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Psychiatric Epidemiology and Neuroscience Unite in the Pursuit of Reformulated Schizophrenia Nosologies

Karyn Groth

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Psychiatric Epidemiology and Neuroscience Unite
in the Pursuit of Reformulated Schizophrenia Nosologies

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B.A., Quinnipiac College, 1999

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Master of Public Health Thesis

Psychiatric Epidemiology and Neuroscience Unite in Pursuit of Reformulated Schizophrenia Nosology

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Abbreviations

basal ganglia (BG)
cerebrospinal fluid (CSF)
computerized axial tomography (CT)
gray matter (GM)
heteromodal association cortex (HASC)
independent component analysis (ICA)
inferior parietal lobule (IPL)
magnetic resonance imaging (MRI)
planum temporale (PT)
positron emission tomography (PET)
region of interest (ROI)
superior temporal gyrus (STG)
voxel-based morphometry (VBM)
white matter (WM)
Introduction:

Schizophrenia (SZ) remains one of the least understood mental disorders despite extensive study. Efforts to better characterize the illness have led to advancements in nosology and classification of subtypes through clinical observation and research. The clinical manifestations of the illness are hypothesized to originate as abnormalities in brain structure and function which are in turn hypothesized to be the expressions of gene variants. Since the classification system used for diagnosis is based on clinical representation rather than pathophysiological etiology, subtyping by modern diagnostic criteria (e.g., Diagnostic and Statistical Manual for Mental Disorders) may be incorrect, or at least inexact, which may obscure attempts to accurately differentiate population groups. Given the complex heterogeneity of SZ, improved nosology may contribute substantially to proper diagnosis.

The principles of psychiatric epidemiology are particularly useful when attempting to reconceptualize the nosology of psychosis because they provide information necessary to significantly improve the validity of the diagnostic systems. The clinical course of schizophrenia has been well documented but epidemiological study of pathophysiological markers is lacking. Advancements in vivo neuroimaging during the past few decades have allowed for extensive study of the brain both structurally and functionally and support the role of distributed aberrations of brain morphology in the etiology and expression of schizophrenia. Psychiatric epidemiology plays a pivotal role in improving our understanding of the brain variations detected in individuals with schizophrenia. Specifically, epidemiological study of pathophysiological traits in large, representative populations will determine the existence of and rates for phenotypic
subtypes of neurophysiology. Simultaneous assessment of clinical symptomology and cognitive expression with these pathophysiological traits will allow for multifactorial patterns to emerge, thereby bridging the gap between pathophysiology and clinical manifestation. Thus, psychiatric epidemiology lies at the forefront of improving the nosology of SZ and the many efforts which employ this nosology.

In light of the inherently physiological etiology of the disorder, I assert that there is great potential to reassess the diagnostic criteria and current subtyping systems using biological paradigms. In the final chapters, I apply a novel technique for identifying natural patterns of structural variation in patients and discuss the potential for such research to detect more homogeneous subgroups which could lead to more valid diagnostic criteria.
CHAPTER 1: Epidemiology of Schizophrenia

Psychiatric epidemiology is the study of rates of mental illness and associated factors which impact onset, course and outcome. It relies on the descriptive and analytic principles of epidemiology to provide substantive information that can be utilized in a variety of clinical, research, public health, and community settings. The first psychiatric epidemiology study was a census of the “insane” in the 1840 (1). Rudimentary compared to the field today, the census was the first effort to define rates of mental illness in the population. As a scientific discipline, psychiatric epidemiology differs from standard psychiatry in its emphasis on epidemiological and biostatistical concepts in the classification and nosology of psychopathology rather than the diagnosis and treatment of individuals.

One of the first to strongly embody epidemiological principles in the study of mental illness was Emil Kraepelin. As part of his extensive work to classify mental disorders into different categories, Kraepelin, in 1893, was the first to draw a distinction between what he termed dementia praecox and other psychotic illnesses. He focused on patterns in cause, symptomology, course, final stage, and pathological anatomical findings when defining this diagnostic classification (2). In 1911, Eugen Bleuler coined the term ‘schizophrenia’ in response to the misleading use of the term dementia. By this time, interest in the clinical syndrome had taken root. Between the late 1800’s and mid-20th century, epidemiological study of schizophrenia flourished. European researchers studied large populations for incidence and prevalence of mental disorders with special attention to heredity (3). Their extensive studies resulted in information on population incidence, prevalence, age at onset curve, age- and sex-specific morbid risk, and
morbidity risks for biological relatives of a schizophrenic proband (3) which remain consistent with current estimates. Americans focused on the social ecology, or correlates and risk factors, of psychosis (3). Demographic characteristics, innate factors that could be either predisposing to psychosis or protective from it, and environmental factors, such as nurturing style, were three major areas of interest (4). Although slight variations in the concept and classification of SZ occurred over the past century, the epidemiology of the illness has remained remarkably consistent (5).

**Clinical Phenotype**

Schizophrenia is characterized by a variety of symptoms that are traditionally organized into two categories. Positive (psychotic) symptoms represent aberrations of mental processing such that normal functions are distorted or in excess (1). They include hallucinations, delusions, disorganized speech/thought, and disorganized/catatonic behavior. Negative symptoms refer to a diminution or loss of normal function and include alogia, affective blunting, and avolition (1). Although not explicitly defined as symptoms in the diagnostic criteria, cognitive deficits are a major component of the illness that underlie the impairment in social and occupational function that is required for the diagnosis of SZ. Patients with SZ, on average, experience impairments in neurocognition in the order of 1.5 to 2 standard deviations below normal controls on tests of language, executive function, memory, attention, and motor processing (6, 7). Cognitive deficits are the most disabling symptoms of SZ in terms of leading a normal life (8).

With the heterogeneity of the symptoms in SZ, several subtypes are used to further characterize patients with the illness (1). Paranoid subtype refers to patients
whose cardinal features are delusions and auditory hallucinations. These psychotic symptoms are often paranoid and persecutory in nature. Paranoid is the most common subtype. Disorganized subtype, also termed Hebephrenic, refers to patients whose behavior is characterized by incoherent speech, behaviors inappropriate to the situation, or other behaviors that indicate confusion. Catatonic subtype refers to patients who are socially and emotionally withdrawn and have marked psychomotor disturbance. The Residual subtype categorizes those patients who are no longer actively psychotic but still experience symptoms. Undifferentiated subtype serves as a catchall for patients who do not conform to the previous four subtypes or to patients who display features of more than one subtype without a clear predominance for a single type.

**Incidence and Prevalence**

Lifetime prevalence of schizophrenia generally has been cited at one percent of the population. The most recently published prevalence rate for non-affective psychosis over the lifetime in the United States was 5.0 per 1000 population (9). Other current studies which utilized representative community samples in both the United States and Israel estimated lifetime and 6-month prevalence rates at 0.7% (10, 11). Differences in reported rates over time are hypothesized to reflect changes in diagnostic criteria rather than a changes in disease prevalence. These include changes in the criteria for diagnosis of SZ or differences in the methods used to ascertain or identify patients (4, 5). Incidence rates are available from 16 countries sampled for the World Health Organization (WHO) Determinants of Outcome of Severe Mental Disorders study and a review of European countries by Jablensky (12). Both sources cite incidences of schizophrenia at approximately 0.2 per 1000 population (4). While some communities may demonstrate
substantially higher prevalence rates for indigenous reasons, schizophrenia appears in similar rates throughout the world (5, 13).

Demography

Onset of schizophrenia usually occurs in late teens and early twenties, with some severe cases presenting with earlier onset in the mid-teens. Onset is preceded by a prodromal phase which lasts, on average, 5 years (14) during which less severe traits of the disorder are present. Onset for women occurs approximately 5 years later than for men (13). Differences in prevalence rates between the sexes are cited by some to be non-existent (15) while others claim a 2-fold increase in males (13). Differences in perceived rates may be attributed to sex differences in expression of the disease. Females tend to show less severe psychopathology which may reduce occasions that require clinical contact (16). For example, females tend to have better premorbid functioning, less disability, and higher percentage of remitting course (17) although symptomology is very similar (15). As discussed earlier, SZ appears to occur at comparable rates in many cultures and races (5, 13), however racial differences in cultural norms or racial disparities in healthcare access can impact diagnosis and treatment (10).

Heredity/Genetics

Early studies of mental illness recognized the tendency for psychosis to run in families (3). Contemporary studies of heritability demonstrate significant increases in rates of the illness as the amount of shared genetic information increases. Compared to the baseline risk of 1% in the general population, 1st degree relatives (siblings) have a 9% risk of developing the illness and children of parents who both have schizophrenia (full genetic loading) show a risk of
about 46% of developing the illness (18). Twin studies provide further support in that fraternal (dyzygotic) twins of affected individuals show a rate of risk similar to other siblings while identical (monozygotic) twins show a risk of almost 50% of developing the illness if the co-twin is affected (19). Adoption studies demonstrate that the disease is more than a function of environment. Schizophrenia twins or offspring of schizophrenic parents adopted away from the schizophrenic environment still show increased risk while children adopted into schizophrenia families do not show increased risk for the disease (20). Alternatively, the influence of environment is reinforced by the fact that identical twins show at most a 50% risk if the co-twin is affected. Specifically, geneticists have calculated that approximately 70-80% of the liability for schizophrenia is genetic while 20-30% is environmental (21-23). While 70-80% of the liability is estimated to come from genetics, the 20-30% of liability attributed to environmental factors may translate into a much greater that 20-30% influence on expression. The fact that individuals with a genetic liability for the disease are at significantly increased risk compared to the general population but still have at most a 50% chance supports the theory that what is inherited is a predisposition to developing schizophrenia (21).

Social Burden

Marked by debilitating mental function, people with schizophrenia have long periods of illness, are unable to work, and have difficulty in sustaining family relationships (21, 24) causing major strain for those who care for them (24) and society in
general (13, 25, 26). Although patients vary in course and outcome, the majority require psychiatric, community, or social services for the duration of their lives (27). For instance, a review of the literature on course and outcome suggested that “21% to 57% of individuals achieve a relatively good outcome, whereas others continue to have significant impairment” (28). This dependence on others combines with early onset and poor outcome to become the 2nd ranked mental illness for the global burden of disease based on 2.3 million years of potential life lost due to premature mortality or due to loss of productivity resulting from disability (25). Given the level of required care and treatment services and the chronicity of the illness, it is not surprising that the direct costs of schizophrenia exceed those of unipolar depression (29). In 1990, the direct cost of treating individuals with schizophrenia totaled 17.3 billion, or about 53.2% of the total expenditures for hospitalization, treatment and rehabilitation, and lost productivity of 32.5 billion (29).
CHAPTER 2: Diagnostic Nosology

Kraepelin postulated that psychiatric diseases are principally caused by biological and genetic disorders. He believed that the natural patterns of the clinical syndromes could provide a provisional measure of validity of the disease concept until final verification could be achieved by establishing brain pathology and etiology (2, 3). Both Kraepelin and Bleuler emphasized that schizophrenia was a disorder in which a morbid fragmentation of cognitive processes developed unusually early in life (30). The terms “dementia praecox” and “schizophrenia”, chosen separately by these scientists, reiterated this conceptualization. The severity and variety of symptoms associated with schizophrenia were not considered to be the defining traits. Positive symptoms, for example, were recognized to occur in a number of other psychiatric disorders mitigating any specificity to schizophrenia. Rather, Kraepelin “saw the diversity of symptoms as unified by the underlying destruction of cognitive processes” (31). Kraepelin’s systematic investigations of the symptoms, course, outcome and correlates of schizophrenia were aimed at improving the conceptualization of the illness and compensated for limited capacities for pathophysiological study. His precocious use of the principles of psychiatric epidemiology were remarkably comparable to modern scientific psychiatry and his classifications served as the foundation for the modern nosological systems in use today (2, 3).

