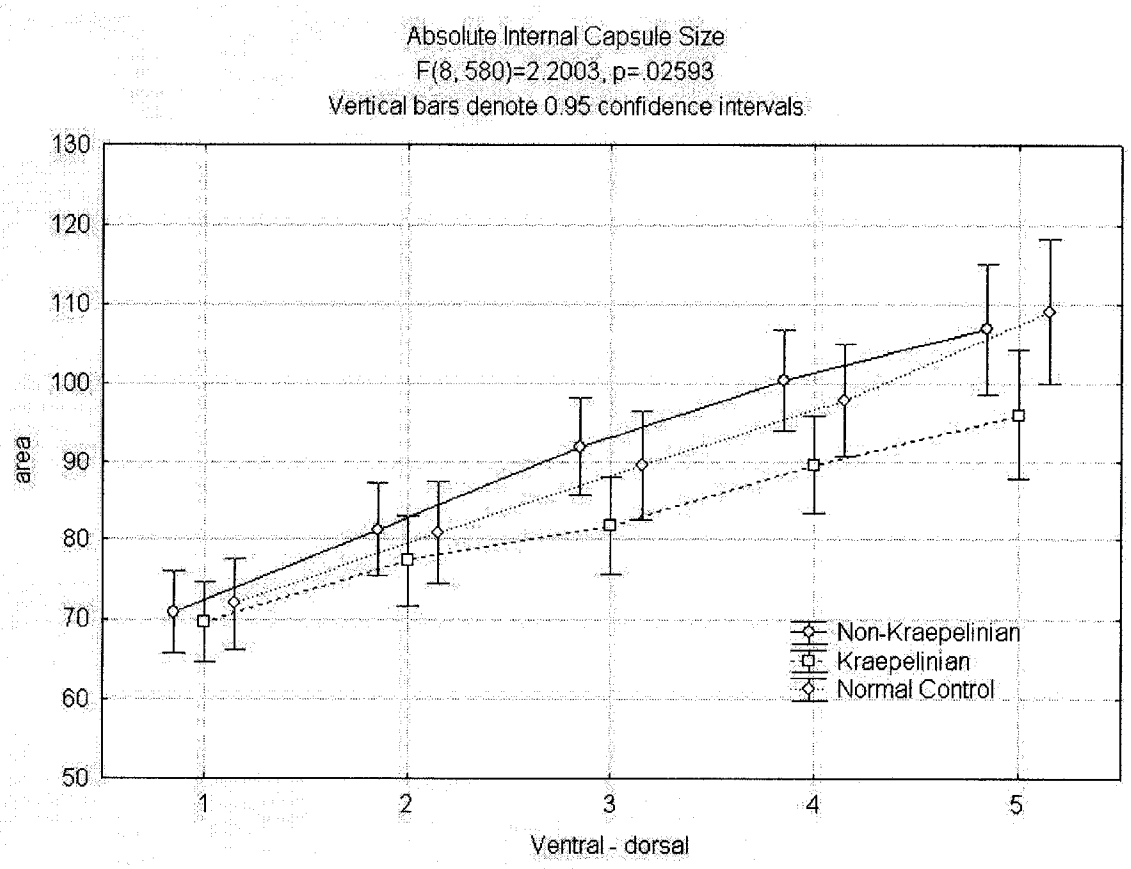

Table 6. Correlation coefficients between ventral and dorsal internal capsule size and thalamus at the five ventral to dorsal slices. Significant values ($p<0.05$) are indicated with an asterisks (*).

Patient Group	Internal Capsule Level	Thalamus Slice 1 (ventral)	Thalamus Slice 2	Thalamus Slice 3	Thalamus Slice 4	Thalamus Slice 5 (dorsal)
Normal Controls (n=42)	Ventral	0.29	0.27	0.23	0.12	0.24
	Dorsal	0.33*	0.18	0.04	0.21	0.47*
All sz patients (n=106)	Ventral	0.13	0.12	0.17	0.20*	0.14
	Dorsal	0.04	0.02	0.01	0.10	-0.01
Non-Kraepelinian (n=52)	Ventral	0.11	0.12	0.16	0.29*	0.29*
	Dorsal	-0.04	-0.03	-0.09	0.14	025
Kraepelinian (n=54)	Ventral	0.10	0.08	0.13	0.11	0.06
	Dorsal	0.02	-0.04	-0.03	0.03	-0.19

Table 7. Correlation coefficients between ventral and dorsal internal capsule size and caudate at the five ventral to dorsal slices. Significant values ($p<0.05$) are indicated with an asterisks (*).

Patient Group	Internal Capsule Level	Caudate Slice 1 (ventral)	Caudate Slice 2	Caudate Slice 3	Caudate Slice 4	Caudate Slice 5 (dorsal)
Normal Controls (n=42)	Ventral	0.27	0.43*	0.29	0.42*	0.28
	Dorsal	0.02	0.46*	0.21	0.23	0.15
All sz patients (n=106)	Ventral	0.12	0.08	0.21*	0.08	0.05
	Dorsal	0.15	-0.03	0.12	0.02	0.08
Non-Kraepelinian (n=52)	Ventral	0.21	0.04	0.18	0.02	0.06
	Dorsal	0.14	-0.01	0.17	0.05	0.25
Kraepelinian (n=54)	Ventral	-0.08	0.14	0.28*	0.17	0.10
	Dorsal	0.08	-0.03	0.14	0.02	0.01

Table 8. Correlation coefficients between ventral and dorsal internal capsule size and putamen at the five ventral to dorsal slices. Significant values ($p<0.05$) are indicated with an asterisks (*).

Patient Group	Internal Capsule Level	Putamen Slice 1 (ventral)	Putamen Slice 2	Putamen Slice 3	Putamen Slice 4	Putamen Slice 5 (dorsal)
Normal Controls (n=42)	Ventral	-0.04	0.37*	0.27	-0.09	0.20
	Dorsal	-0.34*	0.48*	0.34*	-0.10	0.10
All sz patients (n=106)	Ventral	0.10	0.07	0.25*	0.18	0.14
	Dorsal	0.02	0.10	0.25*	0.20*	0.09
Non-Kraepelinian (n=52)	Ventral	0.26	0.24	0.09	0.14	0.21
	Dorsal	0.13	0.34*	0.24	0.10	0.06
Kraepelinian (n=54)	Ventral	-0.07	-0.18	0.36*	0.18	0.03
	Dorsal	-0.05	-0.25	0.18	0.25	0.13

Table 9. Correlation coefficients between ventral and dorsal internal capsule sizes and the anterior horn, temporal horn, and lateral aspects of the lateral ventricles. Significant values ($p<0.05$) are indicated with an asterisks (*).

