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Identifying Subtypes of Schizophrenia Through Differential Neurocognitive and Symptomatic Profiles

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Philadelphia College of Osteopathic Medicine

Department of Psychology

IDENTIFYING SUBTYPES OF SCHIZOPHRENIA THROUGH DIFFERENTIAL
NEUROCOGNITIVE AND SYMPTOMATIC PROFILES

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Submitted in Partial Fulfillment of the Requirements for the Degree of

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DEPARTMENT OF PSYCHOLOGY

Dissertation Approval

This is to certify that the thesis presented to us by Brille Marino
on the 10 day of April, 2018, in partial fulfillment of the
requirements for the degree of Doctor of Psychology, has been examined and is
acceptable in both scholarship and literary quality.

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Abstract

Schizophrenia has long been characterized solely by positive and negative symptoms of psychosis. It has also been typified by its widespread heterogeneity, which has impeded treatment outcomes. Previous attempts at reducing this heterogeneity via identifying symptom-based subtypes has been unhelpful and unreliable. More recently, cognitive deficits have been identified as prominent features of the disorder and are now included as necessary diagnostic criteria. The present study aimed to identify the unique relationships between cognitive deficits and psychotic symptoms and to establish subtypes based on these profiles. The findings suggest two distinct subtypes: (a) a deficit subtype wherein individuals display more severe psychotic symptoms and more severe cognitive deficits overall, and (a) a nondeficit subtype wherein individuals have less severe psychotic symptoms, as well as less severe cognitive deficits overall. These subtypes also differed on the following variables of interest: race, employment, education, and history of antipsychotic medication. Specifically, the Deficit subtype was composed of more Black participants than White, had fewer years of education, and had a longer duration since first prescribed antipsychotic medication. The Nondeficit subtype, conversely, was composed of more White participants, a longer work history, more education, and fewer years since first prescribed antipsychotic medication. These findings have potential implications for the efficacy of diagnosis, treatment, and prevention strategies.

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IDENTIFYING SUBTYPES OF SCHIZOPHRENIA

Chapter 1: Introduction

Statement of the Problem

Schizophrenia is among the most severe forms of mental illness (Arieti, 1974). Positive and negative symptoms are prominent features of this disorder and have thus become central targets for treatment (Geddes, Freemantle, Harrison, & Bebbington, 2000). Positive symptoms include auditory and visual hallucinations, delusions, suspiciousness, hostility, and conceptual disorganization, while negative symptoms include blunted affect, emotional withdrawal, apathy, stereotyped thinking, and poor rapport with others (Kay, Fiszbein, & Opfer, 1987). More recently, cognitive deficits have garnered attention as viable indicators of both positive and negative symptom severity and have warranted further study based on their resistance to traditional treatment methods and high correlation with functional outcomes (Gold, 2004). Namely, severe cognitive deficits tend to persist despite positive and negative symptom abatement and therefore inhibit treatment success as a result of their hindrance on one's ability to carry out activities of daily living (Gold, 2004). This finding suggests the unidirectional relationship between cognitive deficits and positive and negative symptoms in that severity of cognitive deficit is a marker of positive and negative symptom severity, though the same is not necessarily true in the reverse (Arieti, 1974).

Since its inception, schizophrenia has been thought of as a multidimensional construct (Carpenter, Bartko, Carpenter, & Strauss, 1976). The term *schizophrenia* was originally used to denote a group of mental illnesses that were comprised of any combination of positive and negative symptoms of psychosis (Carpenter et al., 1976).

The widespread heterogeneity inherent in schizophrenia has been observed and documented since antiquity, eventually inciting the use of subtypes meant to categorize these differences (Fenton & McGlashan, 1991). Historically, a symptom-focused approach to differentiating subtypes dominated clinical manuals (Fenton & McGlashan, 1991). Some of these subtypes include paranoid, disorganized, catatonic, undifferentiated, and residual and were based solely on an individual's most prominent symptoms (Hoenig, 1983).

The most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association, 2013) has eliminated these subtypes because of their lack of reliability and clinical utility. Namely, a symptom-focused approach to diagnostic delineation is unreliable because of the transient nature of the symptoms and tendency for symptom overlap (Fenton & McGlashan, 1991). Moreover, positive and negative symptom fluctuation hinders the ability to measure and thus accurately diagnose subtypes within schizophrenia (Carpenter et al., 1976).

Despite these challenges, identifying subtypes remains an important endeavor. Previous researchers have successfully demonstrated that identifying phenotypic subtypes of heterogeneous disorders has improved diagnostic accuracy, expounded upon genetic etiology, and bettered treatment outcomes for autism spectrum disorder (Shao et al., 2002), Parkinson's disease (Dekker et al., 2003), and Alzheimer's disease (Scott et al., 2003). These findings suggest that this same type of refinement may be applied to schizophrenia to yield similar advances in conceptual, diagnostic, and treatment domains.

In response to a failed symptom-focused approach to identifying effective and accurate subtypes, researchers and clinicians have considered the utility of cognitive deficits as markers of subtypes within schizophrenia instead (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005). Refocusing on cognitive deficits as a method of differentiation emerged as a result of increasing support for their correlation with distinct positive and negative symptoms (Elvevag & Goldberg, 2000). Furthermore, cognitive deficits are easily measured and observed and tend to be enduring features of schizophrenia (Hoenig, 1983). Thus, cognitive deficits can provide information about symptom patterns and severity while being less susceptible to some of the limitations set forth by a symptom-focused paradigm (Elvevag & Goldberg, 2000).

Although cognitive deficits are at present acknowledged as longstanding and central features of schizophrenia, researchers have disagreed on whether cognitive deficits are generalized or domain specific (Lencz et al., 2006). While some argue that individuals with schizophrenia have deficits across all cognitive domains, others argue that the deficits are specific to certain functions and based on particular symptom presentations (Dickinson, Ragland, Gold, & Gur, 2008). With increasing consistency, researchers have demonstrated that negative symptoms are correlated with frontal functional deficits, while positive symptoms are associated with auditory deficits and more widespread neural networks that underlie attention (O'Leary et al., 2000). Based on these emerging patterns of positive and negative symptoms, generalized deficits clearly do not account for the full range of symptom presentations observed in clinical practice. These differential impairments support the domain-specific theory of cognitive deficits in

schizophrenia and further suggest the existence of subtypes within schizophrenia that can be classified based on these cognitive deficits.

Neuropsychological tests have been used extensively with this population to further investigate the notion of generalized versus specific cognitive deficits in schizophrenia. Studies that support the generalized-deficit theory, however, have demonstrated controversial methodologies, small sample sizes, and various other shortcomings that belie the veracity of their results (Fioravanti et al., 2005). Researchers have acknowledged that a domain-specific approach to understanding neurocognitive deficits would lend itself more easily to profiling individuals with schizophrenia (Gray, McMahon, & Gold, 2013). This notion parallels the emergence of domain-specific cognitive deficits that are correlated with specific positive and negative symptoms (Gold, 2004). These correlations between psychotic symptoms and specific cognitive deficits further implicate the existence of subtypes within schizophrenia.

Furthermore, studies that investigate specific versus generalized cognitive deficits have been ill equipped to address the question of targeted neurocognitive profiles in relation to symptom presentation, as they have investigated these constructs only in isolation (Gray, McMahon, & Gold, 2013). Distinguishing subtypes within schizophrenia based on differential neurocognitive profiles is essentially a novel approach to exploring the widespread variability of cognitive deficits observed in this disorder. Effective treatment is contingent upon an accurate understanding of the illness, which requires specification through subtypes to decrease the widespread heterogeneity of symptom presentations (O'Leary et al., 2000).

Interventions, nonetheless, have aimed at only positive and negative symptom reduction and have had limited success with the latter (Dickinson et al., 2008). The treatment for schizophrenia is essentially a generalized regimen, regardless of variations in symptom presentation, and is often ineffective for individuals who deviate from the typical symptom profile (Arieti, 1974). The reason for this generalized treatment approach is trifold: (a) Clinicians lack a clear understanding of the nature of neurocognitive deficits and their correlation with symptom presentations, (b) positive symptoms have been erroneously correlated with functional outcomes and therefore given precedence over other features of the illness, and (c) subtypes of schizophrenia based on neurocognitive profiles and associated symptom presentations have yet to be identified (Gold, 2004). As such, identifying subtypes of schizophrenia using a domain-specific neurocognitive approach may help to target and improve treatment, with particular emphasis on fostering clinical, genetic, and pharmacological studies (Velligan, Bow-Thomas, Mahurin, Miller, & Halgunseth, 2000). Moreover, accuracy in diagnostic delineation has the potential to improve not only treatment strategies and functional outcomes, but also prevention and research (Velligan et al., 2000).

Purpose of the Study

The purpose of the present study was to stimulate the delineation of subtypes of schizophrenia through identifying patterns of cognitive deficits as they relate to patterns of symptoms in schizophrenia. Identifying these patterns of cognitive deficits and related symptoms was achieved through an examination of domain-specific cognitive deficits

and their correlations with positive and negative symptoms among individuals suffering from schizophrenia.

Chapter 2: Review of the Literature

Background and Overview

Schizophrenia, as it is now conceptualized, is a relatively new diagnostic entity. The term itself is fewer than 100 years old and was coined by Swiss psychiatrist Paul Eugene Bleuler in 1910 (Ciompi, 1980). The word is derived from the Greek words *schizo*, meaning split, and *phren*, meaning mind (Johnstone et al., 1978). Thus, historically, schizophrenia was characterized predominantly by the division or loosening of cognitions that are apparent in the disorder. Despite variations in name, the incidence of schizophrenia has been well documented since antiquity. *Dementia Praecox*, which means dementia of early life, was the original term used to classify the disorder (Bleuler, 1950). *Dementia Praecox* was conceived by German psychiatrist Emil Kraepelin and was based on the overt cognitive deficits that characterized his patients (Johnstone et al., 1978).

More generally, the term *psychosis* was used to typify individuals who would meet present-day criteria for schizophrenia. Psychosis was originally an abbreviation for psychic neurosis, which essentially referred to a symptom of brain disease (Aderibigbe, Theodoridis, & Vieweg, 1999). Brain disease was the hypothesized cause of schizophrenia-like symptoms, with particular emphasis given to cognitive decline and general impairments in cognitive processes, such as memory, speech, ideations, and problem solving (Bleuler, 1950). Despite an overt historical emphasis on cognitive deficits as its hallmark, the focal point of schizophrenia shifted once clinicians looked to treat, rather than to define, the disorder.

At present, the term psychosis is a prominent feature of schizophrenia and is primarily composed of positive and negative symptoms (Aderibigbe et al., 1999). Positive symptoms refer to delusions, hallucinations, and thought disorganization, whereas negative symptoms refer to blunted affect and avolition (Liddle, 1987). Only more recently have cognitive deficits attained recognition as mainstays of schizophrenia and psychosis in general, despite being historically regarded as the apex of the disorder (Lewis & Lieberman, 2000). This re-focus on cognitive deficits is likely owing to the covert nature of cognitive deficits, rather than to the more overt portrayal of positive and negative symptoms in schizophrenia (Gold & Harvey, 1993). Cognitive deficits in schizophrenia refer to problems with attention, memory, verbal fluency, verbal learning, and executive functioning (Gold, 2004; Gold & Harvey, 1993; Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999).