A marked divergence between Kraepelin’s work and modern diagnostic systems is the attention to non-clinical factors. Coinciding with the increasing awareness of schizophrenia, the first half of the 20th century experienced a dramatic expansion in
psychiatric and medical research on an international level (3). Bourgeoning needs for a unified psychiatric nomenclature led to the development of the first Diagnostic and Statistical Manual: Mental Disorders (DSM-I) in 1952 which focused on clinical utility rather than the coding of disease which was provided by the International Classification of Disease (1). In 1980, the third version of the Diagnostic and Statistical Manual of Mental Disorders was published. The DSM-III was developed to serve as a guideline for establishing universal and reliable psychiatric diagnoses using the manual’s explicit diagnostic criteria, a multi-axial system, and descriptive approach (1). The nature of this classification system demanded that a particular psychiatric disorder be delineated by its observable behaviors or symptoms. The goal was to provide a reliable, clinical guideline for the field of psychiatry such that formally trained clinicians could use the manuals as a reference but not a finality when making diagnoses (2). As the versions of the DSM developed so did dependence on the manual for communication, education, and training. The DSM became a textbook rather than a guideline and the skill of diagnosis was often replaced by a checklist of symptoms (32). This is particularly true with researchers in psychiatry, neuroscience, and epidemiology who applied the diagnostic criteria rigidly, often without formal clinical training. In reference to schizophrenia, conceptual shifts throughout the century refocused attentions toward the symptoms associated with the disorder, particularly positive symptoms, and were reflected in the DSM by concomitant shifts toward positive symptoms in the criteria for diagnosis (33, 34). Despite the fact that both Kraepelin and Bleuler emphasized that the disorder was not defined by clinical symptoms (31), current diagnostic classification systems use symptom constellations to diagnose schizophrenia.
Modern diagnostic classification systems may have sacrificed validity for the sake of reliability (35). Attempts over the last 100 years at finding a test, any test, which can give a deterministic diagnosis of SZ have been unsuccessful. It is quite possible that these failures are due, in part, to the invalidity of symptom-based assessments for diagnosis and the failure to incorporate the biological principles of schizophrenia in the study of the disease. The DSM-IV addresses the limitations of its categorical system, stating that “a categorical approach to the classification works best when all members of a diagnostic class are homogeneous, when there are clear boundaries between classes, and when the different classes are mutually exclusive” (1). In the case of SZ, none of these conditions is met. In tune with the modern conceptual shifts that emphasize biology and genetics in the development of psychiatric diseases, diagnostic classification systems that utilize a “definition of the phenotype...that is heuristic for studying mechanisms of the illness” (31) may greatly improve both the validity and reliability of the diagnoses. The current diagnostic system with its dependence on descriptive psychopathology creates a divide between the goals of clinicians and the goals of researchers. For an effective transition of information between fields, clinicians and researchers need to utilize the same constructs.

Compilation of the original diagnostic manuals occurred prior to the emergence of extensive scientific study in neuroscience, pathophysiology, and genetics. Research over the past two decades in each of these fields has imparted unique contributions to conceptualization of the etiology and presentation of the illness. With advancements in science and technology, it is now possible to test whether schizophrenia, as postulated by Kraepelin, is an expression of altered brain pathology and to reformulate the
diagnostic criteria for schizophrenia to encompass the nature of the illness as a fragmentation of the mind while still lending itself to both clinical application and scientific study. Psychiatric epidemiology lies at the forefront of this endeavor. Before an improved nosological system can be created, the foundation for the system must be established. “The acceptance of a particular diagnostic concept or a classification scheme is usually based on the interpretation of converging evidence from multiple sources, including descriptive psychopathology, neuropathology, pathophysiology, genetics, and epidemiology” (3). The study and treatment of SZ would benefit greatly from an innovative epidemiological perspective which seeks to improve upon current diagnostic practice in each of these fields.
One of the most defining characteristics of schizophrenia as a disease concept is its complexity, both clinically and pathophysiologically. Interest in the illness has incited extensive academic pursuit evidenced by a overabundance of research reports over the past century. Based on these reports and clinicians’ experience, several theories regarding the etiology of schizophrenia have evolved, often in parallel with secular trends and scientific/technological advancements. The 1990’s, referred to as the ‘decade of the brain’, experienced substantial growth in in-vivo imaging as technological improvements in computerized axial tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) combined with researchers’ increased access to scanners. Psychiatric researchers, previously constrained by the limitations of post-mortem assessments, now had opportunities to explore both structure and function in the living brain. Several theories about the etiology of schizophrenia as neuroanatomical in nature have been supported by these research findings. “Evidences from these studies have strongly demonstrated that schizophrenia is a chronic brain disorder, structurally and functionally affecting various cortical and subcortical regions involved in cognitive, emotional, and motivational aspects of human behavior” (36). As of yet, however, no single abnormality of brain structure has been found to be ‘pathognomonic’ for SZ (37).

Two theories have prominently addressed the role of brain anatomy in the development of the illness. Andreasen’s “cognitive dysmetria” theory proposes that the root of the disorder is a disruption of neuronal connectivity of the prefrontal-thalamic-cerebellar circuitry which evokes the clinical manifestations (38, 39). Pearson’s
“heteromodal association cortex” theory asserts that schizophrenia is caused by aberrant network function due to structural impairments to brain regions that are uniquely ‘human’, such as the heteromodal association cortex (HASC) (40). Both theories recognize that schizophrenia is not the result of a single focal abnormality nor does it appear to be the result of pathological neural markers like those detected in Alzheimer’s disease (plaques, tangles) (31, 41). The evidence of widespread, distributed anatomical aberrations supports the perspective that SZ results from disruption in neural circuitry, either anatomically or neurochemically (31, 37).

Applying the principles of epidemiology to the study of psychiatric neuroscience creates many opportunities for innovative explorations of brain-behavior phenotypes. Epidemiology is a propitious next step in schizophrenia research espoused by several researchers in the field. Excerpts from two review articles are presented here:

“In the 20th century the range of methodological and analytical tools available in psychiatric epidemiology was enormously expanded (Jablensky, this volume). Epidemiological research into the frequency, distribution and course of abnormal brain morphology (Jones et al. 1994), already underway, and the dawning epidemiology of functional anomalies and brain processes will be developed further on the neurobiological and psychological level” (42).

“The relationship between schizophrenia epidemiology and molecular genetics is considered to be one of incremental mutual support; the power of molecular genetic studies depends critically on the ability of epidemiological work to delineate homogeneous subgroups of the disorder in whom the share of genetic risk is assumed to be particularly large” (43).

Specifically, two prime uncertainties can be addressed with the epidemiological study of neuroanatomy. One uncertainty addresses the conceptualization of the illness
itself. The heterogeneity in the expression of the illness has fueled long-standing doubts about the diagnosis of SZ representing a single disease entity or a mixture of various disease processes (35, 44, 45). Studying variations in clinical and anatomical phenotypes and their relationships with each other may reveal how aberrations in neuroanatomy manifest clinically. Jointly characterizing multiple phenotypic presentations may uncover the commonalities and differences of various subgroups of patients which provide insight into the validity of current subtypes and the disease process overall. Identifying both unique and common etiologies of brain structure and function is one promising approach to determining whether schizophrenia is a single illness with a broad spectrum or an amalgamation of several illnesses into one diagnosis. Thus, large scale studies of both clinical expression and pathophysiology using epidemiological principles are vital to the development of a revised taxonomy.

The second uncertainty is whether neuroanatomy can be so well characterized that an individual can be reliably and validly diagnosed with schizophrenia based on neuroanatomical measurement. Variability in affected brain areas as well as variability in the severity of the morphological aberration can obscure attempts to discriminate patients from controls based on brain structure. In addition, aberrations in morphology occur along a continuum that overlaps considerably with normal controls and diminishes the ability to define ‘abnormal’. These two inherent qualities of SZ continue to impede efforts to define distinct phenotypes. Scientific methodologies also have hindered efforts to distinguish anatomical phenotypes. Many research reports in psychiatric neuroscience employ small sample sizes (N<40) which undermine the success for detecting meaningful differences. Specifically, smaller sample sizes increase the likelihood for
type II errors, especially with the high variability in brain morphology in patients but not control subjects. Despite the fact that neuroanatomy is theorized to play an integral role in the etiology of SZ, few studies have assessed the ability for neuroanatomical measures to predict diagnosis and/or outcomes (28) perhaps for the reasons discussed here. The collection of large scale neuroanatomical studies that embody the principles of epidemiology may achieve new heights in the characterization of neuroanatomy on an individual level and foster interest in its predictive potential.

Several epidemiological principles, in particular, have been lacking in the majority of modern research endeavors. First, as discussed above, small sample sizes inherently weaken the likelihood of detecting differences between patients and controls, limit the potential for detecting more uniform subgroups of patients, and limit the generalizability of the results. Large-scale studies, in the order of 100 or more per diagnostic group, can substantially reduce these limitations (see (46-48) for examples). Second, neuroimaging studies often require the comparison group to be both physically and mentally 'healthy' in order to reduce confounds and increase the likelihood for detecting differences. A population study of brain anatomy using community controls, not 'healthy' research controls, will provide a normative and generalizable characterization of brain morphology. The inclusion of other mental illnesses in the development of normative measures will allow for the emergence of aberrations that are specific to SZ and not to mental illness. Third, associations between patients' presentation and course and the patient's brain morphology are rarely tested. Exceptions to this are the growing number of researchers who attempt to correlate symptomology and/or neurocognitive performances with neuroanatomical measures. Patients' course
and outcome are intrinsic qualities of the illness which necessitate increased attention. The development of hypotheses \textit{a priori} and the application of more advanced statistical tests (which will also be feasible with larger sample sizes) will help researchers capitalize on these variables. To recapitulate, "closer links between epidemiology and structural neuroimaging... will enable us to further define structural abnormalities associated with each [psychiatric] disorder and their specificity" (49).
CHAPTER 4: Evidence of Structural Differences and their Clinical Correlates

Identification of structural abnormalities in SZ has been a primary area of interest since the increased accessibility of in vivo assessment techniques. Reports of volumetric differences between patients and controls have been reported for most parts of the brain although this literature has been pray to inconsistent reports regarding the location and direction of volumetric differences. Several reviews attempt to summarize the vast literature on this topic and I refer you to them for a full understanding of the reported structural aberrations in SZ (see (37, 50) for reviews). In this chapter, I will comment on the most consistent and relevant findings.

Chronicling the morphometric differences between healthy control subjects and persons with schizophrenia provides insight into where disruptions in normal functioning may occur. Associating a brain structure with an observable behavior creates a conceptual bridge that is important to cross when attempting to determine the role of structure in clinical expression and in the definition of subtypes. Evaluation of the existence of morphology-symptom and morphology-cognition associations increases our understanding of how numerous brain regions may synergize to create the heterogeneous clinical expression of SZ. “It is unclear if there are subgroups of SZ with distinct clusters of particular volume abnormalities that involve discrete neuroanatomic circuits” (37). Several morphometric studies of brain structure have found significant associations between regional brain volumes and severity of symptoms and cognitive performances. Relevant studies are included in the discussion of structural differences.

For the purposes of this thesis, I will limit the scope of structural abnormalities to brain volumes. Structural assessments that involve shape, connectivity (e.g. diffusion
tensor imaging), or occur at a cellular level are beyond the purview of this thesis. Volumetric structural measurements will predominately come from MRI assessments. Differences between volumetric measurement tools, such as region of interest (ROI) vs. voxel-based morphometry (VBM), can introduce variability in findings. I give equal credit to reports using either methodology, however, for direct comparison of our findings to previous work, I will focus on prior VBM studies in the final chapters.

Global Volumes

Global brain volumes can be divided into 4 categories: whole brain, gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Assessments of whole brain size in schizophrenia have not typically found significant size differences between patients and controls (51) but global GM has been found to be reduced in patients in the order of 2-4% (52, 53). Literature reviews that included WM have reported tendencies for both decreases (32) and increases (52). White matter increases may occur in proportion with GM decreases (52) offsetting any whole brain volume loss in patients with GM decreases. The ratio of gray to white matter within the brain has been suggested to be of interest, although no major findings have been reported. Pearlson and Marsh (1999) suggest that global volume reductions such as those seen with GM do not always reach statistical significance despite focal deficits of 10%-15% (37).

Overall, global measures of brain volume have not been a fruitful area of study in schizophrenia research with the exception of cognitive function. Whole brain volume has a non-specific association with cognitive performances in both patients and controls (6, 54-56). For example, Antonova (2005) reported smaller global GM volume correlated with lower premorbid IQ in patients but also in controls. Kareken (1995) reported that
deficit but not non-deficit patients had reduced whole brain volumes compared to controls. Since cognitive impairments are more severe in deficit patients, brain volume deficits may be a key element to understanding the clinical manifestations of select subgroups of patients.