Patient Group	Internal Capsule Level	Anterior Horn	Temporal Horn	Lateral Ventricles
Normal Controls (n=42)	Ventral	-0.34*	-0.35*	-0.39*
	Dorsal	-0.35*	-0.36*	-0.35*
All sz patients (n=106)	Ventral	-0.12	-0.11	-0.16
	Dorsal	-0.23*	-0.14	-0.20
Non-Kraepelinian (n=52)	Ventral	-0.29*	-0.15	-0.27
	Dorsal	-0.36*	-0.13	-0.28*
Kraepelinian (n=54)	Ventral	0.08	-0.03	-0.06
	Dorsal	-0.07	-0.06	-0.11

Table 10. Correlation coefficients between ventral and dorsal internal capsule sizes and frontal and temporal lobe grey and white matter volume. Significant values ($p<0.05$) are indicated with an asterisks (*).

Patient Group	Internal Capsule Level	Frontal White Matter	Frontal Grey Matter	Temporal White Matter	Temporal Grey Matter
Normal Controls (n=42)	Ventral	-0.14	0.00	-0.17	0.03
	Dorsal	-0.01	0.28	-0.28	-0.17
All sz patients (n=106)	Ventral	0.06	0.11	-0.05	-0.15
	Dorsal	-0.07	0.02	-0.14	-0.07
Non-Kraepelinian (n=52)	Ventral	0.12	0.12	0.07	-0.17
	Dorsal	0.03	-0.03	-0.06	-0.07
Kraepelinian (n=54)	Ventral	0.04	0.06	-0.16	-0.16
	Dorsal	-0.09	0.06	-0.19	-0.12

References

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Ananth, H., Popescu, I., Critchley, H.D., Good, C.D., Frackowiak, R.S., & Dolan, R.J. (2002). Cortical and subcortical gray matter abnormalities in schizophrenia determined through structural magnetic resonance imaging with optimized volumetric voxel-based morphometry. *American Journal of Psychiatry, 159,* 1497-1505.

Andreasen, N.C., Arndt, S., Swayze, V. 2nd, Cizadlo, T., Flaum, M., O'Leary, D., Ehrhardt, J.C., & Yuh, W.T. (1994). Thalamic abnormalities in schizophrenia visualized through magnetic resonance image averaging. *Science, 266,* 221.

Andreasen, N.C., Flaum, M., & Arndt, S. (1992). The Comprehensive Assessment of Symptoms and History. *Archives of General Psychiatry, 49,* 615-623.

Andreasen, N.C. & Olsen, S. (1982). Negative v positive schizophrenia: Definition and validation. *Archives of General Psychiatry, 39,* 789-794.

Antonova, E., Sharma, T., Morris, R., & Kumari, V. (in press). The relationship between brain structure and neurocognition in schizophrenia: A selective review. *Schizophrenia Research.*

Arciniegas, D., Rojas, D.C., Teale, P., Sheeder, J., Sandberg, E., & Reite, M. (1999). The thalamus and the schizophrenia phenotype: Failure to replicate reduced volume. *Biological Psychiatry, 45,* 1329-1335.

Army Individual Test Battery (1944). *Manual of directions and scoring.* Washington, D.C.: War Department, Adjutant Generals Office.

Ahurner, J. & Friston, K.J. (2000). Voxel-basd morphometry: The methods. *Neuroimage, 11,* 805-821.

Axer, H., Lippitz, B.E., von Keyserlingk, D.G. (1999). Morphological asymmetry in anterior limb of human internal capsule revealed by confocal laser and polarized light microscopy. *Psychiatry Research, 91,* 141-154.

Axer, H. & von Keyserlingk, D.G. (2000). Mapping of fiber orientation in human internal capsule by means of polarized light and confocal scanning laser microscopy. *Journal of Neuroscience Methods, 94,* 165-175.

Baare, W.F., Hulshoff Pol, H.E., Hijman, R., Mali, W.P., Viergever, M.A., & Kahn, R.S. (1999). Volumetric analysis of frontal lobe regions in schizophrenia: Relation to cognitive function and symptomatology. *Biological Psychiatry, 45,* 1597-1605.

Barta, P.E., Pearlson, G.D., Powers, R.E., Richards, S.S., & Tune, L.E. (1990). Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. *American Journal of Psychiatry, 147,* 1457-1462.

Bilder, R.M., Goldman, R.S., Robinson, D., Reiter, G., Bell, L., Bates, J.A., Pappadopulos, E., Willson, D.F., Alvir, J.M.J., Woerner, M.G., Geisler, S., Kane, J.M., & Lieberman, J.A. (2000). Neuropsychology of first-episode schizophrenia. *American Journal of Psychiatry, 157,* 549-559.

Bleuler, E. (1950). Dementia Praecox or The Group of Schizophrenias. New York: International Universities Press.

Borod, J.C., Alpert, M., Brozgold, A., Martin, C., Welkowitz, J., Diller, L., Peselow, E., Angrist, B., & Lieberman, A. (1989). A preliminary comparison of flat affect schizophrenics and brain-damaged patients on measures of affective processing. *Journal of Communication Disorders, 22,* 93-104.

Borod, J.C., Martin, CC., Alpert, M., Brozgold, A., & Welkowitz, J. (1993). Perception of facial emotion in schizophrenic and right brain-damaged patients. *Journal of Nervous and Mental Disease, 181,* 494-502.

Borod, J.C., Welkowitz, J., Alpert, M., Brozgold, A.Z., Martin, C., Peselow, E., & Diller, L. (1990). Parameters of emotional processing in neuropsychiatric disorders: Conceptual issues and a battery of tests. *Journal of Communication Disorders, 23,* 247-271.

Breier, A., Buchanan, R.W., Elkashef, A., Munson, R.C., Kirkpatrick, B., Gellad, F. (1992). Brain morphology and schizophrenia. A magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. *Archives of General Psychiatry, 49,* 921-926.