Currently, the *DSM-5* requires two or more of the following symptoms to warrant a diagnosis of schizophrenia: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (American Psychiatric Association, 2013). The presence or absence of symptoms presented by any given patient varies considerably. Following the onset of psychosis, patients may exhibit predominantly negative symptoms, predominantly positive symptoms, or both (Carpenter Jr., & Kirkpatrick, 1988). Thus, the potential for widespread variability among individuals diagnosed with schizophrenia is evidenced by the magnitude of potential symptom combinations (Carpenter Jr., & Kirkpatrick, 1988).

Owing to this variability, schizophrenia has been deemed pathophysiologically heterogeneous, thus posing several obstacles to the conceptualization, course, and treatment of the disorder (Arango, Kirkpatrick, & Buchanan, 2000). A number of studies have employed factor analyses to reduce heterogeneity via the establishment of homogenous subtypes. Despite minor differences, these studies have fairly consistently demonstrated the emergence of at least three subtypes of schizophrenia: hallucinations and delusions, disorganization of thought and behavior, and negative symptoms, all of which were included in subsequent editions of diagnostic manuals (Arango et al., 2000; Brazo et al., 2002; Gilbert et al., 2014).

Previous editions of the *DSM*, for example, have included these three subtypes. The most recent edition, however, has eliminated them based on symptom fluidity and poor clinical utility (Keefe & Fenton, 2007). Namely, these subtypes have been based on the symptoms of schizophrenia, which are transient and thus unreliable indicators of group membership (Addington, Addington, & Maticka-Tyndale, 1991; Gilbert et al., 2014). Researchers have instead looked to cognitive deficits to understand the pathophysiology of positive and negative symptoms through an examination of the relationship of positive and negative symptoms to particular cognitive domains (Strauss, 1993). In contrast to positive and negative symptoms, cognitive deficits are stable features of schizophrenia and more likely to produce consistent and reliable information upon further investigation (Che et al., 2012).

Identifying subtypes through phenotypic refinement has been successfully applied in other psychiatric disorders. For example, researchers studying autism spectrum

disorder (ASD) employed a factor analysis to identify homogenous subtypes based on repetitive, stereotyped behaviors that are common in ASD (Shao et al., 2002). The results of the analysis narrowed the chromosomal focus for the complex traits of the disorder. As a result, the authors suggested that phenotypic subtypes can allow for mapping of disease susceptibility genes, or risk factors, that can therefore have implications for prevention as well (Shao et al., 2002).

Other studies have had similar success with complex disorders, such as Parkinson's disease and Alzheimer's disease. Parkinson's disease varies in presentation and onset (Dekker et al., 2003). A study that aimed to identify homogenous subtypes of the disorder found etiological differences between groups, which have had immediate implications on genetic counseling, treatment approaches, and risk prediction (Dekker et al., 2003). Alzheimer's disease is an equally complex and heterogeneous disorder. The use of subtypes in Alzheimer's disease has yielded homogenous groups based on age at onset (Scott et al., 2003) Specifically, three groups were identified: early onset, late onset, and very late onset (Scott et al., 2003) Genetic differences among groups have verified these subtypes, and they have allowed for a more thorough etiological understanding of the disease. Moreover, identifying these subtypes has expanded the conceptualization of Alzheimer's disease beyond familial forms of the disease to include the sporadic forms of it as well, meaning that identifying subtypes of a heterogeneous disease has advanced the understanding of its pathophysiology, as well as increased diagnostic acuity (Scott et al., 2003).

Although recent advances have expounded the pathophysiology of schizophrenia, the extreme variability in cognitive and clinical symptoms hinders a more thorough understanding of the disorder, as well as impedes accurate diagnosis and efficient treatment options. Thus, as has been successfully demonstrated with other disorders, identifying subtypes based on homogenous groups within schizophrenia may likely benefit each of these aims.

Cognitive Deficits

There is little doubt regarding the existence of cognitive deficits in schizophrenia. Cognitive deficits are well-replicated, stable identifiers of the disorder (Gold, 2004). Two theories compete, however, on the nature of cognitive deficits in schizophrenia. The first theory postulates that cognitive deficits in schizophrenia are broad, generalized, and undifferentiated (Dickinson & Harvey, 2009). The second theory states that cognitive deficits in schizophrenia are domain specific and focal to particular symptoms of the disorder (Schatz, 1998). Each of these theories has garnered a substantial amount of attention in schizophrenia research in recent years. The generalized-deficit theory is not amenable to identifying subtypes through differential neurocognitive profiles because its main principle states that cognitive deficits in schizophrenia are broad and homologous. Thus, to support the use of cognitive deficits as markers of subtypes in schizophrenia, the general-deficit theory must be examined and deemed unfounded.

General Cognitive Deficits

Cognitive deficits in schizophrenia typically predate disease onset and remain stable over time (Fioravanti et al., 2005). A body of literature supports a generalized-

deficit approach to understanding cognition in schizophrenia. The generalized-deficit approach refers to studies that have identified a commonality across all cognitive domains, referred to as “g” (Dickinson et al., 2008). Specifically, researchers have demonstrated that cognitive deficits in schizophrenia are mediated by a common ability factor, which is illustrated by widespread deficits in neuropsychological performance across all cognitive domains (Mohammed et al., 1999). Researchers further postulate that this mediation is a result of high correlations between schizophrenia-related cognitive deficits (Gold & Harvey, 1993). A sample of studies have attempted to support the notion of undifferentiated cognitive impairment through analyzing neuropsychological profiles of individuals with schizophrenia. One of these studies has implicated as much as 63% of all diagnosis-related variance in cognitive performance as being accounted for by this general ability factor alone (Dickinson et al., 2008).

Similarly, studies that have compared individuals with schizophrenia to healthy subjects have determined that those with schizophrenia display significant cognitive impairments across all cognitive domains, thus supporting the generalized-deficit theory (Dickinson, Iannone, Wilk, & Gold., 2004; Dickinson et al., 2008; Mohammed et al., 1999). Nonetheless, these very studies have simultaneously illustrated some domain-specific variance for verbal memory and processing speed, indicating that at least two domains are specific to schizophrenia and differentiated from a general ability factor (Cohen, Forbes, Mann, & Blanchard, 2006; Elvevag et al., 2000). These findings, among others, led to the scrutiny of research that supported the generalized-deficit theory.

In response, lead researchers in favor of the generalized-deficit theory worked to minimize methodological flaws. For example, in an attempt to avoid potential confounds inherent in medication effects, researchers began studying first-episode patients to amass support for the generalized-deficit theory (Heydebrand et al., 2004). These studies have also demonstrated diffuse cognitive deficits across all domains (Fioravanti et al., 2005). Despite seemingly generalized impairments, however, more pronounced impairments were evident in the results as well, specifically in verbal learning, memory, attention, and processing speed (Gold, 2004). More recently, a study concluded similar findings in that individuals with schizophrenia demonstrated generalized deficits across all functions, with the exception of motor skills and verbal memory (Franck et al., 2001). Thus, across all studies in support of the generalized-deficit theory, differential impairments in verbal memory are a consistent exception (Fioravanti et al., 2005; Franck et al., 2001; Gold, 2004; Mohammed et al., 1999).

In addition to the emergence of domain-specific deficits in the literature, studies that attempt to support the generalized-deficit theory have further methodological limitations, including small sample sizes, insufficient within-group experimentation, and poor reliability (Gold, 2004). Moreover, the vast majority of these studies likely reflect a sampling bias, as they have examined almost exclusively chronically ill patients (Bryson, Bell, & Lysaker, 1997). In doing so, these studies have not accounted for potential confounds that are attributable to institutionalization or long-term medication effects that can worsen cognitive deficits (; Bryson et al., 1997; Gold, 2004). The broad variability in kind and magnitude of impairment necessitates a more thorough understanding of

cognitive deficits in schizophrenia via a domain-focused approach. Identifying independent dimensions of cognitive deficits would thus allow for the development and implementation of effective interventions for differential impairments (Gold, 2004).

Overall, relevant literature suggests that the type and severity of cognitive deficits vary widely by patient, in much the same way that particular positive and negative symptoms vary by patient (O'Leary et al., 2000). Individuals with schizophrenia perform worse than healthy subjects on neuropsychological assessments across all domains, despite having within-group domain specificity (Gold & Harvey, 1993). Both within-group analyses and analyses that compare individuals with schizophrenia to healthy controls often fail to detect domain-specific deficits as a result of this widespread variation. Conversely, studies that have compared the deficit subtype of schizophrenia (i.e., those high on negative symptoms and low on positive symptoms) to the nondeficit subtype have been able to identify domain-specific deficits, such as differential impairments in cognitive flexibility, by analyzing more homogenous groups (Rethelyi, Benkovits, & Bitter, 2012). Consequently, domain-specific deficits likely are masked by the clinical heterogeneity of schizophrenia, but are nonetheless present. Moreover, the presence of domain-specific deficits increases the plausibility of utilizing differential neurocognitive profiles to identify subtypes of schizophrenia.

Domain-Specific Cognitive Deficits

The existence of differential domains in cognition is undisputed, and the reliable measurement of these domains via neuropsychological assessments is equally uncontested (Nuechterlein et al., 2008). Moreover, neuropsychological assessments were

developed to capture and measure different cognitive processes, such as memory, attention, and problem solving (Hartlage & DeFilippis, 1983). Namely, neuropsychological assessments are already categorized into various domains that purport to measure distinct neurological substrates. The domain-specific theory, then, suggests differential impairment among these cognitive domains, in opposition to the generalized-deficit theory, which acknowledges these domains but suggests they are equally impaired (Gold, 2004).

The majority of the literature suggests that attention, working memory, processing speed, verbal learning, and executive functioning are characteristically impaired in schizophrenia (Strauss, 1993). In a recent study, authors explored whether cluster analysis of these cognitive domains would define separate subtypes of schizophrenia (Gilbert et al., 2014). The analysis yielded three clusters: one who performed in the near-normal range of cognitive functioning; one with severe, general impairments across all cognitive domains; and one with severe, selected cognitive impairments in the visual episodic memory and processing-speed domains (Gilbert et al., 2014). A major limitation of this study that likely accounts for the supposition of a generally impaired subtype rests in its inclusion of only four cognitive domains, with three of them related to memory. These domains include verbal memory, visual memory, working memory, and processing speed (Gilbert et al., 2014). Thus, a more inclusive analysis likely would have identified domain-specific deficits for this subtype as well. One also should note that the two severely impaired clusters were nearly indistinguishable across measures of psychiatric symptom severity (i.e., positive and negative symptoms of psychosis) at disease onset

(Gilbert et al., 2014). This finding is consistent with the general literature that suggests psychiatric symptoms alone are insufficient for distinguishing subtypes of schizophrenia.