**Ventricles**

Ventricular enlargement is a highly consistent finding in SZ. The ventricles are sub-divided into lateral, third, and fourth. The lateral ventricles are further defined with a frontal horn, body, occipital horn, and temporal horn. Lateral ventricular enlargement, especially in the temporal horn, has been well documented, as well as enlargement of the third ventricle (50) while the fourth ventricle has not shown enlargement in patients. Pearlson and Marsh (1999) remark that it is difficult to determine if increased ventricular size is itself an anatomic abnormality or if it is a proxy for changes in neighboring brain structures (37). Enlargement of the temporal horns may reflect GM reductions in the temporal gyri (50) and enlargement of the third ventricle may relate to the reported reductions in thalamic volume (57). It is important to note that despite the consistency of enlarged ventricles in SZ, ventricular enlargement is commonly found in a variety of other psychiatric and non-psychiatric conditions (37), thereby minimizing the contribution of this abnormality to the isolation of schizophrenia’s etiology. A recent study of the heritability of ventricular size suggested that genetics have a stronger influence over ventricle size than schizophrenia-related changes (58) further supporting an indirect association between ventricle size and schizophrenia.

Studies testing the correlations between cognition and ventricular size have failed to find consistent associations in patients, although studies utilizing ventricular-to-brain
volume ratios have been more reliable (6). Enlargement of ventricles may be a non-specific indicator of decreased brain tissue for which more localized assessments of tissue volume correlate better with cognitive measures.

**Temporal lobe**

The temporal lobe is comprised of 1) the superior temporal gyrus which includes the primary (Heschl’s gyrus) and secondary auditory cortices and the planum temporale, 2) the middle and inferior temporal gyri, and 3) the medial temporal structures of the limbic system. Smaller volume in the superior temporal gyrus (STG) of the temporal lobe is the most robust finding for a focal region in SZ research (59) and is principally GM in origin (50). Volume loss in the STG is also highly specific to SZ unlike the ventricular volumes noted above (37). Reports for volume changes in the middle or inferior temporal gyri are less consistent (60, 61).

The role of the temporal lobe in processing sensory inputs, speech and language has incited extensive interest in the relationship between temporal structure and function and the existence of auditory hallucinations, delusions, and impaired language(61). Numerous studies have studied the associations between structure and clinical symptoms with promising results. For positive symptoms, GM volume loss in the STG, in particular, has correlated with hallucinations (28, 62-64) and formal thought disorder (60, 64-66) but not with delusions (28). Negative symptoms have also correlated with temporal lobe volume loss (67, 68). Neuropsychological performance in a variety of cognitive domains have positively correlated with temporal or STG volume in patients (65,
69-72) although some studies have not shown associations (6, 73).

The Planum Temporale (PT) is a discrete region of the posterior STG which is believed to be the “neural substrate of language” (50, 74). The PT displays a discernible left greater than right asymmetry in the normal population that is diminished in patients with schizophrenia (75-80). The disrupted asymmetry is attributed to enlarged right PT volumes and/or left PT reductions (77, 78, 81, 82). Pearlson (1996, 1997) suggests that the PT is a primary ROI in the structural basis of SZ (40, 61) for which anatomical aberrations have yet to be identified in any other psychiatric disorder (40, 50). Although the PT is a portion of the STG which has been heavily correlated with symptomology, the PT as a discrete sub region of the STG has also correlated with thought disorder (65, 66, 82-84) and higher scores on the suspiciousness/persecution subscale of the Positive and Negative Symptom Scale (78).

**Medial Temporal Lobe**

The medial temporal structures are the amygdala, hippocampus, and parahippocampal gyrus. These structures, also known as the limbic system, mediate emotion and memory and are implicated as aberrant in SZ based on the observation that memory is one of the most marked impairments exhibited in schizophrenia (6).

Early post-mortem studies reported tissue loss in these medial regions (50) followed by MRI studies reporting reductions in the amygdala-hippocampal complex (83), amygdala alone (53, 69, 85), hippocampus alone (53, 69, 85), and parahippocampal gyrus (53) in SZ both in chronic and first episode patients (36, 59, 68). Volume in limbic structures have been positively correlated with thought disorder (83), symptom severity (37), and negative symptoms (68). Results of studies relating performance on memory-
related tasks to medial temporal lobe volumes in patients have been mixed: several report positive correlations (70, 86-88) while others report no association (86, 87, 89) depending on the structure and the memory task being assessed. No studies that assessed medial temporal volumes and cognition found an association between parahippocampal gyrus volume and cognition in controls suggesting a specificity of the parahippocampal gyrus to cognitive functions in SZ (6).

Frontal lobe

Frontal lobe dysfunction is considered to be an important cause of the specific abnormalities of cognition and behavior that are commonly seen in SZ (6, 38, 40). Conventionally divided into the superior, middle, inferior, medial, and orbital gyri, the frontal cortex is highly connected with every other cortical structure in the brain (90). The frontal cortex is also a significant part of neural circuitry and a number of cortical-subcortical networks evidenced by reciprocal connections to all other areas of the cortex, as well as to limbic and basal ganglia structures (91, 92). While reports using whole lobe volume measurements have been inconsistent, recent parcellation studies of prefrontal subregions have reported specific volume reductions in discrete areas including the inferior, middle, and orbital gyri, and dorsolateral and dorsomedial regions (6, 36, 50, 59). Frontal lobe volumes have correlated with both positive (62) and negative symptoms (68, 93) but not as robustly as the temporal lobe.

On the other hand, impaired cognitive performance and frontal lobe reductions have been well documented. Irrespective of volumetric differences between patients and controls, several studies have reported significant relationships between volumes in the frontal lobe and performance on cognitive measures—particularly on tasks that engage
the frontal cortex (executive functioning, working memory, verbal fluency, immediate memory) (6, 7, 31, 54, 59, 70, 94). Variability in the existence of and associations between cognitive deficits in frontal function and volumetric deficits in the prefrontal cortex indicate that abnormalities in other brain regions may impact frontal functions (6) and that there may be select subgroups of patients who present with disruptions in either neuronal circuitry or anatomy.

**Parietal lobe**

The parietal lobe is comprised of the post-central gyrus, superior parietal lobule, and inferior parietal lobule. Although the parietal lobe has not been a major ROI in investigating volume abnormalities in SZ, the supramarginal and angular gyri that constitute the inferior parietal lobule (IPL) are critical parts of the heteromodal association cortex (40, 92, 95). Located close to the PT, the IPL is hypothesized to be involved with language development and comprehension (40, 91, 95). The IPL is also implicated in visuospatial processing, visual working memory, and attention (50). Similar to the PT, the IPL shows a left greater than right asymmetry in normal subjects which is important for normal language development (50, 96). Of the few studies that have assessed subregions of the parietal lobe in schizophrenia, volume or GM density reductions were reported for the supramarginal gyrus (85, 97) and IPL (98, 99). Further, there was reported reversal of the left greater than right asymmetry in the angular gyrus in males and in the supramarginal gyrus (50, 100, 101).

Exploration of the association between symptoms or cognition in SZ and parietal lobe size is minimal. Sullivan (1996) reported no significant differences in parietal or parietal-occipital volumes between male patients and controls nor did they find
significant correlations between parietal volumes and cognitive functioning in 4 domains (executive, verbal, memory, motor). Antonova (2004) suggests that the global measurement of the parietal region may have negated the detection of associations with cognitive functions given the differences in functionality for subregions of the parietal and occipital region. Bilateral parietal lobe volume reductions were found to be associated with the auditory oddball fMRI task in schizophrenia, using joint independent component analysis (102).

**Cerebellum**

The cerebellum has been implicated as a ROI in SZ because of its role in a variety of motor tasks (neuromotor function is often irregular in SZ), connectivity with cortical and limbic structures, and role in cognition (30, 38, 50). Decreased cerebellar volumes in patients compared to controls are typically found (38, 73, 99, 103); increased volumes (104) but the reports of correlations to symptoms are lacking. Bottmer (2005) found smaller cerebellar volumes in patients inversely correlated with soft signs but showed no relation to clinical course (105) while Szeszko (2003) reported a lack of association between cerebellar volume and overall cognition in patients that was evident in healthy controls (106). Smaller cerebellar volumes were associated with neuromotor abnormalities which were in turn (but not directly) associated with poorer cognition and more severe symptomology (107). Associations of cerebellar volumes with cognitive functions were found for controls and affected women but not affected men (6). Further research is needed to clarify the associations of cerebellar structure with clinical presentations.

**Thalamus**
Known for its role as a major relay station in the brain, the thalamus is responsible for much of the communication between cortical areas by modulating the incoming sensory information and outputting information to other cortical areas. It has been implicated specifically in attention, information processing, and gating (50) and has reciprocal connections with a variety of brain structures as evidenced by the delineation of several cortical circuits that involve the thalamus (108-112). Thalamic explorations have been thwarted by the difficulties in reliable delineation of the structure using MRI. While several groups have reported decreased thalamic volumes, others have reported no differences between diagnostic groups. Even with improvements in imaging technology and assessment/quantification methods (113), recent studies continued to report mixed findings regarding volume reductions in patients (73, 99, 114-116) but often report correlations with other regional brain volumes (57, 113, 117), symptoms (118, 119), and illness course (120-123).

**Basal Ganglia**

The Basal Ganglia (BG) is comprised of the caudate, putamen, and globus pallidus. The caudate and putamen are often referred to as the striatum. Each structure of the basal ganglia is differentially involved in cognitive, sensory, and motor processing (124). Volumetric studies of the BG via MRI have typically reported increases (125, 126) although there is growing evidence for the confounding of BG size from atypical neuroleptics (6, 127, 128). In studies of drug-naïve patients, caudate volumes were found to be no different (128) or decreased (50, 127) compared with controls.

A handful of studies have explored associations between BG volumes and clinical manifestations. Sigmundsson (2001) measured numerous brain regions in patients with
enduring negative symptoms and reported that these patients had increased BG GM volume compared to controls which positively correlated with positive symptoms. Buchanan (1993) reported a trend for deficit patients to have larger right caudate volumes (118). Spinks (2005) reported that volume of the external segment of the globus pallidus was correlated with severity of global symptoms although there were no volumes differences between patients and controls (129). Two studies reported an inverse relationship between volumes in BG structures and cognitive flexibility/abstraction (123, 130).

It is important to note that there are a number of factors which can confound, or at least complicate, detection of structural differences in schizophrenia, such as sex, age at assessment, age at onset, course, medication, treatment regimens, diagnostic criteria, and comorbidities (36). Although the majority of studies comparing patients to controls attempt to match for age and sex on a group level, the potential for additional confounders creates the need for continued study of brain structures, preferably with larger samples sizes and well characterized patient groups. One of the largest obstacles in studying correlates of schizophrenia is that the range of a particular construct usually overlaps considerably with the normal population (37) which prevents the ability to demarcate a point or line for abnormality. Improved characterization of brain anatomy in normal population groups can help define size, shape, variability, patterns and intercorrelations of brain regions.

There are several limitations of the studies associating cognition to brain volumes. One is the variability in measures and interpretation of measures used to assess cognitive
domains, as well as the lack of attention to construct validity (6). Another is equating the level of difficulty to that of controls; it can be difficult to determine whether poorer performance is the result of smaller volumes, overall impaired neuronal networks and circuitry, or inequality in cognitive load (6).
CHAPTER 5: Alternative Subtyping

Past efforts to define subgroups of schizophrenia that do not conform to the criteria set forth in the DSM-IV have been fueled by salient issues. Subgrouping patients based on neuropsychological function (131-133), familial or sporadic (134, 135), course and outcome (136, 137) or symptom presentation (135, 138-141) strive to identify homogeneous subpopulations that may be more conducive to exploration of biological etiologies. Second, these subgroups may address lingering concerns over the validity of the current diagnostic subtypes and SZ as a single unified pathological process. In addition, subsetting patients based on positive responses to certain medications and exploring associated factors may improve treatment regimens (142), essentially using evidence based practices. However, alternate subtyping in SZ is defunct if no additional information can be gleaned from the revised classification. Although there are a number of concerns over the validity of current diagnostic subtypes and there have been a number of attempts to define alternative subtypes, only a few have been examined for biological or phenotypic correlates (34).

Leonhard’s classification of SZ subtypes is one alternative that has been studied for a variety of disease correlates. Leonhard subdivided schizophrenia into three subtypes based on different types of symptomology, long-term course, and clinical outcome: systematic schizophrenia, unsystematic schizophrenia, and cycloid psychosis (36). Several researchers have utilized these subtypes in their studies with promising results. Systematic SZ had significantly more maternal gestational infections during pregnancy and significantly more obstetric complications than unsystematic SZ or controls (143). Differences in P300 topographies and latencies between Leonhard’s three
subtypes have been reported (36). Genetic studies have reported different genetic backgrounds between the subtypes; for example, systematic catatonia is usually sporadic not familial (144). A recent MRI study that used both DSM-IV and Leonhard’s classifications reported significant aberrations in brain morphology for Leonhard’s systematic SZ compared with controls but not for non-systematic forms or for any of the DSM-IV subtypes (145). Thus, alternative subtypes show promise for detecting associations with a variety of physiological correlates that have not been accomplished using DSM-IV subtype classifications.