Brickman, A.M., Buchsbaum, M.S., Bloom, R., Bokhoven, P., Paul-Oduard, R., Haznedar, M.M., Dahlman, K.L., Hazlett, E.A., Aronowitz, J., Heath, D., & Shihabuddin, L. (in press a.). Neuropsychological functioning in first-break never-medicated adolescents with psychosis. *Journal of Nervous and Mental Disease.*

Brickman, A.M., Buchsbaum, M.S., Shihabuddin, L., Byne, W., Newmark, R.E., Brand, J., Ahmed, S., Mitelman, S.A., & Hazlett, E.A.. (in press). Thalamus size and outcome in schizophrenia. *Schizophrenia Research.*

Brickman, A.M., Buchsbaum, M.S., Shihabuddin, L., Hazlett, E.A., Borod, J.C., & Mohs, R.C. (2003). Striatal size, glucose metabolic rate, and verbal learning in normal aging. *Cognitive Brain Research, 17,* 106-116.

Brickman, A.M., Harvey, P.D., Shihabuddin, L., Berwid, O.G., Boccio, J.T., Friedman, J., & Davis, K.L. (2001). Verbal learning in Kraepelinian and non-Kraepelinian schizophrenia [Abstract]. *Biological Psychiatry, 49,* 171S.

Brickman, A.M., Shihabuddin, L., Harvey, P.D., Mitelman, S.A., Tang, C., Prikhryl, R., Miozzo, R., Davis, K.L., & Buchsbaum, M.S. (2002). Recent evidence to support a "Kraepelinian" subtype of schizophrenia [Abstract]. *Journal of the International Neuropsychological Society, 8,* 242.

Brickman, A.M., Harvey, P.D., Shihabuddin, L., Berwid, O.G., Boccio, J.T., Friedman, J.I., Buchsbaum, M.S., & Davis, K.L. (2004). *Further characterization of very poor outcome schizophrenia: Neuropsychological status.* Manuscript in preparation.

Brickman, A.M., Ivanov, Z.S., Shihabuddin, L., & Buchsbaum, M.S. (2003, May). *Morphometric analysis of the anterior internal capsule in schizophrenia.* Poster session presented at the annual meeting of the American Psychiatric Association, San Francisco, CA.

Brickman, A.M., Buchsbaum, M.S., Shihabuddin, L., Ivanov, Z.S., Hahn, E., Mitelman, S.A., Hazlett, E.A., Byne, W., & Davis, K.L. (2004). *Morphometric analysis of the anterior internal capsule in good- and poor-outcome schizophrenia.* Manuscript in preparation.

Brickman, A.M., Paul, R.H., Cohen, R.A., Williams, L.M., MacGregor, K.L., Jefferson, A.L., Tate, D.F., Gunstad, J., & Gordon, E. (2004). Semantic and phonemic verbal fluency across the adult lifespan: Relationship to EEG theta power. Manuscript submitted for publication.

Bridle, N., Pantelis, C., Wood, S.J., Coppola, R., Velakoulis, D., McStephen, M., Tierney, P., Le, T.L., Torrey, E.F., & Weinberger, D. (2002). Thalamic and caudate volumes in monozygotic twins discordant for schizophrenia. *Australia and New Zealand Journal of Psychiatry, 36,* 347-354.

Buchanan, R.W., Kirkpatrick, B., Heinrichs, D.W., & Carpenter Jr., W.T. (1990). Clinical correlates of the deficit syndrome of schizophrenia. *American Journal of Psychiatry, 147,* 290-294.

Buchanan, R.W., Strauss, M.E., Kirkpatrick, B., Holstein, C., Breier, A., & Carpenter Jr., W.T. (1999). Deficit psychopathology and a paradigm shift in schizophrenia research. *Biological Psychiatry, 46,* 352-360.

Buchanan, R.W., Strauss, M.E., Breier, A., Kirkpatrick, B., & Carpenter Jr., W.T. (1997). Attentional impairments in deficit and nondeficit forms of schizophrenia. *American Journal of Psychiatry, 154,* 363-370.

Buchanan, R.W. & Carpenter, W.T. (1994). Domains of psychopathology. An approach to the reduction of heterogeneity in schizophrenia. *The Journal of Nervous and Mental Disease, 182,* 193-204.

Buchanan, R.W., Vladar, K., Barta, P.E., & Pearlson, G.D. (1998). Structural evaluation of the prefrontal cortex in schizophrenia. *American Journal of Psychiatry, 155,* 1049-1055.

Buchsbaum, M.S. (1990). The frontal lobes, basal ganglia and temporal lobes as sites for schizophrenia. *Schizophrenia Bulletin, 16,* 379-390.

Buchsbaum, M.S., Ingvar, D.H., Kessler, R., Waters, R.N., Cappelletti, J., van Kammen, D.P., King, A.C., Johnson, J.L., Manning, R.G., Flynn, R.W., Mann, L.S., Bunney, W.E. Jr., & Sokoloff, L. (1982). Cerebral glucography with positron tomography. *Archives of General Psychiatry, 39,* 251-259.

Buchsbaum, M.S., Shihabuddin, L., Brickman, A.M., Miozzo, R., Prikryl, R., Shaw, R., & Davis, K. (2003). Caudate and putamen volumes in good and poor outcome patients with schizophrenia. *Schizophrenia Research, 64,* 53-62.

Buchsbaum, M.S., Shihabuddin, L., Hazlett, E.A., Schroder, J., Haznedar, M.M., Powchick, P., Spiegel-Cohen, J., Wei, T., Singer, M.S., & Davis, K.L. (2002). Kraepelinian and non-Kraepelinian subgroup differences in cerebral metabolic rate. *Schizophrenia Research, 55,* 25-40.

Buchsbaum, M.S., Someya, T., Teng, C.Y., Abel, L., Chin, S., Najafi, A., Haier, R.J., Wu, J., & Bunney, W.E. (1996). PET and MRI of the thalamus in never-medicated patients with schizophrenia. *American Journal of Psychiatry, 153,* 191-199.

Buchsbaum, M.S., Tang, C.Y., Peled, S., Gudbjartson, H., Lu, D., Hazlett, E.A., Downhill, J., Haznedar, M., Fallon, J.H., & Atlas, S.W. (1998). MRI white matter diffusion anisotropy and PET metabolic rate in schizophrenia. *Neuroreport, 9,* 425-430.