Furthermore, this study identified relationships between clusters of cognitive deficits and related functional outcomes (Gilbert et al., 2014). Functional outcomes are defined in the literature as an individual's ability to carry out activities of daily living, including independent living (Bowie et al., 2008), social functioning (Addington & Addington, 1999; Addington & Addington, 2000), and employment (Midin et al., 2011; Sanchez et al., 2009). This study used the lifetime best estimate of response to treatment (BER) assessment to measure functional outcomes. The BER provides a consensual clinical judgement based on medical records, positive and negative syndrome scale (PANSS) data, and a global assessment of functioning (GAF) score (Gilbert et al., 2014). Individuals in the generalized-cognitive-deficit cluster were more likely to have treatment refractory schizophrenia, whereas individuals with domain-specific cognitive deficits demonstrated greater improvements on the BER (Gilbert et al., 2013). Overall, the findings suggest that neurocognitive deficits are more central to functional outcomes than are psychiatric symptoms of schizophrenia. These findings indicate that cognitive deficits are imperative treatment targets in schizophrenia and could be better utilized in intervention planning through the identification of subtypes.

To identify specific functional outcomes as they relate to specific cognitive domains, a meta-analysis including 37 studies demonstrated moderate to strong effect sizes on functional improvements, such as engaging in community and daily activities, improvements in social problem solving, and psychosocial skill acquisition, for

individuals in the executive-functioning, memory, and attention domains of cognition (Green et al., 2000). This meta-analysis included studies that assessed generalized impairment by calculating the global/composite measures of neurocognition. The results demonstrated that between 20 and 60% of the variance in functional outcomes can be explained by neurocognition (Green, Kern, Braff, & Mintz, 2000). Studies that used a generalized-deficit approach, however, lacked the specificity required to determine which domains should be targeted for interventions (Velligan, 2000). Thus, neurocognition in schizophrenia is a crucial component to treatment success and requires a domain-specific approach for generating effective interventions (Bowie et al., 2008) Despite some variability, four cognitive domains are most commonly implicated in the literature as being differentially impaired in schizophrenia: attention, memory, processing speed, and executive functioning (Fioravanti et al., 2005). Given these deficits are unique to schizophrenia, they may elucidate potential subtypes within this diagnostic category. Deficits in attention, specifically, are considered to be the most fundamental in individuals with schizophrenia and should be the first deficit cluster to examine (Carter et al., 2010).

Attention. Attention, also referred to as vigilance, refers to one's readiness to differentially respond to a target stimulus and inhibit one's response to a nontarget (Saykin et al., 1991). Attentional deficits in schizophrenia are common and are often universally apparent, despite variations in psychiatric symptom presentations (Mass, Schoemig, Hitschfeld, Wall, & Haasen, 2000). Several studies have noted that deficits in attention, like most cognitive deficits in schizophrenia, are detectable before the onset of

the illness (Egeland et al., 2003). Attentional deficits in particular appear to predominate in studies of early schizophrenia, with some researchers illustrating childhood attentional deficits as a predictor for later development of the disorder (Saykin et al., 1994). In an early review of attentional deficits in schizophrenia, 40 studies related to attentional deficits in schizophrenia were examined (Cornblatt & Keilp, 1994). The results from this meta-analysis indicated that attention is uniquely impaired in individuals with schizophrenia, as compared to both healthy controls and individuals with major affective disorders, and were predictive of later pathophysiology (Cornblatt & Keilp, 1994).

To further investigate this notion, efforts shifted toward identifying specific attentional-deficit profiles in schizophrenia as compared to other psychiatric illnesses. In a study that compared subjects with schizophrenia to subjects with major depression and normal controls, subjects with schizophrenia demonstrated greater impairments in attention and speed of processing than both healthy controls and subjects with depression (Egeland et al., 2003). Although subjects with depression demonstrated similar attentional deficits, these deficits were determined to be the result of lack of effort, rather than caused by a manifestation of subcortical dysfunction (Egeland et al., 2003). In addition to attention and speed of processing, subjects with schizophrenia also demonstrated deficits in selective attention, which is indicative of an underlying impairment in executive functioning (Nuechterlein et al., 2004).

One should note that the vast majority of studies that investigate attentional deficits in schizophrenia simultaneously highlight deficits in memory, processing speed, and even executive functioning. The reason is trifold: (a) cognitive deficits are not

mutually exclusive constructs, despite neuropsychological assessments that attempt to categorize them (Nuechterlein et al., 2004); (b) cognitive deficits are hierarchical in nature, often having one (i.e., attention) as a prerequisite for another (i.e., memory; Egeland et al., 2003); and (c) attempts to isolate cognitive deficits in research may limit potential findings (Mass et al., 2000). Despite moderate correlations among cognitive deficits, particularly those related to attention, multicollinearity is insufficient to suggest true linear dependence (Shamsi et al., 2011). This notion does not necessarily support the generalized-deficit approach, however. Rather, it is indicative of complex relationships between and among cognitive deficits and clinical symptoms in schizophrenia that give rise to the need for equally complex and nuanced subtypes meant to categorize them.

In fact, several studies have illustrated within-group differences with reference to attentional deficits in schizophrenia (Braff, 1993; Carter et al., 2010; Lencz et al., 2006; McGhie & Chapman, 1961; Nieuwenstein et al., 2001). One such study found statistically significant differences between individuals with predominantly positive, as compared to predominantly negative, symptoms (Nieuwenstein, Aleman, & de Haan, 2001).

Individuals who scored higher on measures of positive symptoms displayed poorer performances on tests of attention and vigilance, such as the Continuous Pairs Test (CPT), as compared to those with greater negative symptoms (Nieuwenstein et al., 2001).

Conversely, a similar study found differential impairments in attention for those with greater negative symptoms as compared to positive symptoms (Liddle, 1987). Despite these differences (i.e., greater negative symptoms vs. greater positive symptoms being related to deficits in attention), consistent findings have confirmed the existence of

differential impairments in attention as they relate to symptom dimensions, suggesting domain specificity of within-group attentional deficits (Baxter & Liddle, 1998; Grube, Bilder, & Goldman, 1998; Strauss, 1993).

Memory. Memory is related to attention and is defined in several ways within the literature. *Verbal memory, visual-episodic memory, short-term memory, and working memory* are all terms used to denote this cognitive domain in the schizophrenia literature. Verbal memory and working memory, however, have been most consistently examined and demonstrate differential impairments in schizophrenia as compared to both healthy controls and individuals with other psychiatric illnesses (Lee & Park, 2005). Verbal memory refers to an individual's ability to recall without delay as many words as possible from a list verbalized by an examiner, whereas working memory refers to one's ability to hold and manipulate information that is held in awareness (Heinrichs & Vaz, 2004). Verbal memory is often assessed using the Hopkins Verbal Learning Test (HVLT), and working memory is most often assessed using the Letter-Number Sequencing Test (LNS; Keefe et al., 2003).

A meta-analysis that included 70 studies revealed a large effect size for both verbal-memory and working-memory deficits in schizophrenia (Aleman, Hijman, de Haan, & Kahn, 1999). These deficits were stable and widespread, despite differences in moderating factors, such as illness duration (Aleman et al., 1999). Furthermore, findings regarding memory deficits in schizophrenia are largely consistent across studies, despite variations in assessment tools (Lee & Park, 2005). This variation demonstrates that memory impairments in schizophrenia are significant enough to be detected across

multiple measures and are thus modality independent (Park & Holzman, 1992). Similar studies have demonstrated homogeneous findings, with large effect sizes for memory impairments in schizophrenia (Achim & Lepage, 2005).

In addition to between-group differences, several studies have outlined memory-related deficits that are specific to individuals with predominantly negative symptoms (Addington et al., 1991; Carter et al., 1996; Cuesta & Peralta, 1995; Milev, Ho, Arndt, & Andreasen, 2005). One study in particular investigated the domain specificity of spatial-working-memory deficits in schizophrenia for nonmedicated subjects (Carter et al., 1996). The results indicated that those with higher scores on negative-symptom inventories produced lower scores on spatial-working-memory tasks, indicating that this cognitive domain is differentially impaired in individuals with fewer positive symptoms and greater negative symptoms (Carter et al., 1996). Additionally, these results suggest that these differences stem from an organic, neuropathological origin rather than from medication effects (Carter et al., 1996). Similar studies have had parallel findings indicating a strong association between greater negative symptoms and poorer memory, thus lending support to the domain-specific deficit theory (Addington et al., 1991; Cuesta & Peralta, 1995; Milev et al., 2005).

Processing speed. Processing speed is positively correlated with memory and is defined by one's ability to quickly and correctly scan and process information. It is typically assessed using timed digit-symbol coding tasks (Schatz, 1998). In Dickinson, Ramsey, and Gold's seminal meta-analytic study (2007), processing speed was identified as the single largest cognitive deficit in schizophrenia (Dickinson et al., 2007). Compared

to healthy controls, individuals with schizophrenia demonstrated significant impairment in processing speed (Dickinson et al., 2007). The second largest effect size among the cognitive domains was in executive-functioning tasks, such as category fluency, wherein subjects are given 1 minute to generate as many unique words within a category as they can (Dickinson et al., 2007). More recently, Knowles, David, and Reichenberg (2010) replicated these findings after adding 11 studies to the original analysis. Their results yielded an almost identical effect size of $d = -1.50$, indicating that processing speed is consistently and significantly deficient in individuals with schizophrenia and is therefore considered a hallmark of the disorder's neurocognitive profile (Knowles et al., 2010).

In addition to studies that compared processing speed to other cognitive domains in schizophrenia, researchers also examined longitudinal changes in relation to processing-speed tasks. In a study that compared 95 hospitalized patients with schizophrenia to 53 healthy age-matched controls, processing speed was found to be the single best predictor of longitudinal outcomes of autonomy, self-care, vocational functioning, and social functioning for individuals with schizophrenia (Sanchez et al., 2009). Furthermore, studies suggest that processing speed mediates the relationship between deficits in executive-functioning and functional outcomes and that processing speed mediates a broader diversity of cognitive deficits overall (Ojeda et al, 2008). Specifically, the severity of processing-speed deficits was predictive of the severity of executive-functioning deficits (Ojeda, Pena, Sanchez, Elizagarate, & Ezcurra, 2008).

Additionally, within-schizophrenia differences were found among individuals with greater negative symptoms. Similar to individuals with differential memory deficits,

individuals who scored higher on measures of negative symptoms than positive symptoms exhibited greater processing-speed deficits (Milev et al., 2005). An early study examined the relationship between prognosis and processing speed. Prognosis was defined by functional outcomes and severity ratings on clinical and cognitive symptoms (Saccuzzo & Braff, 1981). The findings from this study illustrated differential impairments within schizophrenia through identifying those with a poorer prognosis, meaning those likely to have more severe clinical and cognitive symptoms as well as poorer functional outcomes, as having slower processing speed (Saccuzzo & Braff, 1981). Those with a better prognosis, meaning those more likely to have better functional outcomes and less severe cognitive and clinical symptoms as the disorder progressed, had faster processing speed that could even be reversed with remediation and practice (Saccuzzo & Braff, 1981). This finding indicates domain specificity for processing-speed deficits within schizophrenia based on other disorder-related factors.