There is also great potential for biological endeavors to suggest more homogenous phenotypes. Reporting that a substantial subgroup of patients showed ongoing cerebral degeneration, Knoll proposed that a degenerative type of SZ may exist and that this subgroup is similar to the intellectually deteriorated subgroup of patients defined using neuropsychological testing (36). Pearlson and Marsh (1999) also acknowledge that cerebral degeneration may be limited to a subset of patients, notably the Kraepelinian subset (37). Sponheim (2001, 2003) explored whether biological measures known to be deviant in psychosis could discriminate patients from controls (146, 147). Sponheim et al. measured ocular motor functioning, electroencephalogram frequency characteristics, nail fold plexus visibility, and electrodermal activations in 5 study groups: patients with SZ, 1st degree relatives of patient with SZ, patients with affective disorder, 1st degree relatives of patients with affective disorder, and non-psychiatric control subjects (146). The authors compared the sensitivity and specificity of each measure in differentiating diagnostic group pairs. Three out of four of the biological measures significantly differentiated SZ patients from non-psychiatric controls. One of
these measures also significantly differentiated SZ patients from affective patients. Although Sponheim’s predictive values were modest, the potential to tap the predictive ability of biological phenotypes has been considered. Additional statistical methods such as principal components, principal factors and cluster analyses may also advance the delineation of biological subtypes. Future studies should employ more efforts to capitalize on biological indices known to be affected in psychosis.

**Benefits and Limitations of Subtyping Structural Differences and their Clinical Correlates**

Patterns of brain morphology are biological markers, or endophenotypes, which are traits that covary with an illness without being causative agents. Brain morphology represents a halfway point between the genetic/environmental etiologies and the varied clinical presentations (148). As such, these markers are likely to associate with both etiology and expression thereby bridging the gap between cause and effect.

“Th[e] clinically observed presentation of schizophrenia may not in fact represent the true phenotype, since it is comprised of varied symptoms that derive from diverse systems, occurs in non-overlapping patterns, and does not breed true. Instead, the phenotype may perhaps be best defined by a process that lies behind the symptoms, or a metaprocess, sometimes also referred to as an endophenotype, which is a ‘final common pathway’ that defines the illness.” (31)

The use of brain endophenotypes as markers for schizophrenia has a number of advantages in the search for schizophrenia etiologies. Brain structure is more tangible and less state dependent than clinical symptomology allowing for better quantification and classification of affliction. Brain structure is measurable for the entire population, allowing for mapping of risk across the general population and the potential for identifying de novo/isolated incidences of schizophrenia (21). Discrete structural
aberrations may produce specific clinical manifestations which can lead to pharmacological treatments designed to target the specific abnormalities as well as an improved understanding of the relationship between brain structure and function. There is the potential for data-driven techniques, such as factor or cluster analyses, to provide a starting point for exploring whether brain patterns do exist and how they relate to clinical presentation. Two main limitations common to SZ research still remain. Brain sizes and shapes occur on a continuum with no set point of abnormality. Any demarcation made by researchers would, at this time, be arbitrary. Anatomical structure varies extensively from patient to patient (more so that in the general population) with some patients expressing gross morphological abnormalities. Variability in morphology of numerous structures complicates the discrimination of structures that impact the illness from structures that do not impact the disease process.

*Previous Attempts to Define Structural Subtypes*

Previous attempts to define structural subtypes have been largely restricted to one overarching construct—outcome. Poor outcome has been associated with ventricular enlargement (120, 149-151), general GM loss (120, 152), and GM volume reductions in the posterior cingulate (151), retrosplenial cortices (151), cerebellum (153), frontal lobe (120), temporal lobe (28, 152), and thalamus (113). Although many of these studies use a correlational design rather than a comparison of good and poor outcome groups, the association of poor outcome with numerous structures suggests that a dichotomization between outcome groups may successfully associate with brain anatomy.

Deficit symptoms and Kraepelinian subtypes are highly predictive of clinical features of poor outcome (136). It is possible that the “more enduring” nature of deficit
symptoms which lead to poorer outcomes increases the likelihood of an association with pathophysiology compared with the more state-dependent positive symptoms (37, 154). Comparing patients using a Kraepelinian/non-Kraepelinian dichotomy in a series of neuroanatomical reports, Mitelman has detected differences in GM volumes and in patterns of intra-cortical volume correlations in the Kraepelinian subtype compared with the non-Kraepelinian and controls (117, 151, 152, 155, 156) indicating that subtyping by outcome is more discriminatory of structural phenotypes than traditional DSM subtyping (145).
CHAPTER 6: Intercorrelations between Brain Volumes

Exploration of the role of brain structure and volume in SZ usually “follow a traditional ‘lesion’ model in which changes in one anatomic structure are postulated to lead to change in function, symptoms, or outcome….” (28). A major limitation of this approach is the failure to incorporate the dynamic relationships between multiple brain regions (28). Theories regarding the etiology of SZ have emphasized the disruption of brain networks (38, 40, 110, 124, 157) and recognize that no one region is responsible for the illness. Considering there are numerous neural and cognitive networks in the human brain, the progression from exploring static groups differences to exploring intercorrelations between brain structures within groups is natural. A handful of studies have focused specifically on detecting patterns of structural variation in SZ with varying success (100, 117, 155, 156, 158-160).

Considering the ‘extent and complexity’ of the cortical connections between the prefrontal and the temporal lobe structures, Wible (1995) proposed that the variability in significant findings for either region may result from the primary dysfunction of the other region (158). Selecting a small group of patients (N=15) already shown to have volume deficits in left temporal lobe regions, Wible reported no significant differences in prefrontal GM volumes between these patients and matched controls. When entered into a regression analysis, the authors found that of all the temporal lobe structures measured, only the left anterior hippocampal-amygdala complex volume accounted for a significant portion of the variance of the left prefrontal cortex (Rsq = .47) and that this association was not evident in controls. Although the study sample was relatively small, an intercorrelation in patients but not controls between two brain regions that are of primary
interest in SZ suggests that patients may experience a dynamic disruption in brain morphology that has previously been undetected.

The heteromodal association cortex (HASC) is a network of higher-order neural circuits, which mediate complex cognitive tasks such as working memory, language, and attention (161). Primary HASC regions include the dorsolateral prefrontal cortex, Broca’s motor speech region, the STG and PT, and the inferior parietal lobule (40). Abnormalities in the anatomy of primary HASC regions or disruptions in functional connectivity may underlie the abnormalities of speech, language, and perception, as well as the abnormalities in social and occupational functioning that are cardinal features of schizophrenia (40, 161, 162). To explore the pattern of correlations among heteromodal regions, Buchanan (2004) quantified the GM volumes of the STG, supramarginal and angular gyri, and prefrontal volumes parcellated into four ROIs (100). Using Pearson’s partial correlations with each pairwise correlation adjusted for all other volumes considered, the authors reported 7 significant correlations between HASC regions that were similar in patients and controls. In contrast, patients with SZ demonstrated a significant positive association between inferior prefrontal and angular volumes and between supramarginal and angular volumes in the left hemisphere while controls exhibited an inverse association. Although 42 comparisons were made, only 9 intercorrelations were significant in either patients or controls suggesting that volumes of the heteromodal regions may be generally unrelated or that Buchanan’s methodology was unable to detect such associations. Buchanan’s findings are partially consistent with Niznikiewicz (2000) finding that volumes of the inferior parietal cortices correlated with several prefrontal regions in patients but not in controls (98).
In a series of recent reports, Mitelman (117, 155, 156) investigated the potential associations between 39 regional brain volumes in 106 patients with schizophrenia and 42 normal controls. These studies constitute the largest and most extensive assessments of volumetric intercorrelations to date. Given the exhaustive detail in each of these reports, a summarization of the exact findings would still be lengthy. In general, patients showed an “abundance” of stronger than normal positive correlations among temporal, frontal and occipital regions as well as a weakening of the inverse correlations between the frontal and temporal regions (155). The fact that Mitelman identified numerous correlations between Brodmann’s areas (the majority of which were positive) indicates that widespread volumetric change in the same direction usually occurs in both patients and controls. The presence of differences in the pattern of correlations between patients and controls supports the theory of disrupted cerebral networks in SZ. Mitelman also comments that “anatomical connection between two regions is not a sufficient condition for significant inter-correlation of their volumes.... [Instead] the connection must be strong enough or an additional superimposed process, such as consistently coordinated use of the areas, must be at play” (156). Considering that SZ is theorized to result from aberrant connectivity, patterns of regional volumes in patients that deviate from normal controls might implicate alternative ‘altered’ neural networks that either contribute to the expression of the disease or strive to compensate for disrupted neural structures. Investigating the patterns of regional variation is a necessary step in understanding the etiology of SZ.
CHAPTER 7: AIMS and HYPOTHESES

Independent component analysis (ICA) is a statistical approach that has the potential to identify brain patterns that may differentiate intrinsic subtypes. ICA was developed to solve problems similar to the “cocktail party” problem (163) in which multiple conversations can obscure attempts to isolate a single conversation. The ICA algorithm, assuming independence in time or space, can separate mixed signals (noise) into individual sources (voices). In reference to structural imaging, ICA allows for the decomposition of brain areas into those regions that vary together in GM volume from individual to individual (102, 163-165). Each brain is transformed from a three dimensional plane into a two dimensional vector and the vectors for each subject are arrayed into a matrix. An algorithm is then applied to the matrix to detect elements that vary together across subjects (commonalities between vectors) and across the brain areas (commonalities between arrays).

Although this statistical approach is similar to well-known factor analytic approaches (e.g., principle components analysis), a major difference between ICA and other factor analyses is the statistical theory used to detect patterns. The goal of ICA is to detect independence (166). Traditional factor analyses are based on an assumption that the data under study are normally (gaussian) distributed. In gaussian distributions, uncorrelated components are by definition independent so the factors can be extracted successfully. When data are not normally distributed (as traditional methods assume), the assumptions of the model are not met and the results become suspect. ICA detects independent factors with data that are non-gaussian using alternative mathematical assumptions. “ICA could be considered as nongaussian factor analysis, since in factor
analysis, we are also modeling the data as linear mixtures of some underlying factors” (166). I refer you to a technical paper by Hyvarinen (166) for details of the estimation process and the algorithm used to decompose the matrix into independent components. In addition, ICA requires no a priori knowledge of how regions vary between individuals. Thus, using ICA to explore variations in GM segmentation images provides a unique opportunity to identify natural groupings of regions and further the conceptualization of our anatomical network.

The use of alternative diagnostic paradigms is a powerful tool for studying this specific population but, as of yet, no attempts have been made to subtype patients based on brain morphology. Brain anatomy has been explored well enough to conclude that no one aberration lies at the root of the illness (167) and that the brain anatomy in patients is as varied as the manifestations. Considering the hypothesized role of brain anatomy in the etiology of the disease, subtyping patients based on anatomic phenotypes may prove to be more successful for identifying valid subtypes and etiologies. Such a method provides two meaningful benefits to current practice. First, the subtypes are defined by the variation in the population rather than by a somewhat arbitrary clinical definition. Second, since aberrations in physiology are hypothesized to underlie the expression of symptoms, an association of structural subtypes to clinical features may improve the accuracy and validity of a subtype definition. Improved validity can impact both clinical and research endeavors. Furthermore, mapping of structural subtypes using larger study groups can provide information about each of the goals of psychiatric epidemiology and eventually public health’s ultimate goal of prevention.

The HASC hypothesis of schizophrenia postulates that the regions involved in the
HASC and their interconnections are disproportionately disrupted (40). This hypothesis has gathered support from both structural (discussed previously) and functional data (40). Based on previous work by Pearlson and colleagues, I predicted that the regions of greatest distinction between patients with schizophrenia and healthy controls will predominately involve the primary areas of the heteromodal association cortex.