Byne, W., Buchsbaum, M.S., Kemether, E., Hazlett, E.A., Shinwari, A., Mitropoulou, V., & Siever, L.J. (2001). Magnetic resonance imaging of the thalamic mediodorsal nucleus and pulvinar in schizophrenia and schizotypal personality disorder. *Archives of General Psychiatry, 58,* 133-140.

Byne, W., Buchsbaum, M.S., Mattiace, L.A., Hazlett, E.A., Kemether, E., Elhakem, S.L., Purohit, D.P., Haroutunian, V., & Jones, L. (2002). Postmortem assessment of thalamic nuclear volumes in subjects with schizophrenia. *American Journal of Psychiatry, 159,* 59-65.

Cahn, W., Pol, H.E., Lems, E.B., van Haren, N.E., Schnack, H.G., van der Linden, J.A., Schothorst, P.F., van Engeland, H., & Kahn, R.S. (2002). Brain volume changes in first-episode schizophrenia: A 1-year follow-up study. *Archives of General Psychiatry, 59,* 1002-1010.

Cannon, T.D., van Erp, T.G.M., Huttunen, M., Lonnqvist, J., Salonen, O., Valanne, L., Poutanen, V., Standertskjold-Nordenstam, C.G., Gur, R.E., & Yan, M. (1998).

Regional gray matter, white matter, and cerebrospinal fluid distributions in schizophrenic patients, their siblings, and controls. *Archives of General Psychiatry, 55*, 1084-1091.

Cantor-Graae, E., Warkentin, S., & Nilsson, A. (1995). Neuropsychological assessment of schizophrenic patients during a psychotic episode. *Acta Psychiatrica Scandinavica, 91*, 283-288.

Carpenter Jr., W.T., Heinrichs, D.W., & Wagman, A.M. (1988). Deficit and nondeficit forms of schizophrenia: The concept. *American Journal of Psychiatry, 145*, 578-583.

Carter, C.S., Perlstein, W., Ganguli, R., Brar, J., Mintun, M., & Cohen, J.D. (1998). Functional hypofrontality and working memory dysfunction in schizophrenia. *American Journal of Psychiatry, 155*, 1285-1287.

Chakos, M., Lieberman, J., & Bilder, R. (1994). Increase in caudate nuclei volume of first episode schizophrenia patients taking antipsychotic drugs. *American Journal of Psychiatry, 151*, 1430-1436.

Chey, J., Lee, J., Kim, Y.S., Kwon, S.M., & Shin, Y.M. (2002). Spatial working memory span, delayed response and executive function in schizophrenia. *Psychiatry Research, 110*, 103-112.

Chukwudelunzu, F.E., Meschia, J.F., Graff-Radford, N.R., & Lucas, J.A. (2001). Extensive metabolic and neuropsychological abnormalities associated with discrete infarction of the genu of the internal capsule. *Journal of Neurology, Neurosurgery, and Psychiatry, 71*, 658-652.

Crow, T.J. (1980). Molecular pathology of schizophrenia: More than one disease process? *British Medical Journal, 280*, 66-68.

Crow, T.J. (2000). Schizophrenia as the price that homo sapiens pay for language: A resolution of the central paradox in the origin of the species. *Brain Research: Brain esearch Reviews, 31,* 118-129.

Danos, P., Baumann, B., Bernstein, H.G., Stauch, R., Krell, D., Falkai, P., & Bogerts, B. (2002). The ventral lateral posterior nucleus of the thalamus in schizophrenia: A post-mortem study. *Psychiatry Research, 114,* 1-9.

Davidson, L.L. & Heinrichs, R.W. (2003). Quantification of frontal and temporal lobe brain-imaging findings in schizophrenia: Meta-analysis. *Psychiatry Research, 122,* 69-87.

Davidson, M., Harvey, P.D., Powchik, P., Parrella, M., White, L., Knobler, H.Y., Losonczy, M.F., Keefe, R.S., Katz, S., & Frecska, E. (1995). Severity of symptoms in chronically institutionalized geriatric schizophrenic patients. *American Journal of Psychiatry, 152,* 197-207.

Davis, K.L., Buchsbaum, M.S., Shihabuddin, L., Spiegel-Cohen, J., Metzger, M., Frecska, E., Keefe, R.S., & Powchick, P. (1998). Ventricular enlargement in poor-outcome schizophrenia. *Biological Psychiatry, 43,* 783-793.

Davis, K.L., Stewart, D.G., Friedman, J.I., Buchsbaum, M., Harvey, P.D., Hof, P.R., Buxbaum, J., & Haroutunian, V. (2003). White matter changes in schizophrenia: Evidence for myelin-related dysfunction. *Archives of General Psychiatry, 60,* 443-456.

Deicken, R.F., Eliaz, Y., Chosiad, L., Feiwell, R., & Rogers, L. (2002). Magnetic resonance imaging of the thalamus in male patients with schizophrenia. *Schizophrenia Research, 58,* 135-144.

Deister, A. & Marneros, A. (1993). Long-term stability of subtypes in schizophrenic disorders: A comparison of four diagnostic systems. *European Archives of Psychiatry and Clinical Neuroscience, 242,* 184-190.

Delis, D.C., Kramer, J.H., Kaplan, E., & Ober, B.A. (1987). The California Verbal Learning Test: Research edition. San Antonio: Psychological Corporation.

Evans, J.D., Negron, A.E., Palmer, B.W., Paulsen, J.S., Heaton, R.K., & Jeste, D.V. (1999). Cognitive deficits and psychopathology in institutionalized versus community-dwelling elderly schizophrenia patients. *Journal of Geriatric Psychiatry and Neurology, 12,* 11-15.

Fenton, W.S. & McGlashan, T.H. (1992). Testing systems for assessment of negative symptoms in schizophrenia. *Archives of General Psychiatry, 49,* 179-184.

Flaum, M., Swayze, V.W., O'Leary, D.S., Yuh, W.T.C., Ehrhardt, J.C., Arndt, S.V., & Andreasen, N.C. (1995). Effects of diagnosis, laterality, and gender on brain morphology in schizophrenia. *American Journal of Psychiatry, 152,* 704-714.

Foong, J., Symms, M.R., Barker, G.J., Maier,M., oermann, F.G., Miller, D.H., Ron, M.A. (2001). Neuropathological abnormalities in schizophrenia: Evidence from magnetization transfer imaging. *Brain, 124,* 882-892.