Executive functioning. Executive functioning is defined by tasks that require complex thought and problem-solving abilities to carry out goal-directed thoughts and behaviors (Kerns, Nuechterlein, Braver, & Barch, 2008). Executive functioning is thought to engage several regions of the brain and has been consistently noted as a cognitive-deficit domain in schizophrenia (Johnson-Selfridge & Zalewski, 2001). Much like deficits in attention, deficits in executive functioning are present during the prodromal phase of the disorder and have been found in adolescents at risk for developing schizophrenia (Fossati, Amar, Raoux, Ergis, & Allilaire, 1999). Furthermore, executive-functioning deficits in schizophrenia are often typified by psychosocial

impairments and are more highly correlated with functional outcomes than any other cognitive domain (Orellana & Slachevsky, 2013).

Executive functioning is measured by a variety of assessments, including the Wisconsin Card Sorting Test (WCST), Trail Making B (TMB), and verbal/design fluency tests (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). A meta-analysis that included 71 studies revealed that individuals with schizophrenia were impaired in executive functioning relative to healthy controls (Johnson-Selfridge & Zalewski, 2001). Similarly, individuals with schizophrenia performed 0.40 standard deviations below individuals with other psychiatric illnesses on executive-functioning tasks (Johnson-Selfridge & Zalewski, 2001).

Although deficits in executive functioning have been linked to a variety of psychiatric illnesses, neuroimaging studies have illustrated that executive functioning is differentially impaired in individuals with schizophrenia and that relationships between executive functioning and psychiatric symptoms were evident (Elliott, 2003). Findings from several studies indicate that executive-functioning deficits are differentially related to negative symptoms rather than to positive symptoms in a way that suggests that abstract reasoning and problem-solving abilities may be intact in individuals who are high on positive symptoms and low on negative symptoms (Nieuwenstein & Aleman, 2001). A similar study also found that executive functioning was differentially impaired for individuals with a greater number of hospitalizations and a varying degree of severity of executive-functioning-deficit based on positive and negative symptom severity. These

findings lend credence to the notion that positive symptoms are pathologically distinct from other facets of the disorder (Nieuwenstein, Aleman, & de Haan, 2001).

Positive Symptoms

Positive symptoms have been the most widely studied feature of schizophrenia in part because of their overt nature and amenability to assessment tools (Grube et al., 1998). As a result, positive symptoms, particularly auditory hallucinations, have been given precedence over other facets of the disorder (Millan, 2000). An earlier, parsimonious model of schizophrenia attempted to dichotomize psychiatric symptoms through introducing the positive-negative paradigm (Peralta, De Leon, & Cuesta, 1992). This dichotomy was said to emerge as a result of the natural clustering of individuals into either a positive-dominant or negative-dominant group (Liddle, 1987).

Most often in the literature, however, three symptom groups would emerge: (a) individuals who scored high on assessments of positive symptoms, but low on assessments of negative symptoms; (b) individuals who scored high on assessments of negative symptoms, but low on positive symptoms; and (c) individuals who had roughly equal scores on assessments of both positive and negative symptoms (Marneros & Andreasen, 1992). Despite the inclusion of other variables and symptoms over time, the positive-negative symptom paradigm continues to prevail in diagnostic manuals and subsequent treatment strategies for schizophrenia.

Positive symptoms in schizophrenia include hallucinations, delusions, and disorganized speech. More than 50% of all cases of schizophrenia have been reported to include at least one positive symptom (David & Appleby, 1992). One of the largest

criticisms of focusing solely on positive symptoms in schizophrenia is that they have little clinical utility for predicting functional outcomes, whereas the same cannot be said of other features of the disorder, such as negative symptoms and cognitive deficits (Möller et al., 2000). Nonetheless, researchers continued to posit the high frequency, good discriminability, and diagnostic utility of positive symptoms in schizophrenia (Zimmerman, Favrod, Trieu, & Pomini, 2005).

While positive symptoms may be the most characteristic feature of schizophrenia, their utility is limited to detecting the presence of the disorder (David & Appleby, 1992). Positive symptoms alone are not practical markers for identifying schizophrenia subtypes. Furthermore, positive symptoms respond better to psychopharmacological interventions than any other feature of the disorder, and often require self-report as the primary means to detect them (Andreasen & Flaum, 1991). Given that the majority of individuals with schizophrenia are treated psychopharmacologically, positive symptoms will be too transient to detect nuanced subtypes (McGlashan & Fenton, 1991). Specifically, this method of identifying subtypes has been deemed phenomenologically unstable and temporally unsound (McGlashan & Fenton, 1991). Positive symptoms are only one facet of this complex disorder. Thus, identifying accurate and reliable subtypes necessitates a comprehensive examination of the disorder in its entirety, including positive symptoms, negative symptoms, and cognitive deficits.

Negative Symptoms

Negative symptoms of schizophrenia were originally conceptualized as secondary features of the disorder (Andreasen, 1982). Negative symptoms include apathy, flattened

affect, social withdrawal, and avolition (Erhart, Marder, & Carpenter, 2006). The possibility that negative symptoms could be present in the absence of positive symptoms soon became apparent, piquing clinical interest thereafter (Andreasen & Flaum, 1991). Unlike positive symptoms, negative symptoms remain largely unaffected by antipsychotic medications (Erhart et al., 2006). Their resistance to traditional treatment methods, coupled with a growing emphasis on predicting functional outcomes, placed negative symptoms at the forefront of schizophrenia research (Andreasen & Flaum, 1991).

Attempts to subtype schizophrenia through the examination of negative symptoms soon emerged. Researchers believed that patients with predominant negative symptoms belonged to a differentiated “deficit” subtype (Muesser, Douglas, Bellack, & Morrison, 1991). Longitudinal studies attempted to examine the influence of negative symptoms on functional outcomes. The findings from these studies suggested that individuals with many negative symptoms had poorer premorbid functioning, partial to no remissions during the initial phase of the illness, and an overall progressive pathophysiology leading to permanent disability (Fenton & McGlashan, 1991). Individuals with fewer negative symptoms, however, demonstrated a better prognosis, acute onset, and more frequent partial remissions (Fenton & McGlashan, 1991).

Despite some predictive utility, however, negative symptoms were neither common enough nor specific enough to schizophrenia on their own to be useful in identifying subtypes (Andreasen & Flaum, 1991). Studies that have examined the reliability of using symptoms as markers of subtypes alone have demonstrated their lack

of accuracy, soundness, and clinical utility (McGlashan & Fenton, 1991; Spitzer, Endicott, & Robins, 1978), suggesting that a reductionistic model for identifying subtypes of schizophrenia is unfeasible. Instead, the complexities inherent in the disorder must be accounted for to produce a viable model for subtypes. This accountability includes a holistic examination of psychiatric symptoms, both positive and negative, and their relationships with cognitive deficits. Only a comprehensive review of the disorder and its facets can yield a practical and valid basis for schizophrenia subtypes.

Relationship Between Psychiatric Symptoms and Cognitive Deficits

Once cognitive deficits were acknowledged as primary characteristics of schizophrenia, researchers evaluated the relationship between cognitive deficits and positive and negative symptoms (Strauss, 1993). In general, failures of information processing and self-monitoring through interactions of frontal and septohippocampal brain pathways are thought to be implicated in positive symptoms, whereas negative symptoms relate to abnormal interactions between the frontal and striatal systems (Strauss, 1993).

More specifically, positive symptoms are correlated with auditory-processing deficits and broad neural networks that underlie attention (O'Leary et al., 2000), and negative symptoms have been correlated with frontal-functional deficits (Gold, 2004). In an attempt to further specify the nature of these relationships, studies looked to specific symptoms within the positive-negative dichotomy. Namely, researchers determined that hallucinations were correlated with information-processing deficits (i.e., an inability to

accurately identify the source of the information), and delusions were related to abnormal sensory input and faulty inference processes (Strauss, 1993).

Likewise, a study that compared 35 individuals with schizophrenia to 35 healthy age-matched controls found that the individuals with schizophrenia had cognitive-deficit profiles that were distinct from those of healthy controls and were specific to differential symptom profiles (Brazo et al., 2002). Essentially, individuals in the schizophrenia group who scored high on assessments of positive symptoms had some performances of executive functioning in the normal range, indicating some preservation of cognitive skills in that domain (Brazo et al., 2002). This finding is consistent with later reports that suggest executive functioning is differentially impaired in individuals with stronger negative symptoms than positive symptoms and further indicates that negative symptoms have a stronger association than positive symptoms to cognitive deficits (Che et al., 2012; Harvey, Green, Bowie, & Loebel, 2006).

The relationship between negative symptoms and cognitive deficits has attracted much interest in the past 15 years. Though whether these variables are essentially defining the same construct has been debated, negative symptoms have been widely accepted as conceptually distinct from cognitive deficits (Brazo et al., 2002). One of the most significant findings drawn from this literature is that negative symptoms and cognitive deficits are correlated in severity on a cross-sectional basis and that both are highly correlated with functional outcomes (Harvey et al., 2006). Although these constructs seem to overlap, support for models that conceptualize negative symptoms and cognitive deficits as two separate dimensions of schizophrenia rests in their divergent

neuropathology and subsequent variation in associated affected brain regions (Harvey et al., 2006).

Previous studies have reached similar conclusions regarding the correlations between negative-symptom severity and cognitive-deficit severity. Upon evaluating 38 individuals with schizophrenia at two time periods, analyses revealed that higher ratings of negative symptoms were more likely to be associated with cognitive deficits as compared to higher ratings of positive symptoms (Addington et al., 1991). Likewise, a cross-sectional analysis found similar associations between positive symptoms and cognitive deficits, though positive symptoms were also correlated with cognitive deficits in the attention and memory domains (Savilla, Kettler, & Galletly 2008). Most consistently, research has highlighted the relationship between negative symptoms and deficits in visuospatial-constructional skills, language, and executive functioning and the relationship between positive symptoms and deficits in memory and attention (Milev et al., 2005). Processing speed has been shown to be impaired in both positive-symptom-dominant and negative-symptom-dominant profiles (Bowie et al., 2008). An overview of these associations from the most seminal studies are outlined in Table 1.