An overarching goal of anatomical research in schizophrenia is to characterize structural variations so brain morphology can be used in tandem with current clinical methods to properly diagnose patients and to reveal underlying pathophysiology. As noted by Milev (2003), “in comparison with the abundance of outcome studies using demographic and psychopathologic variables, the number of studies that address the predictive potential of neuroanatomical measures is [surprisingly] small” (28). Although ICA summarizes the anatomical relationships in the dataset, the subsequent application of logistic regression to the independent components extends our knowledge further by assessing which components can best differentiate patients with schizophrenia from healthy controls. The combination of these two strategies provides a useful way to increase understanding of how structural changes in anatomical networks may contribute to the disease.
CHAPTER 8: Data Analysis Methods

Subjects:

One hundred and thirty three patients with chronic schizophrenia (53 females, mean age = 41.6, SD = 12.6, range 19-81) and 133 matched healthy control (HC) subjects (69 females, mean age = 41.8, SD = 16.2, range 19-79) were scanned at Johns Hopkins University. Patients with schizophrenia or schizoaffective disorder were included based on a diagnostic approach that utilized the Structured Clinical Interview for DSM-III-R/DSM-IV (SCID) (168, 169), direct assessment, family informants, and past medical records. Clinical measures of onset, course, symptoms, or cognition were not available for the current study. Demographic measures were limited to age and sex of the subject at the time of MRI.

Healthy control subjects were recruited using random-digit dialing as part of Phase 1 of the Johns Hopkins aging brain and cognition study. All HC subjects were evaluated with the same structured interview as the patient group. Subjects were excluded if they had a history of DSM-III-R/DSM-IV Axis I or Axis II disorder based on the SCID. Exclusion criteria for all samples included a history of overt brain disease, mental retardation, head injury with loss of consciousness for greater than 30 minutes, or a diagnosis of substance abuse or dependence within the last 12 months.

MR imaging parameters:

Whole brain MRIs were obtained on a single 1.5T Signa GE scanner (GE Medical Systems, Milwaukee) in the coronal plane using an SPGR (spoiled gradient recall) 3D imaging sequence (35msec repeat time, 5msec echo time, 45° flip angle, 1 excitation, 1.5mm slice thickness, 24cm field of view, and a matrix size of 256 x 256).
Optimized voxel-based morphometry:

Optimized voxel-based morphometry (VBM) (170) has recently gained favor in the field of neuroimaging as a method for comparing localized volumes of brain tissue. Unlike ROI studies which traditionally employ manual tracing of regions over a series of brain slices, VBM is an automated technique that segments GM, WM, and cerebrospinal fluid using structural MRI images for comparison of whole brain or localized measures of volume. As an automated process, VBM offers many advantages over manual tracing methods by assessing both whole brain and localized regions in one process, increasing reliability between studies, and avoiding the time-consuming method of manual tracing which also allows for larger sample sizes. In contrast, the automated method requires that all structural images be normalized to the same stereotactic space. As a result, VBM analyses are less sensitive to shape differences creating a trade-off of validity for the sake of reliability. This is of particular relevance to schizophrenia given that these patients are more likely to show gross aberrations in brain structure. Nonetheless, an increasing number of VBM studies have confirmed and extended the findings of ROI studies (171).

MR images were visually inspected for orientation and movement artifact before preprocessing. VBM analyses employed the SPM2 toolbox (statistical parametric mapping, developed by the Wellcome Institute, London, UK) running in MATLAB (The MathWorks, Natick, MA, USA). All images were preprocessed using the optimized VBM approach described in detail by Good et al. (47, 170). Particulars relevant to this study will be briefly described here. A study-specific anatomical template set consisting of a T1-weighted image and a priori gray, white and cerebrospinal fluid images was created from HC for the VBM analysis in order to control for intensity differences in MR
images due to unique aspects of these data, such as scanner and acquisition parameters. To construct the templates (47), images were first reoriented and volumes roughly normalized, using a 12-parameter affine model, to the 152 average T1 MNI (Montreal Neurological Institute) template provided as part of the SPM2 package. Normalized images were interpolated to voxel dimensions of 1.5mm × 1.5mm × 1.5mm and then segmented into GM, WM, and CSF using a modified mixture model cluster analysis technique, with a correction for image intensity nonuniformity (172). Images were then smoothed with an 8mm full-width half-maximum (FWHM) Gaussian kernel and averaged across subjects to create T1, GM, WM and CSF templates.

For the optimized VBM analysis, all 266 images were segmented in native space into GM, WM and CSF compartments and resulting GM images were normalized to the customized GM template. Normalization parameters were recorded and applied to the raw T1 images (170). The resulting images are probabilistic segmentations of GM; the addition of the first segmentation step minimizes the number of non-brain voxels misclassified as GM (47). Gray matter concentration images (GMC) were then smoothed with a 12mm FWHM isotropic Gaussian kernel to compensate for the inexact nature of normalization and to ensure statistical validity under parametric assumptions (173). To calculate differences in GM volume, the voxel values in the segmented images were multiplied by the Jacobian determinants derived from spatial normalization (47). This modulation step preserves the original volume of the segmented image, which is altered during the transformation into stereotactic space. It is important to note that GM ‘volumes’ as defined in this paper are relative volumes based on the optimized VBM modulation step and are not the absolute volumes as calculated by ROI analyses.
**Independent Component Analysis:**

Images were processed using the GIFT ICA toolbox (http://icatb.sourceforge.net). All GM volume images were entered into the ICA toolbox with the HC images entered first. Each GM image was converted into a one-dimensional vector and each vector was centered to a mean of zero. The 266 vectors were arrayed into a matrix. This subject-by-gray matter data matrix was decomposed into 30 components with the mixing matrix indicating the amount each subject contributed to each component. The number of components was determined using the order estimation tool in the GIFT toolbox (174). Output images and mixing matrix columns for each component were scaled to unit standard deviation.

**Regression Analyses**

After estimating components, the mixing matrix parameters (i.e., component loading scores) for each subject were extracted to SAS v9.1. Since both diagnostic groups were entered into the same ICA matrix, we first compared the diagnostic groups for significant differences in component loading scores using an independent samples t-test. This step aimed to reduce the number of components of interest and to limit further analyses to components where the patient and control groups differed in the magnitude to which they loaded on each component. To test the association of each remaining component with the outcome variable, component loadings that were significantly different by diagnostic group at \( p < 0.05 \) using a t-test were entered into a logistic regression.

Since the outcome variable is dichotomous, binary logistic regression was used 1) to assess which of the independent components significantly predicted diagnostic
group, 2) to rank the relative importance of each predictor, and 3) to determine the amount of variance in the actual diagnoses that can be explained by the observed components. Logistic regression uses the maximum likelihood estimation after first transforming the outcome variable into a logit variable (175). Logit is the natural log of the odds of the outcome occurring or not occurring. Discriminant function analyses could also have been used to test the ability of these components to correctly classify subjects’ diagnosis. In this instance, logistic regression was preferred because it provides the coefficient for each component which allows for the reporting of odds ratios with confidence intervals for each component’s association with the outcome measure (176).

Visualization:

For visualization of group differences identified from logistic regression analyses, voxels for significant components which contributed to the component at a value of $|Z|>3.1$ were superimposed onto SPM2’s spatially normalized template brain. Coordinates were transformed from the MNI coordinate system to the coordinates of the standard space of Talairach and Tournoux (177) using a MATLAB conversion program written by Matthew Brett (MRC Cognition and Brain Sciences Unit, Cambridge, England). Once converted, Talairach coordinates were entered into the Talairach Daemon (178) for localization.
CHAPTER 9: RESULTS

Previous structural MRI studies compare patients and control groups for absolute or relative differences between volumes at a single location in the brain. Although this approach may be useful in the identification of brain regions involved in the expression of the disease for the entire group, it provides minimal information about the natural patterns of brain volumes within groups. ICA decomposes the GM volume variation from the large subject-by-voxel matrix into a smaller subject-by-component matrix. Each component represents a distinct GM volume pattern extracted from the dataset. The component loading score is a quantitative measure of how much each subject correlates with that component/GM volume pattern. Thus, ICA is in a position to detect natural constellations of brain volumes within groups of subjects which may reflect valid neural networks that have been poorly detected using correlational or factor analyses (100, 117, 122, 155, 156, 159).

Thirty components were estimated using ICA. Each component was displayed over a single subject brain image in the GIFT toolbox and visually inspected to identify the major brain regions involved in each component. The primary brain region detected by each component is listed in table 1. Eight components displayed patterns that were suggestive of artifact, such as ringing around the edges of the cerebrum. Three components represented the areas of the ventricles where no GM tissue was expected. These eleven components may have been detecting artifactual variation in brain volume introduced during the image normalization process. Artifact and reduced variability are both limitations incurred by the normalization process that have been acknowledged and accepted by the neuroimaging community as an acceptable trade-off for increased
automation. Since brain size and shape are of particular interest in this study, areas of the brain that are more susceptible to artifactual volume (GM bordering ventricles) are interpreted with caution since patients with SZ are more likely to have gross structural aberrations which require more extensive reshaping during normalization.

**T-test**

Of the 30 components estimated using ICA, a comparison of the patient group to the control group using an independent samples t-test identified 11 components where subjects' component loading scores were significantly different by diagnostic group. Only one of the 11 components previously considered to be artifical was found to be significant. Component 30 was significant at $p<0.05$ with mean SZ scores greater than HC scores. Five of the 11 significant components had mean component loadings that were greater in the HC group. The remaining six components had mean component loadings that were greater in the SZ group.

**Regression analyses**

To estimate the potential for independent components to predict diagnostic group, a multiple logistic regression was run with the 11 components above as the independent variables and with diagnostic group as the outcome measure. Since this analysis is exploratory rather than hypothesis driven, three entry methods (forward conditional, backward conditional, and stepwise) were used to assess the model. Each method resulted in the same six components significant at $p<0.05$ with the full model significant at $p<0.0001$ (table 2). The Hosmer-Lemeshow goodness of fit test (175) was not significant ($X^2 = 3.05, df=8, p=0.93$) indicating that there is no difference between the outcomes observed and the outcomes predicted by the six variables.
Linear regression uses the R-square statistic to quantify the amount of variance in the outcome variable that is accounted for by the predictor variables. In logistic regression, the variance of a dichotomous outcome measure is dependent on its frequency distribution. Since the distribution can vary between samples, there is no accurate measure of variance for comparison between models. Despite this, several alternatives have been proposed that seek to adjust for the limitations of the logistic model (175). Of these alternatives, the Nagelkerke (1991) measure of variance is the most reported (175). In this study, the Nagelkerke R-square estimates that approximately 34.82% of the variation in diagnosis is explained by these six components.

Assessing the accuracy of a predictive model such as this one is critical to evaluating its utility. ROC curves provide a standardized way of quantifying the trade-off between specificity and sensitivity and provide an overall measure of the ability of these components to predict a diagnosis of SZ. The curves are also visually intuitive for the interpretation of predictive accuracy. The overall accuracy of this model in correctly discriminating diagnostic group was 80.5% (using a predicted probability of 0.5 or greater) and is represented by the area under the curve (AUC) (figure 1). The maximum percentage of individuals who were correctly classified by diagnostic group was 73.3, with a sensitivity of 70.7% and a specificity of 75.9% (table 3). In this sample, the positive predictive value of the 6 components was 74.6% and the negative predictive value was 72.1% (table 3). However, in this study there are equal numbers of patients and controls. In the general population, prevalence of SZ is less than 1%. In order for the “true” predictive values of these components to be evaluated, the analyses would need to be repeated with a sample that reflects the actual disease prevalence (176) (see table 3,
Anatomy of the Independent Components

Five components represented heteromodal association cortex areas and one component represented sub-cortical thalamic areas. Three components represented areas where GM volumes were relatively greater in HC than patients (table 4, figure 2) while the remaining three represented regions where GM was relatively greater in schizophrenia (table 5, figure 3). The six components will subsequently be referred to by the anatomical regions they represent and are listed here in order of their respective contributions to the prediction of diagnostic group.

Component 24: HC Parietal

The strongest association with diagnostic group was component 24. This component consisted of bilateral parietal GM volume that was greater in HC than schizophrenia (blue in figure 2). The GM differences were predominately sub-gyral and located medial to the right IPL in the dorsal portion but became bilateral as the GM difference was tracked into the temporo-parietal junction. Although the “HC parietal” component extended into the temporal gyri, its regions were posterior to the STG regions expressed in the “HC temporal” component (discussed next). This component accounted for approximately 11.4% of the variation in diagnostic according to the Nagelkerke R-square statistic.