Friedman, J.I., Harvey, P.D., Coleman, T., Moriarty, P.J., Bowie, C., Parrella, M., White, L., Adler, D., & Davis, K.L. (2001). Six-year follow-up study of cognitive and functional status across the lifespan in schizophrenia: A comparison with Alzheimer's disease and normal aging. *American Journal of Psychiatry, 158,* 1441-1448.

Gold, S., Arndt, S., Nopoulos, P., O'Leary, D.S., & Andreasen, N.C. (1999). Longitudinal study of cognitive function in first-episode and recent-onset schizophrenia. *American Journal of Psychiatry, 156,* 1342-1348.

Goldberg, T.E., Hyde, T.M., Kleinman, J.E., & Weinberger, D.R. (1993). Course of schizophrenia: Neuropsychological evidence for a static encephalopathy. *Schizophrenia Bulletin, 19,* 797-804.

Goldman-Rakic, P.S. & Selemon, L.D. (1997). Functional and anatomical aspects of prefrontal pathology in schizophrenia. *Schizophrenia Bulletin, 23,* 437-458.

Goodglass, H. & Kaplan, E. (1983). *The assessment of aphasia and related disorders* (2nd ed.). Philadelphia: Lea & Febiger Publishers.

Gottesman, I.I. & Gould, T.D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry, 160,* 636-645.

Green, M.F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia. *American Journal of Psychiatry, 153,* 321-330.

Green, M.F., Kern, R.S., Braff, D.L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the "right stuff"? *Schizophrenia Bulletin, 26,* 119-136.

Gur, R.E., Cowell, P.E., Latshaw, A., Turetsky, B.I., Grossman, R.I., Arnold, S.E., Bilder, W.B., & Gur, R.C. (2000). Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Archives of General Psychiatry, 57,* 761-768.

Gur, R.E., Cowell, P., Turetsky, B.I., Gallacher, F., Cannon, T., Bilker, W., & Gur, R.C. (1998). A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Archives of General Psychiatry, 55,* 145-152.

Gur, R.E., Mozley, P.D., Shtasel, D.L., Cannon, T.D., Gallacher, F., Turetsky, B., Grossman, R., & Gur, R.C. (1994). Clinical subtypes of schizophrenia: Differences in brain and CSF volume. *American Journal of Psychiatry, 151,* 343-350.

Harvey, P.D. & Davidson, M. (2002). Schizophrenia: Lifetime course. In K.L. Davis, D. Charney, J.T. Coyle, & C. Nemeroff (Eds.). Neuropsychopharmacology: Fifth generation of progress. Philadelphia: Lippincott.

Harvey, P.D., Davidson, M., Mueser, K.T., Parrella, M., & White, L. (1997). The Social Adaptive Functioning Evaluation: An assessment measure for geriatric psychiatric patients. *Schizophrenia Bulletin, 23,* 131-146.

Harvey, P.D., Howanitz, E., Parrella, M., White, L., Davidson, M., Mohs, R.C., Hoblyn, J., & Davis, K.L. (1998). Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: A comparison across treatment sites. *American Journal of Psychiatry, 155,* 1080-1086.

Harvey, P.D., Palmer, B.W., Heaton, R.K., Mohammed, S., Kennedy, J., & Brickman, A.M. (in press). Stability of cognitive performance in older patients with schizophrenia: An eight-week test-retest study. *American Journal of Psychiatry.*

Harvey, P.D., Putnam, K.M., Davidson, M., Kahn, R.S., Powchick, P., McQueeney, R., Keefe, R.S., & Davis, K.L. (1991). Brief neuroleptic discontinuation and clinical symptoms in Kraepelinian and non-Kraepelinian chronic schizophrenic patients. *Psychiatry Research, 38,* 285-292.

Harvey, P.D., Silverman, J.M., Mohs, R.C., Parrella, M., White, L., Powchik, P., Davidson, M., & Davis, K.L. (1999). Cognitive decline in late-life schizophrenia: A longitudinal study of geriatric chronically hospitalized patients. *Biological Psychiatry, 45,* 32-40.

Hazlett, E.A., Buchsbaum, M.S., Kemether, E., Bloom, R., Platholi, J., Brickman, A.M., Shihabuddin, L., Tang, C., & Byne, W. (2004). Abnormal glucose metabolism in the mediodorsal nucleus of the thalamus in schizophrenia. *American Journal of Psychiatry, 161,* 305-314.

Hazrati, L.H. & Parent, A. (1992). The striatopallidal projection displays a high degree of anatomical specificity in the primate. *Brain Research, 592,* 213-227.

Heaton, R.K. (1981). Wisconsin Card Sorting Test manual. Odess, FL: Psychological Assessment Resources.

Heaton, R.K., Gladsjo, J.A., Palmer, B.W., Kuck, J., Marcotte, T.D., & Jeste, D.V. (2001). Stability and course of neuropsychological deficits in schizophrenia. *Archives of General Psychiatry, 58,* 24-32.

Heaton, R.K., Paulsen, J.S., McAdams, L.A., Kuck, J., Zisook, S., Braff, D., Harris, J., & Jeste, D.V. (1994). Neuropsychological deficits in schizophrenics. *Archives of General Psychiatry, 51,* 469-476.

Heinrichs, R.W. & Zakzanis, K.K. (1998). Neurocognitive deficit in schizophrenia. *Neuropsychology, 12,* 426-445.

Henn, F.A. & Braus, D.F. (1999). Structural neuroimaging in schizophrenia: An integrative view of neuromorphology. *European Archives of Psychiatry and Clinical Neuroscience, 249, Suppl. 4,* 48-56.

Hill, S.K., Ragland, J.D., Gur, R.C., & Gur, R.E. (2001). Neuropsychological differences among empirically derived clinical subtypes of schizophrenia. *Neuropsychology, 15,* 492-501.

Highley, J.R., Walker, M.A., Crow, T.J., Esiri, M.M., & Harrison, P.J. (2003). Low medial and lateral right pulvinar volumes in schizophrenia: A postmortem study. *American Journal of Psychiatry, 160,* 1177-1179.

Hoff, A.L., Sakuma, M., Wieneke, M., Horon, R., Kushner, M., & DeLisi, L.E. (1999). Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. *American Journal of Psychiatry, 156,* 1336-1341.