Table 1
Outcomes of Studies Assessing the Relationship Between Psychotic Symptoms and Cognitive Deficits in Schizophrenia from 1991-2004

Study	Assessment measures	Symptom outcomes	Cognitive outcomes	Combined symptom and cognitive outcomes
Mahurin et al., 1998	<u>Symptom:</u> BPRS <u>Cognitive:</u> TMT, visual search, verbal fluency, HVL, WCST, stroop, digit span, digit symbol	Factor loadings revealed 3 distinct symptom groups with highest ratings: (a) Withdrawal (b) Conceptual disorganization , (c) Reality distortion	Deficits identified in processing speed, attention/vigilance, and verbal memory	1. Withdrawal (negative) symptom group associated with deficits in verbal memory and processing speed 2. Conceptual disorganization (positive) symptom group associated with deficits in verbal memory and attention/vigilance ^a 3. Reality distortion (positive) symptom group associated with deficits in verbal memory ^a
Heydebrand et al., 2004	<u>Symptom:</u> PANSS <u>Cognitive:</u> WMS-R, WCST, RAVLT, CPT-IP, stroop	<u>2 general symptom groups:</u> Negative symptoms and positive symptoms	Differential impairments identified in memory, attention, verbal fluency, psychomotor speed, and executive function	1. Higher rates of negative symptoms were associated with deficits in memory, verbal fluency, psychomotor speed, and executive function

Study	Assessment measures	Symptom outcomes	Cognitive outcomes	Combined symptom and cognitive outcomes
Addington et al., 1991	<u>Symptoms:</u> SAPS, SANS <u>Cognitive:</u> WAIS, Rey's complex figure, word fluency, design fluency, WCST	<u>2 general symptom groups:</u> Negative symptoms and positive symptoms	Differential impairments identified in general intellectual functioning (IQ), executive functioning, verbal fluency, and memory	1. High rates of negative symptoms and low rates of positive symptoms were more likely to be associated with lower general IQ and deficits in executive functioning 2. Higher rates of positive symptoms were associated with deficits in verbal memory ^a

Study	Assessment measures	Symptom outcomes	Cognitive outcomes	Combined symptom and cognitive outcomes
Berman et al., 1997	<p><u>Symptom:</u> PANSS</p> <p><u>Cognitive:</u> WCST, TMT, WAIS-R, verbal fluency, digit span, digit symbol, block design, visual recall/recognition</p>	<p>1. 3 groups: positive symptoms, negative symptoms, mixed positive and negative symptoms</p> <p>2. Positive and negative symptoms showed a trend toward direct correlation ($r = .30$), but were associated with different cognitive deficits</p>	Differential impairments identified in executive functioning, visuospatial constructional skills, verbal memory, and attention	<p>1. Higher rates of negative symptoms are more likely to be associated with deficits in executive functioning and deficits in visuospatial constructional skill^a</p> <p>2. Higher rates of positive symptoms are more likely to be associated with deficits in verbal memory and auditory attention ^a</p> <p>3. No associations were found between positive/negative symptoms and global functioning (i.e., IQ)</p>

Study	Assessment measures	Symptom outcomes	Cognitive outcomes	Combined symptom and cognitive outcomes
Cuesta & Peralta, 1995	<u>Symptom:</u> SAPS, SANS <u>Cognitive:</u> Luria's test (executive functioning), verbal memory, visual memory, digit symbol, TMT, Rey's complex figure, face-matching test	<u>3 groups</u> <u>"syndromes":</u> positive syndrome, negative syndrome, and disorganized syndrome	Differential impairments identified in visual-motor performance, verbal memory, attention, and processing speed	<ol style="list-style-type: none"> 1. Higher rates of positive symptoms were correlated with better performances on visual-motor tasks 2. Higher rates of negative symptoms were correlated with worse performances on visual-motor tasks 3. Higher rates of disorganized symptoms were associated with worse performances on visual-motor functioning, processing speed, and verbal memory

Study	Assessment measures	Symptom outcomes	Cognitive outcomes	Combined symptom and cognitive outcomes
O'Leary et al., 2000	<u>Symptom:</u> SAPS, SANS <u>Cognitive:</u> WAIS-R, WCST, TMT, CPT, logical memory, list learning, verbal fluency, stroop, Rey's complex figure	<u>3 groups</u> "syndromes": positive syndrome, negative syndrome, and disorganized syndrome	Deficits identified in verbal fluency, verbal memory, processing speed	1. Negative symptoms were correlated with greater deficits in verbal memory, nonverbal memory, verbal fluency, and processing speed 2. Disorganized symptoms were correlated with greater deficits in executive functioning and global functioning (i.e., IQ) 3. Positive symptoms were correlated with better performances on the Rey's complex figure drawing test (visual-motor memory)

Note., BPRS = Brief Psychiatric Rating Scale, TMT = Trail Making Test, HVLT = Hopkins Verbal Learning Test, WCST = Wisconsin Card Sorting Test, PANSS = Positive and Negative Syndrome Scale, WMS-R = Wechsler Memory Scale-Revised, RAVLT = Rey Auditory Verbal Learning Test, CPT = Continuous Performance Test, CPT-IP = Continuous Performance Test-Identical Pairs, SAPS = Scale for the Assessment of Positive Symptoms, SANS = Scale for the Assessment of Negative Symptoms, WAIS = Wechsler Adult Intelligence Scale, WAIS-R = Wechsler Adult Intelligence Scale-Revised.
^a indicates patterns of similar findings across studies.

Summary

Despite overt and reliable associations between psychiatric symptoms and cognitive deficits, researchers have yet to utilize these associations as a means to identify

subtypes and thereby decrease the widespread heterogeneity that has impeded treatment success in schizophrenia (Kraus & Keefe, 2007). Three general factors related to treatment success in schizophrenia have been identified in the literature: treatment-related factors, patient-related factors, and system-related factors, such as access to care, socioeconomic status, and level of education (Buckley, 2008). Specifically, utilizing generic treatment protocols without regard for patient-specific variables has led to limited treatment success (Buckley, 2008). This limited success has resulted from a lack of diagnostic precision; unspecific treatment aims; and the employment of singular, symptom-focused interventions (Kraus & Keefe, 2007).

Global perspectives lead to problematic, generalized treatments that hinder functional outcomes. Thus, the need to identify subtypes in schizophrenia is trifold: (a) to improve diagnostic clarity and accuracy, (b) to improve treatment outcomes, and (c) to better the etiological understanding of schizophrenia as a means to support risk and prevention strategies. Support for this tripartite reasoning rests in failed attempts at establishing subtypes of schizophrenia in the past through simplistic models that focused on only one dimension (i.e., clinical symptoms) of schizophrenia. Chiefly, these failures have resulted from oversimplifying the facets of the disorder through a psychiatric symptom-only focus (Keefe & Fenton, 2007). Owing to treatment response and occasional symptom overlap, positive and negative symptoms are unreliable and insufficiently equipped to identify subtypes of schizophrenia in isolation (Liddle, 1987). Instead, the identification of subtypes in schizophrenia requires an all-inclusive model

wherein differential profiles of neurocognition and psychiatric symptoms are taken into account.

The first step toward achieving this goal requires an examination of the relationships between psychiatric symptoms and cognitive deficits in schizophrenia. Next, a broader examination of these relationships should be applied to identify a clustering of homogenous groups, meaning that within these symptom-deficit relationships distinct subtypes will emerge.

Chapter 3: Hypotheses

1. It is hypothesized that negative symptoms of psychosis will be positively correlated with deficits in executive functioning and processing speed for individuals with a diagnosis of schizophrenia, as supported by the literature. This hypothesis is in accordance with previous studies in which distinct neurological substrates are associated with negative, as compared to positive, psychiatric symptoms in schizophrenia (Addington et al., 1991; Berman et al., 1997; Brazo et al., 2002; Cuesta & Peralta, 1995; Mahurin, Velligan, & Miller, 1998; O'Leary et al., 2000).
2. It is further hypothesized that positive symptoms of psychosis will be positively correlated with attentional and memory-related cognitive deficits for individuals with a diagnosis of schizophrenia, as supported by numerous study findings (Addington et al., 1991; Berman et al., 1997; Brazo et al., 2002; Cuesta & Peralta, 1995; Mahurin, Velligan, & Miller, 1998; O'Leary et al., 2000).
3. It is equally hypothesized that the application of a cluster analysis will reveal clinical subtypes of schizophrenia through identifying differential neurocognitive and symptomatic profiles that reflect the aforementioned correlations.

Chapter 4: Methodology

Participants

The present study used a secondary analysis of data collected by the NIMH-funded Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study, which was a nationwide, public-health clinical trial designed to measure the comparative effectiveness of first- and second-generation antipsychotic medications. The CATIE study took place between January 2001 and December 2004 at 57 clinical sites in the United States. Patients were randomized algorithmically under double-blind conditions to receive one of five antipsychotic medications. Eligible participants from the original study ($N = 1,460$) were aged 18 to 65 years and met *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) criteria for schizophrenia as determined by the Structured Clinical Interview for *DSM-IV* Axis I disorders (SCID-I). The original clinical sites involved in recruitment included 16 university clinics, 10 state mental-health agencies, seven Veterans Affairs Medical Centers, six private nonprofit agencies, four private-practice sites, and 14 mixed-system sites. Primary demographic and clinical characteristics are outlined in Table 2.

To eliminate potential confounds inherent in incorporating preexisting categorical differentiations among *DSM-IV* categories, only individuals with a primary diagnosis of schizophrenia were included in the current study. Individuals with a diagnosis other than, or secondary to, schizophrenia as indicated by the SCID-I were excluded. Furthermore, patients with a diagnosis of mental retardation or other cognitive disorders; patients with a history of only one schizophrenic episode; or those with a serious or unstable medical

condition were excluded. Additionally, only individuals with complete neurocognitive and symptomatic data were included in the current study.

Measures

Positive and Negative Syndrome Scale (PANSS)

The Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) is a 30-item, rater-administered scale designed to assess three dimensions of psychosis: positive symptoms, negative symptoms, and general psychopathology (Kay et al., 1987). Each item (symptom) is accompanied by a definition and specific anchoring criteria to assist in scoring. Items are scored on a 7-point Likert scale ranging from 1 (*absent*) to 7 (*extreme*). Anchoring criteria are provided for all seven rating points. Of the 30 total items, seven items correspond to positive symptoms, another seven items correspond to negative symptoms, and the remaining 16 items correspond to general psychopathology. A total symptom severity score is yielded by averaging all 30 item ratings.

The PANSS has been used widely in clinical studies of psychosis and has demonstrated reliability across a variety of patient populations. The average interrater reliability for the PANSS is strong (0.82; Kay, Opler, & Lindenmayer, 1988). At present, the PANSS is the most frequently used assessment of psychotic symptoms, and it has consistently demonstrated reliable and valid psychometric properties that are over and above those of similar instruments, such as the Brief Psychotic Rating Scale (BPRS) (Faustman & Overall, 1999).

Continuous Performance Test, Identical Pairs Versions (CPT-IP)

The Continuous Performance Test, Identical Pairs Versions (CPT-IP; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling., 1988) is an assessment that measures attention and vigilance. The CPT-IP has three conditions that are comprised of 150 trials each. The trials increase in difficulty as the task progresses. The CPT-IP requires the participant to identify identical pairs within a continuous presentation of stimuli. Each stimulus is presented on a computer screen at the rate of one stimulus per second (Cornblatt et al., 1988). The first condition presents two-digit numbers continuously, and the participant is asked to raise his or her finger each time a number presented is identical to the previous number presented. The second condition uses three-digit numbers, and the third condition uses four-digit numbers. The CPT-IP was normed on a schizophrenia and major-affective-disordered population and has high test-retest reliability (Cornblatt et al., 1988). The CPT-IP is scored by the total number of correctly identified pairs, ranging from 0 to 30, with higher scores indicating better attentional capacity (Cornblatt et al., 1988).

Wechsler Adult Intelligence Test-Revised (WAIS-R) Digit Symbol Test

The Wechsler Adult Intelligence Test-Revised (WAIS-R) Digit Symbol Test (Wechsler, 1955) is an assessment of processing speed in which participants are presented with numbers and associated symbols. The participant's task is to copy as many symbols associated with numerals as possible in 90 seconds. The score is derived from the sum of correctly copied symbols, ranging from 0 to 125, with higher scores indicating faster processing speed. The digit symbol subtest on the WAIS-R is considered to be one of the

most reliable indicators of processing speed in a psychiatric inpatient sample with a large reliability coefficient (.77; Boone, 1992).

Wisconsin Card Sorting Test, 64-Card Computerized Version (WCST-64P)

The Wisconsin Card Sorting Test, 64-Card Computerized Version (WCST-64P; Kongs, Thompson, Iverson, & Heaton, 2000) is a measure of executive functioning. The WCST-64P requires complex categorization and problem solving based on the examiner's feedback. The participant is initially presented with four different cards that remain on the screen. The computer then presents one card at a time, and the participant's task is to match the current card to one of the original four. After the participant makes his or her choice, the computer says either "correct" or "incorrect" without further instruction. The cards are appropriately matched on three rules: color, shape, and number. The rule changes after 10 consecutive correct responses throughout the administration, without the participant knowing. The WCST-64P is scored by averaging the number of perseverative errors and the number of categories, or rules, completed. Higher scores indicate better executive functioning. Scores are compared to the corresponding norms located in the manual to determine relative interpretations. The WCST-64P has demonstrated high reliability and validity in psychiatric populations (Lysaker & Bell, 1994).

Hopkins Verbal Learning Test (HVL)

The Hopkins Verbal Learning Test (HVL; Brandt & Benedict, 1991) is an assessment of verbal memory. The examiner reads aloud a list of 12 words. The participant is then asked to recall as many words as possible. There is a total of four trials,

with the same set of 12 words read at the start of each trial. The HVLIT is scored by the sum of words correctly recalled across all four trials. Higher scores indicate better verbal learning and verbal memory and can be compared to the norms provided in the manual to make interpretations relative to an age-matched sample. Scores range from 0 to 36. The HVLIT was designed for repeated testing and demonstrates high test-retest reliability (Benedict, Schretlen, Groninger, & Brandt, 1998).

Letter-Number Span Test of Auditory Working Memory

The Letter-Number Span Test of Auditory Working Memory (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997) is an assessment of working memory. Participants are aurally presented with sequences of letters and numbers combined (e.g., N6G2). Participants are then asked to reorder the sequences by stating the numbers first, from lowest to highest, followed by the letters in alphabetical order. The Letter-Number Span Test of Auditory Working Memory is scored by the sum of correct sequences. Scores range from 0 to 21, where higher sums indicate better working memory. This assessment has been widely used in the schizophrenia population and demonstrates high test-retest reliability (Nuechterlein et al., 2008).

Computerized Test of Visuospatial Working Memory

The Computerized Test of Visuospatial Working Memory (Hershey, Selke, Fucetola, & Newcomer, 1999) is an assessment of working memory with visual stimuli. The participant must focus on a central cross fixation point on a computer screen while a cue appears for 150 milliseconds in one of 32 possible locations around the cross. After a delay period of 5 or 15 seconds, the participant must identify, via pointing, where on the

computer screen they remember seeing the cue. There are eight trials total. The Computerized Test of Visuospatial Working Memory is scored by the mean error in millimeters of the distance between the recalled cue point and the actual cue point. Higher scores, or mean error rates, indicate poorer visuospatial working memory. Mean error rates can be compared to the normative data provided in the manual for interpretation. This test is considered to be a reliable and valid indicator of one's visuospatial working memory (Keefe et al., 2003).

Procedure

The parent study used a Neurocognitive Assessment Unit evaluator to determine proficiency of each tester before the initiation of the trial at its site. The performance of these testers were monitored throughout the study via reviews of their protocols and scoring sheets. Raw data collected from each site were entered into a web-based data entry system. To the extent possible, each participant was rated by the same examiner across all assessments. The timing of the assessments occurred at baseline, 2 months, 6 months, and 18 months or end of study. For the purposes of this study, only data collected at the baseline neurocognitive trials were used. The purpose of using only baseline trials was to minimize the possibility of medication effects on cognitive performance, being that the original study trialed typical and atypical antipsychotic medications. By using baseline data only, participants would have been functioning under their usually prescribed, stabilized medication, which may be an atypical or typical antipsychotic. Being that most individuals with schizophrenia are medicated on one of these two types of antipsychotics, this sample should accurately represent the population, and thus have

good generalizability. The procedure for the present study included entering the symptom and neurocognitive data into a cluster analysis via SPSS. This study is the first known report of identifying subtypes based on differential neurocognitive profiles in relation to symptom patterns from this archival dataset. The dataset was obtained through NIMH via a Data Use Certificate (DUC) request in which the study's aims, investigators, and potential implications were outlined. Upon review by the NIMH, the DUC was approved pending IRB approval, and access codes were provided to the primary investigators to access the data via a web-based system. An expedited application was placed with the IRB board at Philadelphia College of Osteopathic Medicine before the data were accessed.

Chapter 5: Statistical Plan

Descriptive analyses were performed on demographic variables, such as age, gender, and ethnicity.

Hypothesis 1

The first goal of this study was to identify the relationship between negative symptoms of psychosis and distinct neurocognitive deficits. Both symptom scores and neurocognitive scores are continuous measures; therefore, a Pearson correlation was used to identify the relationship between negative symptoms and neurocognitive domains using SPSS.

Hypothesis 2

The second goal of this study was akin to the first, that is, to identify the relationship between positive symptoms of psychosis and distinct neurocognitive deficits. The statistical analysis to examine this aim mirrored that of the first. To identify the relationship between positive symptoms and neurocognitive domains, a Pearson correlation was conducted in SPSS.

Hypothesis 3

The primary aim of this study was to identify subtypes of schizophrenia through identifying homogenous groups that cluster together based on both symptomatic and neurocognitive data. To identify homogenous subtypes of patients that are independent from each other, four cognitive domains and two symptom domains were entered into a cluster analysis using SPSS. The four cognitive domains included attention, processing speed, executive functioning, and memory. The two symptom domains included positive

and negative symptom categories based on the PANSS. The simplest interpretable solution that fit the data was chosen, and each patient was assigned to the most congruent cluster. Listwise deletion was employed for participants with missing values in any domain.

Chapter 6: Results

Descriptive Statistics

A total of 1,147 participants from the parent study met the inclusionary and exclusionary criteria for the present study. Demographics of study participants are outlined in Table 2. Of the participants, 74.4% were male and 25.1% were female. The average age of the participants was approximately 40 years old, with a range of 18 to 67 years old. Participants averaged 11.62 total years of education, with a range of 1 to 21 years of education, and had an average of 13.6 years since first prescribed antipsychotic medication. A majority of the participants were unemployed (82.9%). The sample consisted of 61.6% of people who identified as Caucasian, 33.1% who identified as African American, and 2.4% who identified as Asian. Unknown race accounted for 0.5% of participants.

Table 2
Demographic Characteristics of CATIE Participants with Neurocognitive Data

Variable	Participants with complete data (<i>N</i> = 1,147)		
	Mean	<i>SD</i>	
Age (years)	40.20	10.86	
Patient's education (years)	11.62	3.51	
Duration since first prescribed antipsychotic medication (years)	13.60	10.45	
	<i>n</i>	% Frequency	
Sex	Male	853	74.4
	Female	288	25.1

		Participants with complete data (<i>N</i> = 1,147)	
Race	Unknown	2	0.5
	White	706	61.6
	Black	380	33.1
	Asian	27	2.4
Employment status	Unknown	7	0.6
	Full time	81	7.1
	Part time	102	8.9
	Unemployed	951	82.9

Note. CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness

Hypothesis 1

A Pearson correlation was conducted to evaluate the relationship between negative psychiatric symptom scores and scores on cognitive-deficit domain measures. The results demonstrated significant negative correlations between negative symptoms of psychosis and all cognitive-deficit domains identified for this study: Attention/Vigilance, Processing Speed, Reasoning/Problem Solving, Memory, and overall Neurocognitive Composite score (see Table 3).

Specifically, the results indicated a significant negative correlation between negative symptoms of psychosis and Attention/Vigilance, $r = -.202$, $p < .01$ (see Table 3). This negative correlation suggests that participants with higher scores of negative symptoms had lower scores on measures of attention.

The results also indicated a significant negative correlation between negative symptoms of psychosis and Processing Speed, $r = -.262, p < .01$ (see Table 3). This negative correlation suggests that participants with greater negative symptoms of psychosis had lower scores on measures of speed of processing.

Similarly, a significant negative correlation was also identified in relation to negative symptoms of psychosis and Reasoning/Problem Solving, $r = -.118, p < .01$ (see Table 3). This negative correlation indicates that participants with greater negative symptoms scored lower on reasoning and problem-solving measures.

A significant negative correlation was also found between negative symptoms of psychosis and Memory, $r = -.191, p < .01$ (see Table 3). These results suggest that patients with greater negative psychotic symptoms scored lower on memory measures.

Finally, a significant negative correlation was identified between negative symptoms of psychosis and overall Neurocognitive Composite scores, which are an average of one's cognitive abilities on the whole, $r = -.260, p < .01$ (see Table 3). This negative correlation suggests that individuals with greater negative symptoms of psychosis perform lower across all cognitive domains.

Table 3

Hypothesis 1: Correlation Matrix for Variables with Negative Symptoms of Psychosis

Variable	NEGSX	ATT/V	PSP	R/PS	MEM	NCOMP
NEGSX	---	-.202**	-.262**	-.118**	-.191**	-.260**
ATT/V		---	.576**	.388**	.514**	.745**
PSP			---	.520**	.607**	.838**
R/PS				---	.504**	.718**

Variable	NEGSX	ATT/V	PSP	R/PS	MEM	NCOMP
MEM					---	.819**
NCOMP						---

Note. $N = 1,147$. NCOMP = Neurocognitive Composite Score, NEGSX = Negative symptoms of psychosis, Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987). ATT/V = Attention/Vigilance, Continuous Performance Test, Identical Pairs Versions (CPT-IP; Cornblatt et al., 1988). PSP = Processing speed, The Wechsler Adult Intelligence Test-Revised (WAIS-R) Digit Symbol Test (Wechsler, 1955). R/PS = Reasoning and problem solving, The Wisconsin Card Sorting Test, 64-Card Computerized Version (WCST-64P; Kongs et al., 2000). MEM = Memory, The Hopkins Verbal Learning Test (HVLT; (Brandt & Benedict, 1991), The Computerized Test of Visuospatial Working Memory (Hershey et al., 1999).

* $p < .05$. ** $p < .01$.

Hypothesis 2

A Pearson correlation was conducted to evaluate the relationship between positive psychiatric symptom scores and scores on cognitive-deficit domain measures. In particular, a Pearson correlation was conducted to determine relationships, if any, between positive symptoms of psychosis and cognitive-deficit domains identified for this study, including Attention/Vigilance, Processing Speed, Reasoning/Problem Solving, Memory, and overall Neurocognitive Composite. Of the cognitive-deficit domains, only Memory had a significant relationship with positive symptoms of psychosis. Specifically, the results indicated a significant negative correlation between positive symptoms of psychosis and Memory, $r = -.067$, $p < .05$ (see Table 4). This correlation suggests that participants with higher scores on positive symptom measures had lower scores on measures of memory.

In contrast, the results indicated no significant relationships between positive symptoms of psychosis and Attention/Vigilance or Processing Speed, $r = -.001$, $p = .965$, and $r = .021$, $p = .488$, respectively (see Table 4).

Furthermore, no significant relationship was identified between positive symptoms of psychosis and Reasoning/Problem Solving or overall Neurocognitive Composite scores, $r = -.010$, $p = .726$, and $r = -.026$, $p = 0.382$, respectively (see Table 4).

Table 4

Hypothesis 2: Correlation Matrix for Variables with Positive Symptoms of Psychosis

Variable	POSSX	ATT/V	PSP	R/PS	MEM	NCOMP
POSSX	---	-0.001	0.021	-0.010	-.067*	-0.026
ATT/V		---	.576**	.388**	.514**	.745**
PSP			---	.520**	.607**	.838**
R/PS				---	.504**	.718**
MEM					---	.819**
NCOMP						---

Note. $N = 1,147$. NCOMP = Neurocognitive Composite Score, POSSX = Positive symptoms of psychosis, Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987). ATT/V = Attention/Vigilance, Continuous Performance Test, Identical Pairs Versions (CPT-IP; (Cornblatt et al., 1988). PSP = Processing speed, The Wechsler Adult Intelligence Test-Revised (WAIS-R) Digit Symbol Test (Wechsler, 1955). R/PS = Reasoning and problem solving, The Wisconsin Card Sorting Test, 64-Card Computerized Version (WCST-64P; Kongs et al., 2000). MEM = Memory, The Hopkins Verbal Learning Test (HVLT; Brandt & Benedict, 1991), The Computerized Test of Visuospatial Working Memory (Hershey et al., 1999). * $p < .05$. ** $p < .01$.

Hypothesis 3

A nonhierarchical K -mean cluster analysis was performed to identify homogenous groups based on standardized scores across all neurocognitive and symptom domains.

The clustering method used assumes a number of clusters (K) apriori. Each data point is subsequently combined with other data points with the closest Euclidean distance to the K cluster center. Cluster cohesion was optimal at the two-cluster level (i.e., $K = 2$), as the Cluster 1 and Cluster 3 solutions did not create cohesive clusters. Closeness was determined by identifying the centroids of each cluster. Centroids are artificial data points that represent the average of all data points in the cluster. Once the centroids were determined, Euclidean distance of each data point from its centroid was then calculated, producing successive iterations until the maximum number of iterations was achieved (Table 5). The maximum number of iterations performed was 10, and the iterations failed to converge. Nonetheless, each successive iterative yielded a smaller variance, indicating strong cohesion between each data point and its assigned cluster. The maximum absolute coordinate change for any center was .010, with the minimum distance between initial cluster centers being 10.889.

Table 5
Hypothesis 3: Iteration History of Change in Cluster Centers

Iteration	Change in Cluster Centers	
	<u>Cluster 1</u>	<u>Cluster 2</u>
1	4.856	4.158
2	.314	.201
3	.156	.105
4	.068	.046
5	.045	.031

6	.045	.033
7	.037	.027
8	.029	.022
9	.017	.013
10	.015	.012

The final cluster centers differed on the two variables of interest: cognitive domains and psychotic symptoms. That is, Cluster 1 was representative of participants who scored high on both positive and negative symptoms of psychosis and were more compromised across all cognitive domains as compared to Cluster 2. Conversely, Cluster 2 was representative of participants who had a lower presence of both positive and negative symptoms and displayed better cognitive functioning overall. These differences are noted in Table 6.

Table 6
Hypothesis 3: Final Cluster Centers from the K-Means Cluster Analysis (N = 1,147)

Variable	Cluster 1	Cluster 2
ATT/V	-.661	.525
PSP	-.773	.608
R/PS	-.614	.483
MEM	-.764	.601
NEGSX	.368	-.289
POSSX	.094	-.074

Note. NEGSX = ATT/V = Attention/Vigilance, Continuous Performance Test, Identical Pairs Versions (CPT-IP; Cornblatt et al., 1988). PSP = Processing speed, The Wechsler Adult Intelligence Test-Revised (WAIS-R) Digit Symbol Test (Wechsler, 1955). R/PS = Reasoning and problem solving, The Wisconsin Card Sorting Test, 64-Card Computerized Version (WCST-64P; Kongs et al., 2000). MEM = Memory, The Hopkins Verbal Learning Test (HVLT; Brandt & Benedict, 1991) & The Computerized Test of Visuospatial Working Memory (Hershey et al., 1999). Negative symptoms of psychosis, POSSX = Positive symptoms of psychosis, Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987).

A posthoc analysis was performed by way of an analysis of variance (ANOVA) between Cluster 1 and Cluster 2. The ANOVA supported the cluster findings, as evidenced by significant differences across all variables between clusters. The effect size, calculated using eta squared, was large for all four cognitive domains and small for positive and negative symptoms. Findings from the ANOVA are summarized in Table 7.

Table 7.

Hypothesis 3: Analysis of Variance (ANOVA) Between Cluster 1 and Cluster 2

	Mean square	<i>df</i>	Mean square	<i>df</i>	<i>F</i>	Sig.	Eta squared
ATT/V	393.040	1	.657	1143	598.227	.000**	0.225
PSP	537.625	1	.531	1143	1013.409	.000**	0.372
R/PS	339.884	1	.704	1143	483.124	.000**	0.341
MEM	525.410	1	.541	1143	970.828	.000**	0.351
NEGS X	121.766	1	.894	1143	136.151	.000**	0.098
POSS X	7.934	1	.994	1143	7.982	.005*	0.015

Note. *N* = 1,147. ATT/V = Attention/Vigilance, Continuous Performance Test, Identical Pairs Versions (CPT-IP; Cornblatt et al., 1988). PSP = Processing speed, The Wechsler Adult Intelligence Test-Revised (WAIS-R) Digit Symbol Test (Wechsler, 1955). R/PS = Reasoning and problem solving, The Wisconsin Card Sorting Test, 64-Card Computerized Version (WCST-64P; Kongs et al., 2000). MEM = Memory, The Hopkins Verbal Learning Test (HVL; Brandt & Benedict, 1991) & The Computerized Test of Visuospatial Working Memory (Hershey et al., 1999). NEGSX = Negative symptoms of psychosis, POSSX = Positive symptoms of psychosis, Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987).

p* < .05. *p* < .01.

A chi-square analysis using cross-tabulation was performed to determine whether the clusters differed on demographic variables. The differences between clusters based on

race were significant. That is, Cluster 2, which was determined to be less compromised overall, was comprised of significantly more White participants than Black participants as compared to Cluster 1, ($X^2(7) = 33.049$, $p < .001$; see Table 8). Employment was also found to be significantly different between the two clusters. Specifically, participants in Cluster 2 were more likely to have a work history as compared to those in Cluster 1, ($X^2(4) = 16.940$, $p = .002$; see Table 9). Gender was not significantly different between the two clusters.

Table 8.
Chi-Square Analysis for Race

	Value	<i>df</i>	Asymptotic significance
Pearson chi-square	33.049 ^a	7	.000
Likelihood ratio	35.009	7	.000
<i>N</i> of valid cases	1,145		

Note. ^a Eight cells (50.0%) have expected count less than 5. The minimum expected count is .88.

Table 9.
Chi-Square Analysis for Employment

	Value	<i>df</i>	Asymptotic significance
Pearson chi-square	16.940 ^a	4	.002
Likelihood ratio	17.524	4	.002
<i>N</i> of valid cases	1,145		

Note. Four cells (40.0%) have expected count less than 5. The minimum expected count is 1.76.

Next, a multivariate analysis of variance (MANOVA) was performed to test differences between the clusters on two variables: (a) the number of years since first prescribed antipsychotic medication, and (b) number of years of education. However, a

significant Levene's test, $F = 20.25, p < .001$, indicated a violation of the homogeneity of variance, prompting the use of a Welch's t test. Findings from the Welch's t test (see Table 10) indicate significant differences between the two clusters on these variables. That is, the participants in the more compromised group (Cluster 1) have fewer years of education, $t(972.03) = -5.92, p < .001$, and more years since first prescribed antipsychotic medication, $t(924.80) = 7.53, p < .001$, as compared to the less compromised group (Cluster 2).

Table 10.
Independent Samples Test Between Education Years and Years Prescribed

		Levene's test for equality of variances				t-test for equality of means		
		<i>F</i>	Sig.	<i>t</i>	<i>df</i>	Sig.	Mean Difference	Std. Error Difference
Education years	Equal variances assumed	20.25	.000	-6.03	1132	.000	-1.25	.207
	Equal variances not assumed			-5.92	972	.000	-1.25	.211
Yrs_pres	Equal variances assumed	28.34	.000	7.72	1112	.000	4.75	.615
	Equal variances not assumed			7.53	924	.000	4.75	.631

Note. Education years = Number of years of education. Yrs_pres = Number of years since first prescribed antipsychotic medication

Chapter 7: Discussion

The present study aimed to categorize subtypes of schizophrenia based on differences in two symptom types: cognitive deficits and positive and negative symptoms of psychosis. Test scores derived from neuropsychological and positive/negative psychotic-symptom measures were obtained via an archival dataset and analyzed with three hypotheses in mind. The first two hypotheses suggested distinct relationships between positive and negative symptoms of psychosis and domain-specific cognitive deficits. These hypotheses originated from the assumption that cognitive deficits in psychosis are specific to certain cognitive domains depending on the type and severity of the psychotic presentation (Gilbert et al., 2014). The assumption of domain-specific deficits contrasts with other schools of thought in which globalized cognitive deficits (i.e., deficits across all cognitive domains) are thought to be implicated in schizophrenia.

Specifically, the first hypothesis suggested negative symptoms of psychosis would be positively correlated with deficits in executive functioning and processing speed, meaning individuals who scored high on negative symptoms would have more severe deficits in complex problem solving and rapidity of processing tasks. Conversely, the results indicated that individuals who scored high on negative symptoms, scored lower across *all* cognitive domains: memory, attention, problem solving, and processing speed. Thus, the results were inconsistent with the domain-specific cognitive-deficit theory and instead supported the globalized-deficit approach.

Similarly, the second hypothesis posited that individuals who scored high on measures of positive symptoms would score lower on measures of memory and attention.

The results indicated a significant relationship between memory and positive symptoms only, suggesting that individuals with greater positive symptoms performed poorer on memory tasks as compared to other cognitive domains. Since attention deficits were not significantly related to positive symptoms, one can surmise that individuals with predominant positive symptoms have difficulty encoding and thus later recalling information, but do not necessarily have difficulty attending to the information in the first place.

On the whole, individuals with more severe negative symptoms than positive symptoms experience greater deficits across all cognitive domains, whereas individuals with more severe positive symptoms experience deficits that are specific to memory. One theory to explain this notion is that positive symptoms and negative symptoms of psychosis likely have distinct neurological substrates. Moreover, negative symptoms, such as apathy, flattened affect, social withdrawal, and avolition, are components that necessitate and underlie many cognitive processes (Erhart et al., 2006). Thus, without motivation, attention, and emotional interest, all types of cognitive processes are hindered.

Positive symptoms, however, require an overproduction of the perceptual system, whereby attention and problem solving are germane to hypervigilance, paranoia, and delusions. Recent studies have identified a relationship between working-memory deficits and delusions, with the idea being that working memory is required for coming to rational conclusions about everyday experiences (Freeman et al., 2013). Thus, a positive correlation between positive symptoms of psychosis and memory deficits is conceivable.

The final hypothesis suggested that subtypes of schizophrenia could be gleaned from the application of a cluster analysis. The results obtained herein suggest the existence of two subtypes of schizophrenia. The first subtype, hereafter referred to as the Deficit subtype, was comprised of participants who scored lower across all cognitive domains and higher on scores of positive and negative symptoms of psychosis. Conversely, the second subtype, hereafter referred to as the Nondeficit subtype, was comprised of individuals who scored higher across all cognitive domains and lower on positive and negative symptoms. The delineation of these subtypes was clear. Thus, schizophrenia as a broad diagnostic category is actually comprised of two distinct phenomena, and possibly two distinct diagnoses entirely.

Moreover, the two subtypes identified in the present study differed significantly on the following variables of interest: race, employment, education, and history of antipsychotic medication. Specifically, the Deficit subtype was comprised of more Black participants than White, had fewer years of education, and had a longer duration since first prescribed antipsychotic medication. The Nondeficit subtype, conversely, was comprised of more White than Black participants, had a longer work history, had more education, and had fewer years since first prescribed antipsychotic medication. One potential explanation is that socioeconomic factors play a large role in onset and course of illness in schizophrenia. Specifically, education and work history may serve as protective factors against an earlier age at onset, as well as against symptom severity and associated cognitive deficits.

Implications

Individuals with schizophrenia vary considerably in onset, severity, course, and duration of their illness (Buchanan & Carpenter, 1994). The need for subtypes to reduce this variability has been well documented in the literature (Fenton & McGlashan, 1991). The implications for this study are trifold: (a) Identifying subtypes of schizophrenia may reduce the widespread heterogeneity inherent in the disorder, and thus perhaps improve diagnostic clarity; (b) Using a neurocognitively driven approach to conceptualizing the disorder can elucidate the etiology and pathophysiology of schizophrenia through identifying brain-behavior relationships, which may have further implications on risk management and prevention; and (c) diagnostic clarity and specificity can foster accurate treatment targets, which could consequently improve treatment outcomes.

Subtypes based on attempts at symptomatic differentiation from previous editions of the *Diagnostic and Statistical Manual of Mental Disorders* were unsuccessful in clarifying the etiopathophysiology or heterogeneity in schizophrenia (Braff et al., 2013). Essentially, the tendency for symptom overlap and transient manifestations of symptoms detracted from their utility, meaning that symptoms were unreliable markers of subtypes (Tandon et al., 2013). Nonetheless, the need to identify homogenous groups within schizophrenia to inform treatment remains evident. The neurocognitive correlates of schizophrenia are stable and reliable indicators of the disorder (Bora, 2014). Thus, basing subtypes on neurocognitive, rather than symptomatic, data will likely yield lasting etiological subtypes.

Furthermore, this type of phenotypic refinement has been applied successfully in other complex disorders, such as Parkinson's disease (Dekker et al., 2003) and Alzheimer's disease (Scott et al., 2003), both of which have demonstrated advances in diagnostic, conceptual, and treatment dimensions as a result (Geisler et al., 2015). The primary implication of identifying subtypes of schizophrenia based on differential neurocognitive profiles rests in its ability to explicate distinct etiologic mechanisms. Research suggests that the etiology and onset of schizophrenia can be caused by a multitude of factors and that differences at onset might likely account for the heterogeneity in schizophrenia as a whole (Rajji, Ismail, & Mulsant, 2009). Research has further suggested that factors at onset, such as age, severity, and type of episode, may be linked to specific subtypes. For example, individuals with an earlier age at onset are more likely to have profound memory deficits and experience more positive symptoms than those who develop schizophrenia later on (Johnstone et al., 1989). Thus, identifying subtypes in this way may further an understanding of the relationship between the onset and course of schizophrenia, which may in turn inform prevention strategies and risk management (Zhang et al., 2015).

Finally, this study has implications on the course and type of treatment in schizophrenia. Reducing the heterogeneity aids in individualized treatment plans (Gilbert et al., 2014). Tailoring treatment to the individual is especially important in schizophrenia, given the extraordinary variability among patients. In addition to individualized treatment protocols, identifying neuropsychologically based subtypes may alter the focus of treatment from traditional to computerized approaches. Recently,

cognitive-based interventions akin to those used in cases of traumatic brain injury and neurological disorders, such as cognitive remediation now used in schizophrenia, have surged (Medalia & Saperstein, 2013). Identifying subtypes of schizophrenia based on differential neurocognitive profiles can inform cognitive-remediation regimens that target the cognitive deficits that are specific to that subtype. In turn, these individualized treatment plans will likely engender better treatment outcomes. Specifically, cognitive deficits in schizophrenia have been highly correlated with functional outcomes (Medalia & Saperstein, 2013). Thus, this treatment approach will likely have implications on patients' quality of life, activities of daily living, and general social and occupational functioning.

The Deficit and Nondeficit subtype groups outlined in this study can assist in improving diagnostic accuracy. Specifically, individuals may be diagnosed based predominantly on their neurocognitive profiles. Neurocognitive profiles with globalized cognitive deficits would likely fit the Deficit subtype, whereas those scoring low only in memory would likely belong to the Nondeficit subtype. This categorization would then aid in the selection of appropriate treatment options. Those belonging to the Nondeficit subtype would likely benefit from cognitive remediation of memory, in hopes that improved memory will assist in the cognitive restructuring of delusions and thereby reduce positive symptoms, whereas the Deficit subtype would likely benefit from a globalized cognitive-remediation approach. Moreover, education and work history may serve as protective factors against symptom severity and associated cognitive deficits.

Therefore, prevention strategies could utilize this subtyping method for early intervention via the implementation of education and employment programs for at-risk individuals.

Limitations

A potential limitation of this study is the exclusion of psychotic-spectrum disorders that are not schizophrenia. Some researchers conceptualize schizophrenia as a part of a continuum along the psychotic disorders spectrum and believe that its current classification is erroneous, limited, and flawed. Through excluding other psychotic-spectrum disorders, one risks subscribing to the confines of a diagnostic category that might limit or impede a more thorough understanding of psychosis in general. Therefore, a possible limitation of this study is that the results are reflective of an already flawed diagnostic system.

Other potential limitations may stem from the archival dataset used in the current study. Namely, the aims of the parent study required a sampling of typical and atypical antipsychotics. It is widely acknowledged that typical, or first-generation, antipsychotics often impair cognitive functioning further in schizophrenia (Han et al., 2015). By not controlling for these variables, some of the neuropsychological performances across participants might have been unduly influenced by medication effects. Similarly, participants with incomplete data were deleted from the present study; therefore, whether the missing data was the result of random or systematic occurrence cannot be determined. Therefore, another limitation is possibly unaccounted-for differences between the sample and population that cannot be ascertained in the current analysis.

Furthermore, the present study examined the associations between positive and negative symptoms of psychosis as they relate to cognitive deficits. Some researchers argue that this binary conceptualization is, in fact, a false dichotomy and that psychosis is actually composed of a variety of symptom domains (David & Appleby, 1992). Similarly, neurocognitive deficits included in this study were based on cognitive domains most commonly implicated in schizophrenia. The results must be interpreted with the limitation that other cognitive domains, such as social cognition, were not included.

Likewise, despite growing research in favor of a domain-specific deficit approach to cognition in schizophrenia, a body of literature favors the generalized-deficit theory. The generalized-deficit theory states that individuals with schizophrenia have cognitive deficits across all domains, such as memory and executive functioning, and that differential impairments do not exist (Dickinson et al., 2008). A major limitation of this study, then, is that it is based on the assumption that individuals with schizophrenia are differentially impaired across cognitive domains and that these differences are associated with specific symptom presentations as well. The present study failed to align with the domain-specific theory, but rather more so supported the globalized-deficit approach. Moreover, one should note that the correlations presented between cognitive deficits and psychotic symptoms are likely attenuated by the limited reliability of the measures. What has been presented herein are the raw correlations.

Likewise, this study is limited by not controlling for differences in premorbid adjustment and age of onset. Studies have consistently indicated that premorbid adjustment and age of onset can have a profound impact on the nature, course, and

severity of both cognitive deficits and symptom presentations in schizophrenia (Rund et al., 2004). The findings often indicate that earlier age of onset yields a poorer prognosis in regard to cognitive deficits and that better premorbid adjustment can predict better cognitive performances at later points in time (Fuller et al., 2002). Thus, not controlling for these variables suggests the results may be a reflection of differences that predate the disorder itself.

Future Research

Future research should include all psychotic-spectrum disorders to determine whether greater clusters of subtypes are more representative of psychosis than are the predetermined diagnostic categories in the *DSM-5*. This delineation might help to fully restructure the current criteria from which diagnoses are made. Furthermore, future research should include a measure of social cognition, as it is another cognitive domain implicated in schizophrenia that was not examined in the present study. Social cognition is an emerging dimension of schizophrenia that is linked to functional outcomes (Fett, Viechtbauer, Penn, van Os, & Krabbendam, 2011). Therefore, identifying patterns of social cognition as they relate to other cognitive deficits and psychotic symptoms may elucidate another subtype that has yet to be explored, and one that may have implications on functional outcomes for individuals with schizophrenia. Additionally, future studies should work to control for variations that predate disease onset and to attempt to replicate the current findings.

Finally, future research should look to converge the literature on structural magnetic resonance imaging (MRI) in schizophrenia with the literature on subtypes.

Previous studies have attempted to demonstrate structural differences in the brain among previously established subtypes of schizophrenia (Gur et al., 1994; Turetsky et al., 1995; Sallet et al., 2003). Future research should look to validate the subtypes outlined in this study via structural MRI differentiation. Doing so may explicate the pathophysiology and etiology of schizophrenia, with subsequent implications on intervention strategies as well.

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