Component 13: HC Temporal

The most extensive contiguous region of GM differences between diagnostic groups was found in the region of the STG (red in figure 2) with healthy controls having more GM than patients with schizophrenia. These GM differences were notably
constrained to the STG and its medial counterparts, the transverse temporal gyrus and insula, suggesting a clear distinction between these structures (as a single component) and the rest of the temporal lobe. The GM differences were slightly lateralized (R>L) posteriorly in the PT and became increasingly lateralized as the gyrus descended toward the temporal pole. The larger STG and its lateralization are consistent with previous findings. This component accounted for an additional 7% of the variation in diagnostic group.

Component 27: SZ Thalamic/Hippocampal

Component 27 consisted of substantially larger GM in schizophrenia patients in the thalamus, hippocampi and parahippocampal gyri, and medial temporal regions (green in figure 3). The thalamic increases in schizophrenia were localized to the medial, anterior, and ventral nuclei and hypothalamus, but did not extend into the lateral thalamic areas. Both hippocampi were larger in schizophrenia and this effect extended focally along the parahippocampal gyri. The thalamic and hippocampal regions covaried with two bilateral nodes located medial to the temporal lobe (BA 21, 22). This component accounted for an additional 7% of the variation in diagnostic group.

Component 25: HC Frontal/Occipital

This component represented greater GM volumes in HC compared with schizophrenia and was expressed bilaterally in the middle frontal gyri, extending medially into sub-gyral areas (green in figure 2). The isolated region along the middle frontal gyrus covaried with GM volumes in the posterior regions of the STG bilaterally, the middle temporal-middle occipital junction, and the primary visual areas (BA 17, 18). This component accounted for an additional 2.5% of the variation in diagnosis.
Component 2: SZ Parietal

In the parietal lobe, patient with schizophrenia also showed greater volumes bilaterally in portions of the IPL (red in figure 3). The increases in schizophrenia patients were less medial than those in the “HC Parietal” component and did not extend ventrally into the STG or medial temporal areas. The regions comprising this component were more extensive in the right hemisphere. Furthermore, the IPL regions in this component showed a covariance with a posterior section of the medial temporal gyrus bilaterally and the lingual areas (BA 17, 18). This component accounted for an additional 6% of the variation in diagnostic group.

Component 3: SZ Frontal/Temporal

While the majority of components comprised focal GM differences, this component consisted of several regions scattered throughout the brain (blue in figure 3). Areas in this component included discrete nodes in the superior, middle, and medial frontal gyri (along the GM/WM border), the temporo-parietal junction, and the posterior STG. The varied location of these small nodes likely contributed to the diminished significance of this component in the regression model. However, the correlated regions all represent areas of the HASC and are suggestive of a GM volume basis to the HASC network. This component accounted for an additional 1.5% of the variation in diagnosis.
CHAPTER 10: DISCUSSION

Unlike traditional GLM studies which test for a static, absolute difference in volume at a given voxel between diagnostic groups, ICA explores patterns of variation that occur within and between subjects. Each component extracted using ICA represents a set of brain regions that covary in a particular way between subjects (as indicated by the mixing matrix parameters). In this study, patients with schizophrenia and healthy controls were analyzed as a single dataset to allow the extraction of natural variations in structure. Significant components do not represent absolute GM volume differences but represent areas of GM volume where the individuals of one diagnostic group positively correlate with the given GM volume pattern (on average) while the subjects in the other diagnostic group negatively correlate with the component.

Regression Analyses

By itself, ICA provides a decomposition of data into a smaller set of structural patterns. In order to identify group differences, significance testing was performed on the component loading scores. Since both diagnostic groups were included in our model, testing for group differences using component loadings identified regions of the brain where one diagnostic group had significantly different GM patterns than the other group. A binary multiple logistic regression of the component loadings identified six components that were highly predictive of diagnostic group: overall the model was able to correctly discriminate diagnostic group 80.5 percent of the time. With further research, anatomical differences in GM volumes such as those identified using ICA might be capable of predicting diagnosis on an individual level.

Predictability
Although this model appears to be a good predictor of diagnostic group based on the sample at hand, the utility of this model should be interpreted with caution. Briefly discussed in chapter nine, under real world conditions, this model is unlikely to retain its rather high predictive ability. This is because the samples included in the study are not fully generalizable to their respective populations (176).

The measures of predictive value are based on the proportion of subjects who do or do not have the disease. The study prevalence of disease positive subjects substantially influences measures of predictive value. For example, positive predictive value is a ratio of true positives to all positives. In this study, 94 out of 126 subjects were accurately predicted to be positive (74.6%) with a 1:1 ratio of patients to controls. In a sample where disease-free subjects are much more common, say a ratio of 1:9 for patients to controls, the sensitivity and specificity of the test remain the same but the predictive ability of the test changes (table 3, panel B). When the prevalence of disease individuals is substantially lower than the disease free individuals, the ability to predict a positive status is reduced while predictive ability of negative status is greatly increased. Prevalence of SZ is estimated to be less than 1% of the population (less than a 1:100 ratio of SZ to non-SZ) suggesting the PPV of these 6 components will be remarkably lower while the NPV will be close to 100%. One additional point to consider is the context in which a test such as this one will be applied. Although prevalence is very low for SZ in the general population, the proportion of individuals who present for diagnosis upon whom this test may be used will have a much higher ratio of SZ to non-SZ. Thus, in actual applied settings, the low prevalence of SZ may be less of an issue.

Spectrum refers to the sampling of the population. Although the patients in this
study fall along a wide-spectrum of age, sex, and chronicity, the fact that these patients participated in a research study indicates that they are relatively high functioning and able to provide informed consent. In addition, patients with schizoaffective diagnoses were included in the sample. These factors are likely to impact the sensitivity of this model in SZ only populations. The same effect is seen on specificity when the comparison population does not adequately reflect the real world population. Neuroimaging studies routinely require control subjects to be psychiatrically and physically healthy. Not only does this make the control sample less generalizable to the real world population, but it undermines the nature of specificity. The goal of specificity is to distinguish one type of illness from another. Thus, as an example for this study, a good control group would include patients with non-SZ psychiatric illnesses, relatives of patients with SZ, and persons that demonstrate similar symptoms or cognitive deficits but for reasons other than SZ. Given that the nature of this study was exploratory, wide spectrum control populations may mask the detection of an effect and are perhaps premature in this context. With more refined hypotheses and meaningful applications, the dependence on wide-spectrum study groups reiterates the importance of large-scale epidemiological studies of brain structure, clinical presentation, and genotypes in the search for anatomical predictors of schizophrenia.

Bias, on the other hand, is less of an issue in this study. Bias can falsely inflate sensitivity and specificity when the examiner is aware of the test result during diagnosis or is aware of diagnosis when evaluating a test result. Any subjectivity in this study is limited to diagnosis of the subject prior to imaging. Since a diagnosis is required for inclusion in the study, all diagnoses are unaffected by the imaging results. Alternatively,
the brain scans are evaluated by an automated, bias free process during both VBM and ICA. In this study, experimenter bias is completely independent of the predictor variables and is not likely to impact this study’s predictive efficacy. The impact of bias will reemerge in these types of studies, however, should brain morphology become part of the diagnostic workup for schizophrenia.

Structural Differences

The application of ICA to detect structural GM volume differences between healthy controls and patients with schizophrenia successfully identified six components that differentiated diagnosis. Five of the six components corresponded to areas of the heteromodal association cortex that have been implicated in the disorder; the remaining component is hypothesized to subserve the HASC network. Our findings of smaller GM volumes in the patient group in the STG, IPL, and prefrontal regions are consistent with past research (100).

The ability for ICA to detect discrete regions of variation is particularly valuable. The “HC Temporal” component indicates that healthy controls consistently possess more GM volume bilaterally in a large, continuous region of the temporal lobe that included the STG, PT, transverse temporal gyrus, and insula. Restriction of the volume disparities between groups to this temporal region suggests that GM volumes in these areas, but not in the middle or inferior temporal regions, were a discriminating anatomical difference between patients and controls and is consistent with previous reports of selective reductions in the STG (61, 77, 155). A similar effect was seen with the “HC Parietal” component with relative increases in controls bilaterally in the medial regions of the inferior parietal lobule. These two components suggest that STG and IPL structures are
each internally consistent in volumetric changes. This uniformity may underlie the power of these two components in this regression model. These two components alone correctly classified 68.8% of the individual diagnoses.

The remaining four components demonstrated several inter-correlations in volume change throughout the brain. Notably, both the “HC Frontal/occipital” and “SZ Frontal/temporal” components revealed several non-prefrontal GM changes that covaried with the prefrontal volumes. This is consistent with Mitelman’s (2005) reports of inter-correlations between prefrontal volumes and temporal and occipital volumes in patterns that differed between patients and controls (156). Although it is not possible to demonstrate connectivity between GM regions based on volume correlations, the association in volume change between these regions implies that a search for abnormal connectivity may be fruitful. In addition, the focal GM differences found in these two components may explain the greater success of parcellation studies over whole lobe measurements in detecting anatomical differences. Although past research has mainly detected differences in the inferior and orbital frontal gyri, our findings of GM deficits in schizophrenia in the middle frontal gyrus were consistent with Gur (179) and Goldstein(97).

Relative increases in GM volume in the IPL were evident in both diagnostic groups. In the “HC parietal” component, controls had greater IPL volumes in the right superior parietal lobule and angular gyrus and bilaterally in the supramarginal gyrus and posterior portions of the temporal gyri. In the “SZ Parietal” component, patients exhibited greater GM volumes posterior to and more lateral than the regions in the “HC temporal” component and did not extend into temporal areas. Although volumetric
studies of the IPL in schizophrenia are limited, GM reductions in schizophrenia were consistent with previous reports of volume reductions in the angular and supramarginal gyri in schizophrenia (85, 97, 98, 101). Different but adjacent regions in the parietal cortex that showed consistent volumetric change within subject groups suggests that GM volumes in the parietal lobe may be not be wholly decreased in patients. Instead, patients may display altered morphology that occurs inconsistently between patients. Since ICA is sensitive to variations common among a subset of the population group, it is possible to extract components representing GM variations that were not detectable using traditional VBM approaches. Similar IPL volume reductions in patients were found with joint ICA (jICA), supporting a potential role of the IPL in the expression of the disease (102, 165). In the jICA study as in this study, the smaller GM volumes in patients versus controls were located medially in the GM regions. It is also possible that reductions of GM in patients in this region represent increases in WM. Future studies should investigate GM-WM volume interactions using ICA.

The patient group showed the most intense GM increases in the thalamic and hippocampal regions. MRI studies of thalamic volumes in schizophrenia generally report reductions in patients(57, 180) or no significant differences between patients and controls. In our study, ICA detected increases in thalamic and hypothalamic volumes for patients that correlated with GM decreases in controls. Since ICA detects variations in volumes common within and between individual subjects rather than absolute volume differences between groups, our results may not be fully comparable to those reported using standard volumetric methods. The “schizophrenia thalamic\parahipp” component included sizable GM increases in the parahippocampal gyri and the medial portions of the
middle and superior temporal gyri (BA 21, 22) as well.

As an automated procedure, VBM may incorrectly segment voxels along the perimeter of the ventricles as GM (47, 170). The location of the thalamic structures at the base of the ventricles may heighten the likelihood that these structures are misclassified and GM volumes are spurious. Although this is possible, the specificity of the misclassification to one diagnostic group is unlikely, suggesting that anatomical differences detected in this region are real, albeit misclassified. Non-automated analyses of this region may determine the validity of the VBM segmentation and localization of diagnostic group differences to thalamic structures. Alternatively, ICA may serve as a powerful tool for exposing underlying variations specific to overlapping subgroups of a population that are not detectable using univariate methods. Further research on volumetric variations in the thalamus is recommended.

Conclusions

The use of ICA to explore GM segmentation allowed for the identification of natural groupings of regions that showed disparate volumetric variations between schizophrenia and HC. These findings agree with previous reports on GM differences in schizophrenia. Our study provides support for the HASC theory of schizophrenia—five of the six components that significantly predicted diagnostic groups were composed of regions of the HASC. An estimated 34.8% of the variation in diagnosis was accounted for by GM volumes in these six components, which supports a substantial role for structural abnormalities in the expression of schizophrenia. The separation of these regions into different components suggests that there are complex and regionally specific structural
changes occurring in schizophrenia. This may explain variability in previous findings because most methods have simply identified volumetric changes from HC without grouping together regions which exhibit similar changes.