Hokama, H., Shenton, M., Nestor, P., Kikinis, R., Levitt, J., Metcalf, D., Wible, C., O'Donnell, B., Jolesz, F., & McCarley, R. (1995). Caudate, putamen and globus pallidus volume in schizophrenia. *Psychiatry Research: Neuroimaging, 61,* 209-229.

Hulshoff Pol, H.E., Schnack, H.G., Mandl, R.C., Cahn, W., Collins, D.L., Evans, A.C., & Kahn, R.S. (2004). Focal white matter density changes in schizophrenia: Reduced inter-hemispheric connectivity. *Neuroimage, 21,* 27-35.

Hulshoff Pol, H.E., Schnack, H.G., Mandl, R.C., van Haren, N.E., Konig, H., Collins, D.L., Evans, A.C., & Kahn, R.S. (2001). Focal gray matter density changes in schizophrenia. *Archives of General Psychiatry, 58,* 1118-1125.

Ingvar, D.H. (1974). Regional cerebral blood flow in organic dementia and in chronic schizophrenia. *Triangle, 13,* 17-23.

Innocenti, G.M., Ansermet, F., & Parnas, J. (2003). Schizophrenia, neurodevelopment, and corpus callosum. *Molecular Psychiatry, 8,* 261-274.

Jaeger, J., Berns, S.M., & Czobor, P. (2003). The multidimensional scale of independent functioning: A new instrument for measuring functional disability in psychiatric populations. *Schizophrenia Bulletin, 29,* 153-168.

Johnstone, E.C., Crow, T.J., Frith, C.D., Husband, J., & Kreel, L. (1976). Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet, 2,* 924-926.

Jones, E. (1997). Cortical development and thalamic pathology in schizophrenia. *Schizophrenia Bulletin, 23,* 483-501.

Kay, S.R., Fiszbein, A., & Opler, L.A. (1987). The positive and negative syndrome scale (PANSS). *Schizophrenia Bulletin, 13,* 261-276.

Keefe, R.S. (1995). The contribution of neuropsychology to psychiatry. *American Journal of Psychiatry, 152,* 6-15.

Keefe, R.S., Frescka, E., Apter, S.H., Davidson, M., Macaluso, J.M., Hirschowitz, J., & Davis, K.L. (1996). Clinical characteristics of Kraepelinian schizophrenia: Replication and extension of previous findings. *American Journal of Psychiatry, 153,* 806-811.

Keefe, R.S., Lobel, D.S., Mohs, R.C., Silverman, J.M., Harvey, P.D., Davidson, M., Losonczy, M.F., & Davis, K.L. (1991). Diagnostic issues in schizophrenia: Kraepelinian schizophrenia, undifferentiated schizophrenia, and state-independent negative symptoms. *Schizophrenia Research, 4,* 71-79.

Keefe, R.S., Mohs, R.C., Davidson, M., Losonczy, M.F., Silverman, J.M., Lesser, J.C., Horvath, T.B., & Davidson, K.L. (1988). Kraepelinian schizophrenia: A subgroup of schizophrenia? *Psycchopharmacology Bulletin, 24,* 56-61.

Keefe, R.S., Mohs, R.C., Losonczy, M.F., Davidson, M., Silverman, J.M., Kendler, K.S., Horvath, T.B., Nora, R., & Davis, K.L. (1987). Characteristics of very poor outcome schizophrenia. *American Journal of Psychiatry, 144,* 889-895.

Kemether, E.M., Buchsbaum, M.S., Byne, W., Hazlett, E.A., Haznedar, M., Brickman, A.M., Platholi, J., & Bloom, R. (2003). Magnetic resonance imaging of the mediodorsal, pulvinar, and centromedian nuclei of the thalamus in patients with schizophrenia. *Archives of General Psychiatry, 60,* 983-991.

Kenny, J.T., Friedman, L., Findling, R.L., Swales, T.P., Strauss, T.P., Strauss, M.E., Jesberger, J.A., & Schulz, S.C. (1997). Cognitive impairment in adolescents with schizophrenia. *American Journal of Psychiatry, 154,* 1613-1615.

Konick, L.C. & Friedman, L. (2001). Meta-analysis of thalamic size in schizophrenia. *Biological Psychiatry, 49,* 28-38.

Kraepelin, E. (1904). Lectures on Clinical Psychiatry. London: Bailliere, Tendall, & Cox.

Lawrie, S.M. & Abukmeil, S.S. (1998). Brain abnormality in schizophrenia: A systematic and quantitative review of volumetric magnetic resonance imaging studies. *British Journal of Psychiatry, 172,* 110-120.

Lezak, M.D. (1994). *Neuropsychological assessment* (3rd ed.). New York: Oxford University Press.

Liddle, P.F. & Crow, T.J. (1984). Age disorientation in chronic schizophrenia is associated with global intellectual impairment. *British Journal of Psychiatry, 144,* 193-1999.

Lieberman, J.A., Perkins, D., Belger, A., Chakos, M., Jarskog, F., Boteva, K., & Gilmore, J. (2001). The early stages of schizophrenia. *Biological Psychiatry, 50,* 884-897.

Lim, K.O., Hedehus, M., Moseley, M., de Crespigny, A., Sullivan, E.V., & Pfefferbaum, A. (1999). Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. *Archives of General Psychiatry, 56,* 367-374.

McCarley, R.W., Wible, C.G., Frumin, M., Hirayasu, Y., Levitt, J.J., Fischer, I.A., & Shenton, M.E. (1999). MRI anatomy of schizophrenia. *Biological Psychiatry, 45,* 1099-1119.

Meyer, M. (1949). A study of efferent connections of the frontal lobe in the human brain after leucotomy. *Brain, 72,* 265-296.

Minami, T., Nobuhara, K., Okugawa, G., Takase, K., Yoshida, T., Sawada, S., Ha-Kawa, S., Ikeda, K., & Kinoshita, T. (2003). Diffusion tensor magnetic resonance imaging of disruption of regional white matter in schizophrenia. *Neuropsychobiology, 47,* 141-145.

Mishkin, M. & Ungerleider, L.G. (1982). Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. *Behavioral Brain Research, 6,* 57-77.

Mitelman, S.A., Shihabuddin, L., Brickman, A.M., Hazlett, E.A., & Buchsbaum, M.S. (2003). MRI assessment of gray and white matter distribution in Brodmann's areas of the cortex in good and poor outcome schizophrenia. *American Journal of Psychiatry, 160,* 2154-2168.

Mitelman, S.A., Shihabuddin, L., Brickman, A.M., Hazlett, E.A., & Buchsbaum, M.S. (in press). Volume of the cingulate and outcome in schizophrenia. *Schizophrenia Research.*

Mirsky, A.F. (1969). Neuropsychological bases of schizophrenia. *Annual Review of Psychology,* 321-348.

McGlashan, T.H. & Hoffman, R.E. (2000). Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Archives of General Psychiatry, 57,* 637-648.

Nopoulos, P., Flashman, L., Flaum, M., Arndt, S., & Andreasen, N. (1999). Stability of cognitive functioning early in the course of schizophrenia. *Schizophrenia Research, 14,* 29-37.

Paillere-Martinot, M., Caclin, A., Artiges, E., Poline, J.B., Joliot, M., Mallet, L., Recesens, C., Attar-Levy, D., & Martinot, J.L. (2001). Cerebral gray and white matter reductions and clinical correlates in patients with early onset schizophrenia. *Schizophrenia Research, 50,* 19-26.

Parent, A. (1996). *Carpenter's human neuroanatomy* (9th ed.). Baltimore: Williams & Wilkins.

Paulsen, J.S., Salmon, D.P., Monsch, A.U., Butters, N., Swenson, M.R., & Bondi, M.W. (1995). Discrimination of cortical from subcortical dementias on the basis of memory and problem-solving tests. *Journal of Clinical Psychology, 51,* 48-58.

Portas, C.M., Goldstein, J.M., Shenton, M.E., Hokama, H.H., Wible, C.G., Fischer, I., Kikinis, R., Donnino, R., Jolesz, F.A., & McCarley, R.W. (1998). Volumetric evaluation of the thalamus in schizophrenic male patients using magnetic resonance imaging. *Biological Psychiatry, 43,* 649-659.

Rauch, S.L. & Savage, C.R. (1997). Neuroimaging and neuropsychology of the striatum: Bridging basic science and clinical practice. *Psychiatry Clinics of North America, 20,* 741-768.

Raz, S. & Raz, N. (1990). Structural brain abnormalities in the major psychoses: A quantitative review of the evidence from computerized imaging. *Psychological Bulletin, 108,* 93-108.

Rempfer, M.V., Hamera, E.K., Brown, C.E., & Cromwell, R.L. (2003). The relations between cognition and the independent living skill of shopping in people with schizophrenia. *Psychiatry Research, 117,* 103-112.

Roy, M.A., Lehoux, C., Emond, C., Laplante, L., Bouchard, R.H., Everett, J., Merette, C., & Maziade, M. (2003). A pilot neuropsychological study of Kraepelinian and non-Kraepelinian schizophrenia. *Schizophrenia Research, 62,* 155-163.

Roy, M.A., Merette, C., & Maziade, M. (2001). Subtyping schizophrenia according to outcome and severity: A search for homogenous subgroup. *Schizophrenia Bulletin, 27,* 115-138.

Sanfilipo, M., Lafargue, T., Rusinek, H., Arena, L., Loneragan, C., Lautin, A., Feiner, D., Rotrosen, J., & Wolkin, A. (2000). Volumetric measure of the frontal and temporal regions in schizophrenia: Relationships to negative symptoms. *Archives of General Psychiatry, 49,* 921-926.

Saykin, A.J., Gur, R.C., Gur, R.E., Mozley, P.D., Mozley, L.H., Resnick, S.M., Kester, D.B., & Stafiniak, P. (1991). Neuropsychological function in schizophrenia. Selective impairment in memory and learning. *Archives of General Psychiatry, 48,* 618-624.

Seidman, L.J., Yurgelun-Todd, D., Kremen, W.S., Woods, B.T., Goldstein, J.M., Faraone, S.V., & Tsuang, M.T. (1994). Relationship of prefrontal and temporal lobe MRI measures to neuropsychological performance in chronic schizophrenia. *Biological Psychiatry, 35,* 235-246.

Sharma, T. & Antonova, L. (2003). Cognitive function in schizophrenia. *Psychiatric Clinics of North America, 26,* 25-40.

Shenton, M.E., Dickey, C.C., Frumin, M., & McCarley, R.W. (2001). A review of MRI findings in schizophrenia. *Schizophrenia Research, 49,* 1-52.

Shenton, M.E., Wible, C.G., & McCarley, R.W. (1997). A review of magnetic resonance imaging studies of brain abnormalities in schizophrenia. In: K. Krishnan, P. Doraiswamy (Eds.). *Brain Imaging in Clinical Psychiatry.* Marcel Dekker, Inc: New York, pp. 297-380.

Shihabuddin, L., Buchsbaum, M.S., Brickman, A.M., Harvey, P., Mitelman, S., Hazlett, E., Newmark, R., Dorfman, M., Ivanov, Z., Friedman, J., & Davis, K.L. (2004). Volume of the ventricles and cortical volume correlates in poor and good outcome schizophrenia. *Manuscript in preparation.*

Shihabuddin, L., Buchsbaum, M.S., Brickman, A.M., Tang, C., Fleischman, M.B., Bloom, R., Platholi, J., & Davis, K.L. (2001). Diffusion tensor imaging in Kraepelinian and non-Kraepelinian schizophrenia [Abstract]. *Biological Psychiatry, 49,* 19S.

Shihabuddin, L., Buchsbaum, M.S., Hazlett, E.A., Haznedar, M.M., Harvey, P.D., Newman, A., Schnur, D.B., Spiegel-Cohen, J., Wei, T., Machac, J., Knesaurek, K., Vallabhajosula, S., Biren, M.A., Ciaravolo, T.M., Luu-Hsia, C. (1998). Dorsal striatal size, shape, and metabolic rate in never-medicated schizophrenics performing a verbal learning task. *Archives of General Psychiatry, 55,* 235-243.

Shihabuddin, L., Buchsbaum, M.S., Hazlett, E.A., Silverman, J., New, A., Brickman, A.M., Mitropoulou, V., Nunn, M., Fleischman, M.B., Tang, C., & Siever, L.J. (2001). Striatal size and relative glucose metabolic rate in schizotypal personality disorder and schizophrenia. *Archives of General Psychiatry, 58,* 877-884.

Sigmundsson, T., Suckling, J., Maier, M., Williams, S., Bullmore, E., Greenwood, K., Fukuda, R., Ron, M., & Toone, B. (2001). Structural abnormalities in frontal, temporal, and limbic regions and interconnecting white matter tracts in

schizophrenic patients with prominent negative symptoms. *American Journal of Psychiatry, 158,* 234-243.

Silverman, J. (1972). Stimulus intensity modulation and psychological disease. *Psychopharmacologia, 24,* 42-80.

Smith, R.C., Calderon, M., Ravichandran, G.K., Largen, J., Vroulis, G., Shvartsburd, A., Gordon, J., & Schoolar, J.C. (1984). Nuclear magnetic resonance in schizophrenia: A preliminary study. *Psychiatry Research, 12,* 137-147.

Spreen, O. & Strauss, E. (1998). *A compendium of neuropsychological tests: Administration, norms, and commentary* (2nd ed.). New York: Oxford University Press.

Strauss, J.S., Carpenter, W.T., & Barko, J.J. (1974). The diagnosis and understanding of schizophrenia, part III: Speculations on the processes that underlie schizophrenic symptoms and signs. *Schizophrenia Bulletin, 11,* 61-76.

Strungus, S., Christensen, J.D., Holcomb, J.M., & Garver, D.L. (2003). State-related thalamic changes during antipsychotic treatment in schizophrenia: Preliminary observations. *Psychiatry Research, 124,* 121-124.

Sullivan, E.V., Mathalon, D.H., Lim, K.O., Marsh, L., & Pfefferbaum, A. (1998). Patterns of regional cortical dysmorphology distinguishing schizophrenia and chronic alcoholism. *Biological Psychiatry, 43,* 118-131.

Sullivan, E.., Rosenbloom, M.J., Serventi, K.L., Deshmukh, A., & Pfeferbaum, A. (2003). Effects of alcohol dependence comorbidity and antipsychotic medication on volumes of the thalamus and pons in schizophrenia. *American Journal of Psychiatry, 160,* 1110-1116.

Suzuki, M., Nohara, S., Hagino, H., Kurokawa, K., Yotsutsuji, T., Kawasaki, Y., Takahashi, T., Matsui, M., Watanabe, N., Seto, H., & Kurachi, M. (2002).

Regional changes in brain gray and white matter in patients with schizophrenia demonstrated with voxel-based morphometry. *Schizophrenia Research, 55,* 41-54.

Szeszko, P.R., Bilder, R.M., Lencz, T., Ashtari, M., Goldman, R.S., Reiter, G., Wu, H., & Lieberman, J.A. (2000). Reduced anterior cingulate gyrus volume correlates with executive dysfunction in men with first-episode schizophrenia. *Schizophrenia Research, 43,* 97-108.

Tamminga, C.A., Buchanan, R.W., & Gold, J.M. (1998). The role of negative symptoms and cognitive dysfunction in schizophrenia outcome. *International Clinical Psychopharmacology, 13 Suppl. 3,* 21-26.

Tapp, A., Tandon, R., Scholten, R., & Dudley, E. (1993). Age disorientation in Kraepelinian schizophrenia: Frequency and clinical correlates. *Psychopathology, 26,* 225-228.

Townsend, L.A., Malla, A.K., & Norman, R.M.G. (2001). Cognitive functioning in stabilized first-episode psychosis patients. *Psychiatry Research, 104,* 119-131.

Tsuang, M.T. & Faraone, S.V. (1995). The case for heterogeneity in the etiology of schizophrenia. *Schizophrenia Research, 17,* 161-175.

Tsuang, M.T. & Winokur, G. (1974). Criteria for subtyping schizophrenia: Clinical differentiation of hebephrenic and paranoid schizophrenia. *Archives of General Psychiatry, 31,* 43-47.

Velligan, D.L., Ritch, J.L., Sui, D., DiCocco, M., & Huntzinger, C.D. (2002). Frontal Systems Behavior Scale in schizophrenia. *Psychiatry Research, 113,* 227-236.

Velakoulis, D., Wood, S.J., Smith, D.J., Soulsby, B., Brewer, W., Leeton, L., Desmond, P., Suckling, J., Bullmore, E.T., McGuire, P.K., & Pantelis, C. (2002). Increased duration of illness is associated with reduced volume in right medial

temporal/anterior cingulate grey matter in patients with chronic schizophrenia. *Schizophrenia Research, 57,* 43-49.

Waddington, J.L. & Youssef, H.A. (1996). Cognitive dysfunction in chronic schizophrenia followed prospectively over 10 years and its longitudinal relationship to the emergence of tardive dyskinesia. *Psychological Medicine, 26,* 681-688.

Wible, C.G., Shenton, M.E., Hokama, H., Kikinis, R., Jolesz, F.A., Metcalf, D., & McCarley, R.W. (1995). Prefrontal cortex and schizophrenia: A quantitative magnetic resonance imaging study. *Psychiatry Research, 61,* 209-229.

Wright, I.C., Rabe-Hesketh, S., Woodruff, P.W., David, A.S., Murray, R.M., & Bullmore, E.T. (2000). Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry, 157,* 16-25.

Young, K.A., Manaye, K.F., Liang, C., Hicks, P.B., & German, D.C. (2000). Reduced number of mediodorsal and anterior thalamic neurons in schizophrenia. *Biological Psychiatry, 47,* 944-953.

Zaborszky, L., Pang, K., Somogyi, J., Nadasdy, Z., & Kallo, I. (1999). The basal forebrain corticopetal system revisited. *Annals of the New York Academy of Sciences, 29,* 339-367.

Zalewski, C., Johnson-Selfridge, M.T., Ohriner, S., Zarrella, K., & Seltzer, J.C. (1998). A review of neuropsychological differences between paranoid and non-paranoid schizophrenia patients. *Schizophrenia Bulletin, 24,* 127-145.

Zhou, S.Y., Suzuki, M., Hagino, H., Takahashi, T., Kawasaki, Y., Nohara, S., Yamashita, I., Seto, H., & Kurachi, M. (2003). Decreased volume and asymmetry of the

anterior limb of the internal capsule in patients with schizophrenia. *Biological Psychiatry, 54,* 427-436.