The application of ICA to structural brain images creates new opportunities to assess variations in regional brain morphology. Comparisons of the independent regional variations between diagnostic groups may reveal differences not detectable using traditional univariate methods and may provide new insight into the complex structural changes occurring in mental illness. However, this is only a first step in the overall goal of reevaluating the utility of the current diagnostic systems. Future research investigating the anatomical phenotypes should consider the aims discussed in this thesis in an effort to further our understanding of the etiologies and construct of schizophrenia.
Table 1: Each ICA component and the primary region represented by the component. Component loading scores were grouped by diagnosis and descriptive statistics for each group are listed. Results of each independent samples t-test are listed in the final columns. * = p < 0.05, ** = p < 0.01

<table>
<thead>
<tr>
<th>Component</th>
<th>Sig.</th>
<th>Brain Regions</th>
<th>Mean HC</th>
<th>Standard Deviation</th>
<th>Std. Error</th>
<th>Mean SZ</th>
<th>Standard Deviation</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Anterior Cingulate</td>
<td>0.023</td>
<td>0.098</td>
<td>0.054</td>
<td>0.192</td>
<td>0.098</td>
<td>0.054</td>
</tr>
<tr>
<td>2</td>
<td>**</td>
<td>Inferior Parietal, pred. left</td>
<td>-0.224</td>
<td>-0.098</td>
<td>-0.045</td>
<td>0.207</td>
<td>-0.098</td>
<td>-0.045</td>
</tr>
<tr>
<td>3</td>
<td>**</td>
<td>Bilateral Prefrontal and Left Inferior Parietal</td>
<td>-0.171</td>
<td>0.102</td>
<td>0.056</td>
<td>0.192</td>
<td>0.102</td>
<td>0.056</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Articulated: Cerebellar Ringing</td>
<td>0.054</td>
<td>0.098</td>
<td>0.054</td>
<td>0.192</td>
<td>0.098</td>
<td>0.054</td>
</tr>
<tr>
<td>5</td>
<td>**</td>
<td>Bilateral Inferior Parietal</td>
<td>0.192</td>
<td>0.102</td>
<td>0.056</td>
<td>0.192</td>
<td>0.102</td>
<td>0.056</td>
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<td>Bilateral Supramarginal Gyrus</td>
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<td>0.054</td>
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<td>Bilateral Secondary Visual/Occipital lobe</td>
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<td>-0.098</td>
<td>-0.045</td>
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<td>0.192</td>
<td>0.098</td>
<td>0.054</td>
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<td>9</td>
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<td>Bilateral Caudate Nucleus</td>
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<td>0.207</td>
<td>-0.098</td>
<td>-0.045</td>
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<td>0.102</td>
<td>0.056</td>
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<td>11</td>
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<td>Middle Prefrontal Gyr</td>
<td>-0.045</td>
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<td>-0.045</td>
<td>0.207</td>
<td>-0.098</td>
<td>-0.045</td>
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<td>Right Lateral Somatosensory</td>
<td>-0.089</td>
<td>0.098</td>
<td>-0.045</td>
<td>0.207</td>
<td>-0.098</td>
<td>-0.045</td>
</tr>
<tr>
<td>13</td>
<td>**</td>
<td>Bilateral Superior Temporal gyr</td>
<td>0.193</td>
<td>0.098</td>
<td>0.056</td>
<td>0.192</td>
<td>0.098</td>
<td>0.056</td>
</tr>
<tr>
<td>14</td>
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<td>Bilateral Temporal-Occipital junction and Right Precuneus-Angular Gyrus</td>
<td>-0.139</td>
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<td>-0.098</td>
<td>-0.054</td>
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<td>-0.098</td>
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<td>-0.058</td>
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<td>-0.098</td>
<td>-0.054</td>
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<td>-0.054</td>
<td>0.207</td>
<td>-0.098</td>
<td>-0.054</td>
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<tr>
<td>18</td>
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<td>Bilateral Primary Visual</td>
<td>0.075</td>
<td>0.098</td>
<td>0.056</td>
<td>0.192</td>
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<tr>
<td>19</td>
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<td>Anterior Cingulate and Insula</td>
<td>-0.060</td>
<td>0.098</td>
<td>-0.056</td>
<td>0.207</td>
<td>-0.098</td>
<td>-0.056</td>
</tr>
<tr>
<td>20</td>
<td>**</td>
<td>Right Sttium/Globus Pallidus</td>
<td>0.196</td>
<td>0.098</td>
<td>0.056</td>
<td>0.192</td>
<td>0.098</td>
<td>0.056</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>Articulated: Temporal Pole Ringing</td>
<td>-0.014</td>
<td>0.098</td>
<td>-0.056</td>
<td>0.207</td>
<td>-0.098</td>
<td>-0.056</td>
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<td>22</td>
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<td>Articulated: Fourth Ventricle</td>
<td>-0.029</td>
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<td>-0.098</td>
<td>-0.056</td>
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<tr>
<td>23</td>
<td></td>
<td>Articulated: Cerebellar Extrahemispheric</td>
<td>-0.016</td>
<td>0.098</td>
<td>-0.056</td>
<td>0.207</td>
<td>-0.098</td>
<td>-0.056</td>
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<tr>
<td>24</td>
<td></td>
<td>Bilateral Inferior Parietal</td>
<td>-0.292</td>
<td>0.098</td>
<td>-0.056</td>
<td>0.207</td>
<td>-0.098</td>
<td>-0.056</td>
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<tr>
<td>25</td>
<td>**</td>
<td>Bilateral Middle Frontal Gyrus and Primary Visual</td>
<td>0.259</td>
<td>0.098</td>
<td>0.056</td>
<td>0.192</td>
<td>0.098</td>
<td>0.056</td>
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<tr>
<td>26</td>
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<td>Bilateral Middle Frontal Gyrus</td>
<td>0.078</td>
<td>0.098</td>
<td>0.056</td>
<td>0.192</td>
<td>0.098</td>
<td>0.056</td>
</tr>
<tr>
<td>27</td>
<td>**</td>
<td>Thalamus and medial Temporal lobe</td>
<td>-0.195</td>
<td>0.098</td>
<td>-0.056</td>
<td>0.207</td>
<td>-0.098</td>
<td>-0.056</td>
</tr>
<tr>
<td>28</td>
<td></td>
<td>Articulated: Occipital lobe Ringing</td>
<td>0.031</td>
<td>0.098</td>
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<td>0.192</td>
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<td>0.056</td>
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<tr>
<td>29</td>
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<td>Articulated: Occipital Pole Ringing</td>
<td>-0.096</td>
<td>0.098</td>
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<td>0.207</td>
<td>-0.098</td>
<td>-0.056</td>
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<tr>
<td>30</td>
<td></td>
<td>Articulated: Posterior Lateral Ventricles</td>
<td>-0.147</td>
<td>0.098</td>
<td>-0.056</td>
<td>0.207</td>
<td>-0.098</td>
<td>-0.056</td>
</tr>
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Table 2: Regression coefficients and significance levels in order of effect size.

<table>
<thead>
<tr>
<th>Component</th>
<th>Brain Region</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>Sig.</th>
<th>Exp(B)</th>
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</thead>
<tbody>
<tr>
<td>3</td>
<td>SZ frontal/temporal</td>
<td>0.306</td>
<td>0.155</td>
<td>3.918</td>
<td>0.048</td>
<td>1.359</td>
</tr>
<tr>
<td>2</td>
<td>SZ parietal</td>
<td>0.543</td>
<td>0.156</td>
<td>12.147</td>
<td>0.000</td>
<td>1.721</td>
</tr>
<tr>
<td>25</td>
<td>HC frontal/occipital</td>
<td>-0.366</td>
<td>0.152</td>
<td>5.819</td>
<td>0.016</td>
<td>0.694</td>
</tr>
<tr>
<td>27</td>
<td>SZ thalamic/hippocampal</td>
<td>0.591</td>
<td>0.160</td>
<td>13.664</td>
<td>0.000</td>
<td>1.805</td>
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<tr>
<td>13</td>
<td>HC temporal</td>
<td>-0.612</td>
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<td>0.542</td>
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<td>24</td>
<td>HC parietal</td>
<td>-0.723</td>
<td>0.167</td>
<td>18.748</td>
<td>0.000</td>
<td>0.485</td>
</tr>
</tbody>
</table>

Table 3: Observed diagnoses compared to the diagnoses predicted by the regression model. Panel A provides the predictive values for this study sample in which there is a 1:1 ratio of patients to controls. Green represents the number of subjects correctly classified by the model. Red represents the subjects that were incorrectly classified. Overall, the regression model in this study accurately classified 195 (73.3%) of the 266 subjects. Panel B provides the predictive value of this model if the study sample reflected a low prevalence of patients (a ratio of 1:9), as would be the case when applied as a screening tool. PPV = positive predictive value. NPV = negative predictive value.

A. Observed

<table>
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<tr>
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<tr>
<td></td>
<td>SZ (N=133)</td>
<td>HC (N=133)</td>
</tr>
<tr>
<td>Predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ (N=126)</td>
<td>94 32</td>
<td>PPV=74.6%</td>
</tr>
<tr>
<td>HC (N=140)</td>
<td>39 101</td>
<td>NPV=72.1%</td>
</tr>
</tbody>
</table>

Sensitivity Specificity

70.7% 75.9%

B. Observed

<table>
<thead>
<tr>
<th></th>
<th>Observed</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SZ (N=26)</td>
<td>HC (N=240)</td>
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<tr>
<td>Predicted</td>
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<td></td>
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<tr>
<td>SZ (N=77)</td>
<td>19 58</td>
<td>PPV=24.7%</td>
</tr>
<tr>
<td>HC (N=189)</td>
<td>7 182</td>
<td>NPV=96.3%</td>
</tr>
</tbody>
</table>

Sensitivity Specificity

73.1% 75.8%
Table 4: Talairach labels of regions where healthy controls have greater GM volumes than patients. Voxels above the threshold in figure 2 were converted from Montreal Neurological Institute (MNI) coordinates to Talairach coordinates and entered into a database to provide anatomic and functional labels for the left (L) and right (R) hemispheres. The volume of voxels in each area is provided in cubic centimeters (cc). Within each area, the maximum Z value and its coordinate are provided.

<table>
<thead>
<tr>
<th>Comp13: Temporal, HC &gt; SZ</th>
<th>Brodmann Area</th>
<th>R: cc</th>
<th>L: cc</th>
<th>R: Max-Z (x, y, z)</th>
<th>L: Max-Z (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior Temporal Gyrus</td>
<td>22, 42, 41, 13, 38, 29, 21</td>
<td>11.3</td>
<td>5.8</td>
<td>7.6(-50,-6,3)</td>
<td>5.2(50,-20,9)</td>
</tr>
<tr>
<td>Precentral Gyrus</td>
<td>6, 13, 43, 44</td>
<td>1.4</td>
<td>0.3</td>
<td>7.6(-50,-8,6)</td>
<td>5.2(-48,-17,12)</td>
</tr>
<tr>
<td>Transverse Temporal Gyrus</td>
<td>42</td>
<td>0.9</td>
<td>1.4</td>
<td>6.4(-48,-17,12)</td>
<td>5.2(45,-26,12)</td>
</tr>
<tr>
<td>Insula</td>
<td>13, 40, 29</td>
<td>2.1</td>
<td>1.4</td>
<td>6.3(-45,-14,9)</td>
<td>4.7(42,-28,15)</td>
</tr>
<tr>
<td>Postcentral Gyrus</td>
<td>40, 43</td>
<td>2.2</td>
<td>0.3</td>
<td>6.0(-56,-23,15)</td>
<td>3.8(56,-25,15)</td>
</tr>
<tr>
<td>*</td>
<td>Optic Tract</td>
<td>0.4</td>
<td>0.1</td>
<td>5.3(-48,0,3)</td>
<td>3.3(-0,17,4)</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>21, 38</td>
<td>0.7</td>
<td>0</td>
<td>4.7(-53,0,-8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>47</td>
<td>1.6</td>
<td>0</td>
<td>4.6(-48,14,-6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td>40</td>
<td>0.7</td>
<td>1</td>
<td>4.4(-59,-28,24)</td>
<td>3.4(53,-37,24)</td>
</tr>
<tr>
<td>Sub-Gyral</td>
<td>0.4</td>
<td>0</td>
<td></td>
<td>4.2(-48,-11,14)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comp24: Parietal, HC &gt; SZ</th>
<th>Brodmann Area</th>
<th>R: cc</th>
<th>L: cc</th>
<th>R: Max-Z (x, y, z)</th>
<th>L: Max-Z (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior Temporal Gyrus</td>
<td>39, 22, 13</td>
<td>1.8</td>
<td>0.6</td>
<td>12.4(-39,-51,25)</td>
<td>6.1(39,-54,19)</td>
</tr>
<tr>
<td>Supramarginal Gyrus</td>
<td>40</td>
<td>2.1</td>
<td>0.2</td>
<td>12.1(-39,-51,27)</td>
<td>5.9(36,-54,28)</td>
</tr>
<tr>
<td>Sub-Gyral</td>
<td>7.3</td>
<td>4</td>
<td>11.7</td>
<td>36,-51,25</td>
<td>8.2(33,-54,22)</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>39, 22, 19</td>
<td>0.9</td>
<td>0.6</td>
<td>10.8(-36,-54,25)</td>
<td>8.1(36,-54,22)</td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td>40</td>
<td>1.4</td>
<td>0</td>
<td>9.9(-42,-48,25)</td>
<td>3.3(36,-45,27)</td>
</tr>
<tr>
<td>Angular Gyrus</td>
<td>0.6</td>
<td>0</td>
<td>9.9</td>
<td>39,-54,30</td>
<td>n.s.</td>
</tr>
<tr>
<td>Precuneus</td>
<td>7</td>
<td>0.5</td>
<td>0.2</td>
<td>7.0(-27,-47,44)</td>
<td>4.0(21,-48,30)</td>
</tr>
<tr>
<td>Insula</td>
<td>13</td>
<td>0.2</td>
<td>0</td>
<td>5.9(-39,-43,21)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Superior Parietal Lobule</td>
<td>7</td>
<td>0.1</td>
<td>0</td>
<td>5.8(-27,-50,44)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Extra-Nuclear</td>
<td>0.3</td>
<td>0.3</td>
<td>5.3</td>
<td>-33,-46,19</td>
<td>5.3(30,-49,19)</td>
</tr>
<tr>
<td>Postcentral Gyrus</td>
<td>1, 3, 2</td>
<td>0</td>
<td>0.7</td>
<td>3.8(45,-26,62)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>6</td>
<td>0.2</td>
<td>0</td>
<td>3.5(-30,28,32)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Precentral Gyrus</td>
<td>6, 4</td>
<td>0</td>
<td>0.2</td>
<td>3.3(42,-11,61)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comp25: Frontal, HC &gt; SZ</th>
<th>Brodmann Area</th>
<th>R: cc</th>
<th>L: cc</th>
<th>R: Max-Z (x, y, z)</th>
<th>L: Max-Z (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Gyral</td>
<td>2.5</td>
<td>3</td>
<td></td>
<td>7.5(-36,24,24)</td>
<td>8.8(36,21,21)</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>2.8</td>
<td>0.9</td>
<td>7.4</td>
<td>39,24,24</td>
<td>6.5(36,22,27)</td>
</tr>
<tr>
<td>Lingual Gyrus</td>
<td>1.6</td>
<td>1.9</td>
<td>6.9</td>
<td>0,-91,-8</td>
<td>7.3(3,-91,-8)</td>
</tr>
<tr>
<td>*</td>
<td>0.1</td>
<td>0.5</td>
<td>4.8</td>
<td>-3,-88,-11</td>
<td>6.9(3,-91,-11)</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>39</td>
<td>0.6</td>
<td>0.2</td>
<td>5.4(-42,-72,12)</td>
<td>4.3(48,-43,8)</td>
</tr>
<tr>
<td>Middle Occipital Gyrus</td>
<td>19</td>
<td>1.2</td>
<td>1</td>
<td>5.4(-39,-75,9)</td>
<td>4.6(36,-78,12)</td>
</tr>
<tr>
<td>Superior Temporal Gyrus</td>
<td>39, 13, 41</td>
<td>0.8</td>
<td>2.2</td>
<td>4.2(-48,-37,13)</td>
<td>5.4(48,-43,10)</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>0.1</td>
<td>0</td>
<td>4.3</td>
<td>-33,10,27</td>
<td>n.s.</td>
</tr>
<tr>
<td>Insula</td>
<td>13</td>
<td>0.2</td>
<td>0</td>
<td>3.9(-48,-40,19)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
Table 5: Talairach labels for regions where patients with schizophrenia have greater GM volumes than healthy controls. Voxels above the threshold in figure 3 were converted from MNI to Talairach coordinates and entered into a database to provide anatomic and functional labels for the left (L) and right (R) hemispheres. The volume of activated voxels in each area is provided in cubic centimeters (cc). Within each area, the maximum Z value and its coordinate are provided.

<table>
<thead>
<tr>
<th>Comp2: Parietal, SZ &gt; HC</th>
<th>Brodmann Area</th>
<th>R: cc</th>
<th>L: cc</th>
<th>R: Max-Z (x, y, z)</th>
<th>L: Max-Z (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Gyral</td>
<td></td>
<td>1.6</td>
<td>0.5</td>
<td>12.4(-33,-35,39)</td>
<td>7.3(33,-59,39)</td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td>40, 39, 7</td>
<td>2.9</td>
<td>0.9</td>
<td>11.7(-36,-56,39)</td>
<td>6.8(36,-59,39)</td>
</tr>
<tr>
<td>Angular Gyrus</td>
<td>39</td>
<td>0.6</td>
<td>0.2</td>
<td>10.8(-33,-54,36)</td>
<td>6.3(33,-59,36)</td>
</tr>
<tr>
<td>Supramarginal Gyrus</td>
<td></td>
<td>0.4</td>
<td>0</td>
<td>9.3(-33,-51,36)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Superior Parietal Lobule</td>
<td>7</td>
<td>0.5</td>
<td>0.2</td>
<td>7.9(-30,-56,44)</td>
<td>4.8(33,-59,44)</td>
</tr>
<tr>
<td>Precuneus</td>
<td>19, 39, 7</td>
<td>0.5</td>
<td>1</td>
<td>6.6(-36,-62,36)</td>
<td>6.8(33,-62,39)</td>
</tr>
<tr>
<td>Lingual Gyrus</td>
<td>17, 18</td>
<td>1.2</td>
<td>0.5</td>
<td>4.9(-39,-90,-3)</td>
<td>4.9(39,-90,3)</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>19, 39, 22, 21</td>
<td>1.9</td>
<td>0.9</td>
<td>4.7(-45,-63,14)</td>
<td>4.8(42,-66,17)</td>
</tr>
<tr>
<td>Cuneus</td>
<td>17</td>
<td>0</td>
<td>0.4</td>
<td>4.3(0,-85,-1)</td>
<td>4.7(0,-93,3)</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>6</td>
<td>0.3</td>
<td>1.8</td>
<td>4.4(-33,5,44)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Middle Occipital Gyrus</td>
<td>0</td>
<td>0.1</td>
<td>1.1</td>
<td>4.3(-39,-69,17)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Fusiform Gyrus</td>
<td>37, 20, 36</td>
<td>0.9</td>
<td>0</td>
<td>3.5(-42,-50,-15)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Inferior Temporal Gyrus</td>
<td>37</td>
<td>0.1</td>
<td>0</td>
<td>3.3(-45,-42,-18)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comp3: Frontal/Temporal, SZ &gt; HC</th>
<th>Brodmann Area</th>
<th>R: cc</th>
<th>L: cc</th>
<th>R: Max-Z (x, y, z)</th>
<th>L: Max-Z (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Gyral</td>
<td>6</td>
<td>2</td>
<td>1.5</td>
<td>5.4(-21,-1,47)</td>
<td>6.1(24,50,3)</td>
</tr>
<tr>
<td>Superior Frontal Gyrus</td>
<td>10, 9</td>
<td>1.9</td>
<td>1.2</td>
<td>5.4(-27,52,0)</td>
<td>6.0(27,47,6)</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>9, 10, 6, 11</td>
<td>1.8</td>
<td>1.4</td>
<td>5.8(-27,33,26)</td>
<td>5.9(27,50,3)</td>
</tr>
<tr>
<td>Middle Occipital Gyrus</td>
<td>19</td>
<td>1.1</td>
<td>0.1</td>
<td>5.4(-36,75,15)</td>
<td>3.3(33,-78,15)</td>
</tr>
<tr>
<td>Medial Frontal Gyrus</td>
<td>10, 6, 9</td>
<td>1</td>
<td>0.5</td>
<td>5.3(-24,36,26)</td>
<td>4.5(24,44,6)</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>39, 19</td>
<td>0.7</td>
<td>0.4</td>
<td>5.3(-36,75,18)</td>
<td>3.7(48,-55,11)</td>
</tr>
<tr>
<td>Superior Temporal Gyrus</td>
<td>22, 39</td>
<td>1.1</td>
<td>0.4</td>
<td>5.2(-45,-51,19)</td>
<td>4.1(45,-57,17)</td>
</tr>
<tr>
<td>Supramarginal Gyrus</td>
<td>0.1</td>
<td>0</td>
<td>1.1</td>
<td>4.8(-45,-51,22)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>0.2</td>
<td>0.1</td>
<td>4.2(-39,5,33)</td>
<td>4.4(36,10,27)</td>
<td></td>
</tr>
<tr>
<td>Cingulate Gyrus</td>
<td>32</td>
<td>0.2</td>
<td>0</td>
<td>4.3(-18,2,47)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Precentral Gyrus</td>
<td>9</td>
<td>0.2</td>
<td>0</td>
<td>4.2(-39,5,36)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td>0.1</td>
<td>0</td>
<td>3.5(-42,-42,18)</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comp27: Thalamic/Hippo, SZ &gt; HC</th>
<th>Brodmann Area</th>
<th>R: cc</th>
<th>L: cc</th>
<th>R: Max-Z (x, y, z)</th>
<th>L: Max-Z (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-Nuclear</td>
<td>Optic Tract</td>
<td>1</td>
<td>1.2</td>
<td>6.7(-3,-17,1)</td>
<td>7.5(0,-14,3)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>2.2</td>
<td>1.8</td>
<td>7.0(-3,-14,3)</td>
<td>6.4(3,-14,3)</td>
<td></td>
</tr>
<tr>
<td>Sub-Gyral</td>
<td>21, 22</td>
<td>0.4</td>
<td>1.2</td>
<td>4.4(-48,32,2)</td>
<td>5.7(48,-35,2)</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>22, 21, 38</td>
<td>0.4</td>
<td>0.9</td>
<td>4.0(-48,32,4)</td>
<td>5.1(48,-26,-1)</td>
</tr>
<tr>
<td>Lateral Ventricle</td>
<td>20, 28</td>
<td>0</td>
<td>0.4</td>
<td>n.s.</td>
<td>4.9(30,-16,-27)</td>
</tr>
<tr>
<td>Uncus</td>
<td>35, 36, 28, 30</td>
<td>2.2</td>
<td>3.2</td>
<td>3.8(-24,-18,-14)</td>
<td>4.4(30,-16,-24)</td>
</tr>
<tr>
<td>Parahippocampal Gyrus</td>
<td></td>
<td>1.0</td>
<td>0</td>
<td>4.1(-30,-78,20)</td>
<td>3.2(27,-81,21)</td>
</tr>
<tr>
<td>Middle Occipital Gyrus</td>
<td>19</td>
<td>0.1</td>
<td>0</td>
<td>4.1(0,2,-10)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Anterior Cingulate</td>
<td>25</td>
<td>0.3</td>
<td>0</td>
<td>3.7(-36,-45,38)</td>
<td>3.7(36,-48,38)</td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td>40</td>
<td>0.1</td>
<td>0.1</td>
<td>n.s.</td>
<td>3.6(42,14,-11)</td>
</tr>
</tbody>
</table>
Figure 1: Receiver Operator Characteristic (ROC) curve based on the predicted probabilities of the 6 component model. The area under the curve (AUC) indicates that the overall accuracy of the model is 80.5%. 

AUC = 0.805
Figure 2: Of the six components that significantly predicted diagnosis, the three components where GM volumes were relatively greater in controls are displayed here. Blobs represent voxels above the threshold of Z>|3.1|. Red = HC temporal component, blue = HC parietal component, green = HC frontal-occipital component.
Figure 3: Of the six components that significantly predicted diagnosis, the three components where GM volumes were relatively greater in patients are displayed here. Blobs represent voxels above the threshold of $Z > 3.1$. Red = SZ parietal component, blue = SZ frontal-temporal component, green = SZ thalamic component.
REFERENCES:


