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A Meta-Analytic Review of Cognitive Functioning in Negative and Positive Symptoms of Schizophrenia

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ABSTRACT

The purpose of the study was to conduct two meta-analytic reviews examining cognitive functioning and schizophrenia. The first review examined the literature comparing the cognitive functioning of schizophrenic patients to healthy controls. A second review examined the cognitive functioning within schizophrenic patients, examining the differences between individuals with primarily positive symptomatology and those with primarily negative symptomatology. The first meta-analysis included 19 studies which assessed 861 schizophrenic patients and 858 healthy volunteers overall. The second meta-analysis included 10 studies comparing the cognitive functioning of 1,263 schizophrenics across positive and negative symptoms. Results of the first review indicated that healthy controls performed better than schizophrenics in all areas of neuropsychological functioning. Results of the second meta-analysis indicated that schizophrenics with primarily positive symptomatology performed better in all areas of functioning, with the exception of attention.

A Meta-Analytic Review of Cognitive Functioning in Negative and Positive Symptoms of Schizophrenia

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To my daughter, Payton Abilene Forsythe

& my parents, Mr. and Mrs. Jerry Cameron

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A META-ANALYTIC REVIEW OF COGNITIVE FUNCTIONING IN NEGATIVE AND POSITIVE SYMPTOMS OF SCHIZOPHRENIA

Epidemiology and Diagnostic Criteria of Schizophrenia

Researchers have found that 1.1% of the world-wide population are diagnosed with schizophrenia (Schizophrenia and Related Disorders Alliance of America, 2018) and according to the World Health Organization, this number is about 21 million people, worldwide (World Health Organization, 2018). The literature on etiology is continually expanding and suggests a multifactorial etiology including genetic and environmental factors. Schizophrenia is categorized under psychotic disorders, and clinical symptoms include by delusions, hallucinations, disorganized thinking, disorganized motor behavior, blunted affect, avolition, anhedonia, alogia, and asociality (American Psychiatric Association, 2013). Individuals diagnosed with schizophrenia will vary widely in these symptoms due to its heterogeneity (American Psychological Association, 2013). Cognitive symptoms are also present in schizophrenia and include changes in memory, attention, and executive functioning (National Institute of Mental Health, 2016). Cognitive impairment is central in predicting functional outcome of those diagnosed with schizophrenia and predicting the prognosis one might face (Bowie & Harvey, 2006). Declining cognitive abilities can overlap and impact many areas of an individual's life, such as vocational, social, and daily living skills, leading to increased disability reliance.

Schizophrenia has unfolded over the years as a neuropsychological disease, responding to neuroleptic medications and neuropharmacological research (Liberman & Corrigan, 1992).

Genetic Factors and Biology

According to the National Alliance of Mental Illness, schizophrenia is linked to a genetic predisposition (National Alliance of Mental Illness, 1998). Multiple studies have found a high degree of heritability of schizophrenia (Gareeva & Khusnutdinova, 2018). Genetic research is emerging as a promising contribution to understanding schizophrenia development. Bassett, Chow, Weksburg, & Brzustowicz (2002) discussed the identification of 22q deletion syndrome (22qDS), multiple susceptibility genes, and new mutations. The mutation 22qDS is characterized by microdeletions in the "Q" arm of chromosome 2, which increases the risk for schizophrenia (Basset et al., 2002) as well as other neurodevelopmental brain disorders (Larsen, Dzafic, Siebner, & Garrido, 2018). The 22qDS mutation is characterized by abnormalities in sensory processing and cognition (Larsen et al., 2018). Studies that have examined this mutation have found that those individuals with 22qDS are at risk to develop psychosis, and over 25% will develop schizophrenia (Bassett et al., 2002; Murphy, Jones, & Owen, 1999). According to the Encyclopedia of the Human Genome, (Murphy, 2003) 22q11, better known as Velocardiofacial Syndrome, is the most significant risk factor for the development of schizophrenia. Statistically, the rate of 22q11.2 microdeletion is estimated at a rate of 1 per 4,000 live births making it the most common microdeletion syndrome (Bassett et al., 2002).

There is also increased evidence for another gene, DISC1, disrupted in schizophrenia 1 gene, associated with schizophrenia in Scottish and Finnish population (Ekelund et al., 2001; Millar et al., 2000; Prus, 2018). This gene codes for the DISC1 protein, which mediates signaling events occurring within neurons and is involved in the development of neurons (Hayashi-Takagi et al., 2010; Hodgkinson et al., 2004; Mao et al., 2009; Prus, 2018). Hodgkinson et al. (2004) propose that haploinsufficiency is a possible precursor to DISC1 disruption, and Hayashi-Takagi et al. (2010) further posit disturbances in glutamatergic neurotransmission through DISC1 disruption and potential changes to dendritic spines.

Not only can genetic mutations affect risk of schizophrenia but alterations in epigenetic regulation of normal genes through DNA methylation have been reported in the brains of patients with psychosis (Chen et al., 2014). Methylation is the additive of a methyl group. DNA methylation reduces gene expression, and demethylation increases gene expression. These processes are being explored with regard to the etiology of schizophrenia (Grayson & Guidotti, 2013). Jaffe et al. (2016) examined changes in DNA methylation levels in relation to genetic sequence and developmental stage associated with clinical risk for schizophrenia (Jaffe et al., 2016).

Recent evidence also suggests that the cerebellum plays an important role in schizophrenia and other psychotic disorders, leading researchers to search the cerebellum for psychosis (Chen et al., 2014). To date, cerebellar function is associated with depression and mania (Konarski, McIntyre, Grupp, & Kennedy, 2005). Konarski et al. (2005) presented evidence that those with schizophrenia have modified cortico-cerebellar connectivity. Andreasen et al. (1996) and Wiser et al. (1998) reported the role of the

cortico-cerebellar connectivity in monitoring and coordinating the fluid execution of mental activity geared toward normal cognitive functioning. Disruption of these pathways could lead to the disordered cognition and clinical symptoms of schizophrenia.

The prefrontal cortex (PFC) has played a more famously recognized role of schizophrenia symptomatology. The PFC is responsible for language, speech, and executive functions, which are disrupted in schizophrenia (Andreasen, Paradiso, & O'Leary, 1998). The PFC also shows extensive interconnections with other cortical and subcortical regions that are affected by schizophrenia (Andreasen, Paradiso, O'Leary, 1998). Other related areas being researched include the thalamus and hippocampus (Andreasen, Paradiso, & O'Leary, 1998; Pakkenberg, 1990; Stevens, 1982; Vukadinovic, 2014).

Historically, the first etiologic hypothesis for schizophrenia was the dopamine hypothesis (Prus, 2018). The dopamine hypothesis explains positive symptoms of schizophrenia as due to increased dopamine release in the mesolimbic system (Meltzer & Stahl, 1976; Prus, 2018) This hypothesis remains influential in schizophrenia (Howes & Kapur, 2009; Prus, 2018). Glutamate is another neurotransmitter that has been found to play a role in the etiology of schizophrenia, with decreased in glutamate release throughout the cerebral cortex and limbic system of schizophrenia patients (Paz, Tardito, Atzori, & Tseng, 2008; Prus, 2018; 2008; Sesack, Carr, Omelchecnko, 2006).

Overall, the neurological understanding of the development of schizophrenia is complex and intricate, including genetic abnormalities, reduced volume within brain structures, and unusual or atypical connectivity among brain structures (Lewis & Lieberman, 2000; Prus, 2018, Ross, Margolis, Reading, Pletnikov, & Coyle, 2006).

Environmental Factors

Environmental risk factors for schizophrenia include elements of both the prenatal uterine environment and the external environment in which the individual continues to develop following birth. Vulnerability to schizophrenia can be increased by disruptions in brain development as a result of prenatal and perinatal complications, maternal substance misuse, and early life stressors (Howes et al., 2003). The uterine environment is vital to development and decreased folate levels during pregnancy have been linked to schizophrenia risk (Opler et al., 2013). Many schizophrenia studies have reported a linkage with season of birth and schizophrenia (Demler, 2011; Torrey, Rawlings, Ennis, Merrill, & Flores, 1996), and other studies have explored the interaction of folate levels and birth season (Muntjewerff, Ophoff, Buizer-Voskamp, Strengman, & Heijer, 2011). Late winter and early spring births are correlated to increased risk of schizophrenia. Interestingly, summer births are associated with predominantly negative symptoms of schizophrenia (American Psychological Association, 2013).

More recently, research reports that paternal age may be a link to schizophrenic predisposition, and this may be increasingly important as couples are starting to build their families later in life (American Psychological Association, 2013; Bassett, Chow, Weksberg, & Brzustowicz, 2002). Studies suggest that paternal ages 40 years old and above increase the risk for schizophrenia in their offspring (Byrne, Agerbo, Ewald, Eaton, & Mortensen, 2003; Malaspina, Harlap, & Fenning, 2001).

Socioeconomic factors have been considered due to exposure to pollution, stress, and increased risk behaviors (Opler, Charap, Greig, Stein, Polito, & Malaspina, 2013).

By impacting neural and cognitive development, socioeconomic factors can increase an individual's susceptibility to psychosis (Opler et al., 2013; Spauwen, Krabbendam, Lieb, Wittchen, & Van Os, 2004).

Positive and Negative Symptomatology

As early as 1861, Russell Reynolds introduced the distinction between positive and negative neurological symptoms as excess or deficit of vital properties (Pearce, 2004). Reynolds, along with Hughlings Jackson, can be credited with the application of positive and negative symptoms to psychiatry (Pearce, 2004). By 1970, the terms *negative* and *positive* symptoms emerged as diagnostic terminology in schizophrenia (Jablensky, 2010). To date, according to The National Institute of Mental Health (2016), schizophrenic symptoms can be classified into three categories: positive, negative, and cognitive. Schizophrenia symptoms make reliable sub-phenotypes due to the genetic basis for differences in their clinical presentations (Arnedo et al., 2015). These sub-phenotypes also have characteristic heritability of symptoms (Kendler et al., 1993). The availability of valid and reliable measures of negative and positive symptoms such as Positive and Negative Syndrome Scale (PANSS), Scale for Assessment of Positive Symptoms (SAPS), and Scale for Assessment of Negative Symptoms (SANS) (Kay, Flazbein, & Opler, 1987) contribute to the conversation of sub-phenotypes.

Epidemiology and diagnosis. Positive symptoms in schizophrenia include symptoms in excess of normal and healthy functioning. Positive symptoms include hallucinations, delusions, thought disorder, and movement disorder (National Institute of Mental Health, 2016). Negative symptoms in schizophrenia include absences or

disruption to normal emotions and behaviors, such as a flat affect, anhedonia, alogia, and avolition (National Institute of Mental Health, 2016).

Fenton and McGlashan (1991) found that individuals with primarily negative symptoms experience a more severe and progressive course leading to permanent disability, whereas individuals with fewer negative symptoms experience better functioning and better a prognosis. Individuals with positive symptomatology were at higher risk for hospitalization (Fenton & McGlashan, 1991). Positive and negative symptomatology can be measured by scales such as the PANSS (positive and negative syndrome scale; Kay, Fiszbein, & Opler, 1987), SANS (scale for the assessment of negative symptoms; Andreasen, 1989), and SAPS (scale for the assessment of positive symptoms; Andreasen, 1984).

Etiology of positive and negative symptoms. Cognitive dysmetria is a theory that seeks to explain positive and negative symptomatology in schizophrenia (Prus, 2018). Cognitive dysmetria is characterized by abnormalities with receiving and processing information and has been linked to individuals experiencing hallucinations, forming delusions, disorganized speech, impaired attention, and unusual responses to emotions, all characteristic of schizophrenia (Prus, 2018). Negative symptoms of schizophrenia have also been linked to genes in the folate metabolic pathway (Roffman et al., 2011). Folate is an important vitamin involved in intracellular methylation, and alteration in folate metabolism can affect normal brain development and function (Frankenburg, 2007). Dopamine also plays a significant role in negative and positive symptomatology in the mesolimbic pathway (Xavier & Vorderstrasse, 2017) . Abi-

Dargham (2004) concluded that dopamine depletion in the prefrontal cortex produce cognitive impairment and negative symptomatology.

Positive symptoms of schizophrenia have been linked to separate genes such as MDR1 (multidrug resistance 1), with polymorphisms of this gene being associated with hallucinations and bizarre behavior quintessential of positive symptomatology (Tovilla-Za'rate et al., 2014). Excessive dopaminergic action is another contribution to positive symptoms in schizophrenia which has been a long-standing hypothesis in schizophrenia. Anissa Abi-Dargham reported that sustained exposure to D2 receptor agonists induced schizophrenia-like positive symptoms (Abi-Dargham, 2004). Neurotransmitters associated with positive symptoms include dopamine and serotonin (Abi-Dargham, 2004). Abi-Dargham (2004) explains how dopamine excesses and deficits can simultaneously produce positive and negative symptoms, respectively. He reports that this is due to the excess of dopamine in subcortical structures such as the nucleus accumbens and a deficit of dopamine in the cerebral cortex (Abi-Dargham, 2004). The neurotransmitter systems producing positive and negative symptoms include dopamine, serotonin, glutamate, and GABA. Another important neurochemical in schizophrenia is BDNF or brain- derived neurotrophic factor (Chen et al., 2014; Xavier & Vorderstrasse, 2017), which helps maintain and form new neurons (Prus, 2018). More specifically, low levels of plasma BDNF are related to negative symptomatology (Chen et al., 2014; Xavier & Vorderstrasse, 2017).

Neuropsychological Function in Schizophrenia

Multiple studies have found significant deficits associated with schizophrenia in attention, memory, processing speed, motor functioning, and executive functioning

(Martin, Mowry, Reutens, & Robinson, 2015; Schulze-Rauschenbach et al., 2015). Literature has found that cognitive impairment precedes the onset of the first psychotic episode (Muntean et al., 2018).

Negative symptomatology in schizophrenia is associated with a great decline in memory, verbal learning, nonverbal memory, verbal fluency, and processing speed (O'Leary et al., 2000). In terms of neuropsychological testing, subjects with negative symptomatology performed worse on IQ, Wisconsin Card Sorting Test, and The Newcombe Word Fluency (Addington, Addington, & Maticka-Tyndale, 1991).

Positive symptomatology in schizophrenia has not shown associations with cognitive impairment when compared to negative symptomatology. Research has shown that cognitive impairment is far more prominent in negative symptomatology (Addington et al., 1991) and improvement in positive symptoms is related to improvement of cognitive functioning (Addington et al., 1991).

Executive function. Individuals with schizophrenia have difficulty with executive function tasks such as planning, organizing, cognitive flexibility, using new information and problem solving. Cognitive deficits in tasks that measure executive functioning are experienced in a variety of disorders that affect prefrontal regions (Martin, Mowry, Reutens, & Robinson, 2015).

Processing speed. Cognitive functioning depends on uniform activity between brain regions, requiring proper speed and efficiency of information transfer which arises from white matter microstructure (Alloza et al., 2016; Bruce et al., 2017). Processing speed allows multiple cognitive processes to be available to the individual and is a piece of higher order cognition (Alloza et al., 2016; Kail & Salthouse, 1994). Accelerated

aging, which also impacts cerebral white matter, has also been linked to the schizophrenic brain (Alloza et al., 2016).

Attention. Attention is widely dispersed among neurocognitive functions and can encompass a wide range of tasks**.** This makes it difficult to isolate attention impairments in tasks from other impairments in the same tasks (Luck & Gold, 2008). Studies have shown different findings regarding increased and decreased activity in areas of the schizophrenic brain and largely attribute this to the fact that attention is a multi-faceted construct and that certain tasks can measure different areas of attention (Carter et al., 2010).

Memory. Memory deficits seen in schizophrenia have been linked to disruptions to the hippocampus (Zuckerman Institute, 2017). This same team completed an animal study in which schizophrenic-like mice compared to healthy mice were studied for memory by their ability to navigate through an environment that changed (Zuckerman Institute, 2017). Another study indicated that pairing memory tasks with affective stimuli may increase the ability to recall in schizophrenic patients (Fairfield et al., 2016).

Meta-Analysis

A meta-analysis is a quantitative review of the literature that combines data from previous research studies, used to synthesize data. A meta-analysis is conducted by forming a hypothesis and running a search on articles in databases such as PsycINFO. Identifying articles that pertain to the hypothesis is vital and involves identifying studies that meet the specific inclusion criteria of the study. The main statistic used in a meta-analytic review is the effect size. The effect size is a standardized measure of association (like the correlation coefficient) or difference between groups. Effect sizes for group

differences (like Cohen's *d* or Glass' delta) are typically computed by subtracting the mean of the two groups and dividing by a standard deviation. After effect sizes have been identified or calculated for each study, effect sizes are summed and averaged to compute the grand effect size, a single metric that quantitatively summaries the research literature.

Present Study

Schizophrenia is a disabling disease that impacts the individual, the family, and the community. Multiple factors including genetics and environment lead to neuropsychological impairments throughout the course of schizophrenia. Clinicians have identified symptomatologic subtypes of schizophrenia, classified as negative and positive. Identifying the predominance of positive or negative symptom clusters can inform the prognosis for treatment compliance, disease progression, and treatment outcome. Research has found that individuals with schizophrenia have a marked impairment in neuropsychological functioning when compared to healthy controls and that progression of the disease aligns with progression of neuropsychological impairment (Herold, Schmid, Lasser, Seidl, & Schroder, 2017). Research has also found that those individuals with predominantly positive symptoms experience less severe neuropsychological impairment and a better response to treatment (Addington, Addington, & Maticka-Tyndale, 1991).

To date, research has found significant differences in neuropsychological functioning between schizophrenia and healthy controls. However, no quantitative review of the literature has been done. The first goal of the present study is to complete a quantitative review of the literature that has examined neurological functioning in schizophrenic individuals compared to a healthy control sample. It was predicted that the

review will indicate that schizophrenia is associated with reduced executive functioning, processing speed, attention, and memory.

Research has also indicated differences in neurological functioning between negative and positive subtypes of schizophrenia when compared to each other. Currently, however, there is no quantitative review of the literature looking at the relationship of symptomatology with neurological functioning. Consequently, the second goal of the proposed study was to conduct a meta-analytic review comparing neurological functioning between negative and positive symptoms of schizophrenia. It was predicted that individuals with negative symptomatology will show larger deficits in executive functioning, processing speed, attention, and memory.

CHAPTER II

METHOD

Neuropsychological Function: Normal Population vs Schizophrenia

A systematic search was conducted to identify studies that have compared neurological functioning in schizophrenia and healthy control samples. The literature search used databases such as psycINFO. The keyword combination used in the search included combinations of the following: “IQ” (or “Intelligence”), “neurological functioning,” “cognitive performance,” “cognition,” “neurocognitive,” “neuropsychological,” “schizophrenia,” and “psychosis.” The studies were carefully examined and evaluated to determine whether they fulfilled the inclusion criteria and provided descriptive statistics and standard deviations. Additional studies were obtained through cross-references.

Inclusion criteria consisted of the following: 1) Include studies that assessed a sample of persons diagnosed with schizophrenia following the DSM or ICD, 2) Comparison of schizophrenic patients with a healthy control group having no history and familial history of psychosis, 3) Provide quantitative measures of cognitive functioning, and 4) Be published in English in scientific peer-review journals. The effect size was calculated by subtracting group means on cognitive measures and dividing by the pooled standard deviation. The pooled standard deviation was calculated by adding the standard deviations together from both groups and then dividing by two. Grand effect sizes

involved totaling and averaging effect sizes across studies, cognitive function, and assessment instruments.

Based on the above inclusion criteria, 19 studies were included in the meta-analysis. Overall, across these 19 studies, 861 schizophrenic patients were assessed and 858 healthy controls, who were mostly designated as community volunteers (Table 1).

Neuropsychological Function: Positive vs. Negative Schizophrenia

A second systematic search was conducted to identify studies that examined neurological functioning across positive versus negative symptomatology in schizophrenia. The keyword combination used in the search included the following: "negative versus positive symptomatology," "symptomatology in schizophrenia," and "neuropsychological," "cognitive performance," or "performance differences". Studies were carefully examined and evaluated to determine whether they fulfilled the inclusion criteria and provided descriptive statistics and standard deviations. Additional studies were obtained through cross-references.

Inclusion criteria included the following: 1) A sample of schizophrenic patients assessed for negative and positive symptomatology, 2) Provided quantitative measures of cognitive testing or subtests, and 3) Be published in English in scientific peer-review journals. Effect sizes were again calculated by subtracting group means and dividing by the pooled standard deviation.

For this second meta-analysis, 10 studies were identified that met inclusion criteria. Across these 10 studies 1,263 patients were included in the final review (Table 4).

CHAPTER III

RESULTS

Meta-Analysis Comparing Neuropsychological Functioning Between Schizophrenia and Healthy Controls

It will be recalled that the purpose of the first meta-analysis was to look at the comparison of neuropsychological functioning between schizophrenic patients and healthy controls. Based upon the inclusion criteria, 19 studies were identified comparing 861 schizophrenic patients with 858 healthy controls. The schizophrenic sample consisted of a fairly even split between inpatient and outpatient individuals, and most healthy controls were community volunteers. Individual effect sizes were computed for every neuropsychological measure and then averaged to create the grand effect sizes, giving an estimate of the total difference between controls and the schizophrenic group. The overall effect size for each study can be found in Table 1 along with the grand effect size.

As can be seen in Table 1, in all instances but two, normal controls showed better neurological functioning. In two studies, schizophrenic patients outperformed healthy controls (Hager et al., 2015 and Krkovic et al., 2017). Overall, the grand effect size across the 19 studies was .79. According to Cohen's interpretation, an effect size of .79 falls in the large effect size range (Cohen, 1977). This effect size indicates that the average person in the healthy control group outperformed 78.52% of the schizophrenic group.[i]

In addition to calculating the overall effect size for each study, effect sizes were also calculated for different domains of neuropsychological functioning. Table 2 presents effect sizes for neuropsychological functioning across the following domains: Executive functioning, attention, memory, and processing speed. The tests that were used across the studies that assessed executive functioning included: Wisconsin Card Sorting Test, Trails B, Digit Span total, and Stroop Word-Color. The tests that were used for processing speed included Trails A and the Conners' Continuous Performance Test Hit Reaction Time. The test used for attention included the Digit Span Forward and Conners' Continuous Performance Test detectability. The test used for memory included Digit Span Backward.

As can be seen in Table 2, across all measures of executive functioning, processing speed, attention, and memory, healthy controls outperformed the schizophrenic group in all areas. The overall effect size for executive functioning was .83. This was the same effect size for processing speed. These effect sizes represent a large effect per Cohen, with healthy controls performing better than 79.67% of schizophrenics in the areas of executive functioning and processing speed. The overall effect size for attention was .51, resulting in a medium effect size per Cohen. When broken down into percentiles, the average healthy control outperformed 69.35% of the schizophrenic patients in measures of attention. Finally, the overall effect size of memory was .34, which falls into the medium effect size per Cohen. The average healthy control outperformed 63.31% of the schizophrenic patients on measures of memory.

An additional analysis computed effect sizes across assessment instruments. These effect sizes are presented in Table 3. As can be seen in Table 3, the

neuropsychological measures that were used consisted of Trails A, Trails B, Digit Span Forward, Digit Span Backward, Stroop Word-Color, Wisconsin Card Sorting Test, and The Conners' Continuous Performance Test. Across all measurements of neuropsychological functioning, healthy controls outperformed schizophrenics. The lowest effect size was .30 for the Conners' Continuous Performance Test Detectability, and the highest effect size was 1.14 for the Stroop Word-Color Test.

Table 1

Studies in Meta-Analysis, Population, and Overall Effect Sizes

Study:	Schizophrenia *N*	Healthy Controls *N*	*d*
Breton et al. 2011	52 outpatients	53 hospital staff	.89
Egan et al. 2011	30 patients	30 volunteers	.49
Ekerholm et al. 2012	36 inpatients	46 community	.80
Galaverna et al. 2012	32 inpatients	32 community	1.60
Gigaux et al. 2013	10 outpatients	10 community	1.04
Gorissen et al. 2005	64 outpatients	44 community	1.37
Hager et al. 2015	29 in and outpatient	27 community	-.06
Herold et al. 2018	80 inpatients	60 community	.71
Hughes et al. 2002	62 outpatients	25 volunteers	.67
Kalwa et al. 2012	34 outpatients	30 community	1.30
Krkovic et al. 2017	35 in and outpatient	28 community	-.44
Laurensen et al. 2015	19 outpatients	30 volunteers	1.25
Lopez-Luengo et al. 2016	89 inpatients	74 community	.71
Martino et al. 2007	21 outpatients	15 community	1.02
Matsui et al. 2007	35 inpatients	24 community	1.44
Nestor et al. 2014	48 patients	52 volunteers	.74
Perianez et al. 2007	127 inpatients	223 volunteers	.62
Sanz et al. 2012	40 inpatients	40 community	.11
Stone et al. 1998	18 males	15 male community	.70
	N = 861	**N = 858**	**Grand *d* = .79**

Note: Positive d indicates that the healthy controls outperformed the schizophrenic sample

Table 2

Studies in Meta-Analysis, Neuropsychological Functioning, and Overall Effect Sizes

Study:	Executive Functioning	Attention	Processing Speed	Memory
Breton et al. 2011	.86			
Egan et al. 2011	.21	.77		
Ekerholm et al. 2012	.78	.80	.85	
Galaverna et al. 2012		1.60		
Gigaux et al. 2013	1.09		.93	
Gorissen et al. 2005	1.37		1.38	
Hager et al. 2015		.15		-.21
Herold et al. 2018	1.32	.28	.76	.49
Hughes et al. 2002	.70	.51	.73	
Kalwa et al. 2012	1.26	.38	1.41	
Krkovic et al. 2017	-.98		-.71	
Laurensen et al. 2015	1.13		1.50	
Lopez-Luengo. 2016		.20	1.21	
Martino et al. 2007	1.02			
Matsui, 2007	1.44			
Nestor et al. 2014	.74			
Perianez et al. 2007	.63		.61	
Sanz et al. 2012		-.28	.49	
Stone et al. 1998		.65		.75
Grand *d*:	**.83**	**.51**	**.83**	**.34**

Table 3

Studies in Meta-Analysis, Neuropsychological Tests, and Overall Effect Sizes

Study:	STROOP	TMT A	TMT B	DS F	DS B	WCST CC	CPT D	CPT HRT
Breton et al. 2011	1.05					.72		
Egan et al. 2011						.21	.77	
Ekerholm et al. 2012		.85	1.02			.54		
Galaverna et al. 2012				1.60				
Gigaux et al. 2013	.81	.93	1.37					
Gorissen et al, 2005	1.45	1.38	1.66					
Hager et al. 2015				.15	-.21			
Herold, 2018		.76	1.32	.28	.49			
Hughes et al. 2002		.80	.82			.58	.51	.66
Kalwa et al. 2012		1.41	1.58	.38		1.60		
Krkovic et al. 2017		-.71	-.98					
Laurensen et al. 2015	1.23	1.50	1.03					
Lopez-Luengo, 2016							.20	1.21
Martino et al. 2007						1.02		
Matsui, 2007				1.44				
Nestor et al. 2014						.74		
Perianez et al. 2007		.61	.63					
Sanz et al. 2012							-.28	.49
Stone et al. 1998				.65	.75			
Grand *d*:	**1.14**	**.84**	**.94**	**.75**	**.34**	**.77**	**.30**	**.79**

Note: STROOP = Stroop Test, TMT A and B = Trail Making Test A and B, DS F and B = Digit Span Forward and Backward, WCSTCC = Wisconsin Card Sorting Categories Completed, CPT D and HRT = Conners' Continuous Performance Test Detectability and Hit Reaction Time

Meta-Analysis Comparing Negative and Positive Symptomatology of Neurological Functioning

A second purpose of this study was to look at the impact of positive and negative symptomatology upon neuropsychological functioning. Literature suggests that predominantly negative symptomatology is more associated with dysfunction than those experiencing predominantly positive symptomatology (Sarkar, Hillner, & Velligan, 2015). Based on inclusion criteria, 10 studies were identified (Table 4). The 10 studies were comprised of 1,263 patients diagnosed with schizophrenia and consisted of inpatient and outpatient individuals. Most of the studies utilized the PANSS, SAPS, and SANS to assess symptomatology.

For the studies found in Table 4, effect sizes were computed for all neurological assessments comparing negative and positive symptomatology groups and then averaged to create the overall effect size for that study. These effect sizes were then summed and averaged to compute the grand effect size. As can be seen in Table 4, across all studies, with two exception, Cascella et al. (2008) and Zakzanis (1998), predominantly positive symptomatology schizophrenics performed better than predominantly negative. The overall effect size was .51. The lowest effect size observed was -.95 and the highest observed was 1.91. When interpreting the overall grand effect size of .51, Cohen defines this as a medium effect size. Overall, this indicates that the average schizophrenic patient with positive symptomatology performed better than 69.35% of the schizophrenics with negative symptomatology.

Table 4

Studies in Meta-Analysis, Population, and Overall Effect Sizes

Study	Sample	*N*	Negative/Positive Assessment	*d*
Bird, 1990	Outpatient	20	SANS/SAPS	.26
Brazo et al. 2002	Outpatient	26	SDS/PANSS	.65
Cascella et al. 2008	Inpatient/Outpatient	105	SANS/SAPS	-.06
Fervaha et al. 2016	Outpatient	657	PANSS	.29
Jonsdottir, 1992	Inpatient/Outpatient	20	SAPS/SANS	.18
Mattson et al. 1997	Inpatient	40	PANSS	1.91
Murray, 1990	Inpatient	32	SANS/SAPS	.71
Polgar et al. 2010	Inpatient	275	PANSS	.77
Singh et al. 1999	Outpatient	50	SANS/SAP	1.32
Zakzanis, 1998	Inpatient/Outpatient	38	BPRS	-.95
		***N* = 1,263**		**Grand *d* = .51**

Note: SANS= Scale for the Assessment of Negative Symptoms SAPS= Scale for the Assessment of Positive Symptoms PANSS= The Positive and Negative Syndrome Scale BPRS= The Brief Psychiatric Rating Scale

As with the first meta-analysis, effect sizes were also computed for each cognitive function. These effect sizes can be found in Table 5. The same measures went into the same categories of neuropsychological functioning. The results were very widespread. One negative effect size was observed with attention (d = -.12). This score indicates that schizophrenics with negative symptomatology performed better than schizophrenics with positive symptomatology, though this effect was small. The largest effect size was observed for memory (d = 1.15), indicating that schizophrenics with positive symptomatology performed on average over one standard deviation better than

schizophrenics with negative symptomatology. The overall effect size for executive functioning was .54, indicating that schizophrenics with positive symptomatology performed on average a half standard deviation better than the average schizophrenic patient with negative symptomatology. Lastly, the overall effect size for processing speed was observed to be .25, a small effect size, indicated that the average patient with positive symptomatology performed better than 59.99&% patients with negative symptomatology.

Table 5

Studies in Meta-Analysis, Neuropsychological Functioning, and Overall Effect Sizes

Study	Executive Functioning	Attention	Processing Speed	Memory
Bird,1990	.58	-.26	.59	.66
Brazo et al. 2002	.65			
Cascella et al. 2008	-.13		-.03	
Fervaha et al. 2016	.29			
Jonsdottir, 1991	.31	-.24	.50	.00
Mattson et al. 1997	2.66		.40	.52
Murray, 1990	.68	.65	1.01	
Polgar et al. 2010	.77			
Singh, 1999		-.77		3.41
Zakzanis, 1998	-.95		-.97	
Grand *d*:	**.54**	**-.12**	**.25**	**1.15**

Effect sizes were also calculated for each cognitive assessment instrument. These effect sizes can be found in Table 6. The measures included were the WCST, Stroop, DS, TMT, and CPT. Across all measures, except two (DSF, CPT d'), patients with positive

symptomatology performed better. Overall, the effect size for the Stroop was observed to be .56, indicating that the positive symptomatology group outperformed the negative symptomology group on this assessment by over a half standard deviation. Following Cohen's interpretation, this would be a medium effect size. The overall effect size for Trails A was observed to be .22. According to Cohen (1988), this is a small effect size. The overall effect size for Trails B was observed to be .87, a large effect. The overall effect size for Digit Span Forward (DSF) was observed to be -.16, indicating that positive symptomatology group performed worse than negative symptomology group on this measure of attention. The effect size for Digit Span Backward was 1.15, a large effect. The overall effect size for Wisconsin Card Sorting Test was .29, a medium effect indicating that the average participant with positive symptomatology performed better than 61.41% of those in the negative symptomatology group. The effect size for the Conners' Continuous Performance Test Detectability was observed to be negative (d = -.14), indicating that those in the negative symptomatology group performed better on the CPT d' than the positive symptomatology group. The overall effect size for Continuous Performance Test Hit Reaction Time was .18, which is a small effect size per Cohen.

Table 6

Studies in Meta-Analysis, Neuropsychological Testing, and Overall Effect Sizes

Study:	STROOP	TMT A	TMT B	DSF	DSB	WCST CC	CPT D	CPT HRT
Bird, 1990		.59	.58	-.24	.66		-.28	
Brazo et al. 2002	.56					.73		
Cascella et al. 2008		-.23	-.16			-.10	.00	.18
Fervaha et al. 2016						.29		
Jonsdottir, 1991		.50	.43	-.24	.00	.19		
Mattson et al. 1997		.40	4.77			.55		
Murray, 1990		1.01	.70	.65	.52	.65		
Polgar et al. 2010						.77		
Singh, 1999				-.77	3.41			
Zakzanis, 1998		-.97	-1.11			-.78		
Grand *d*:	**.56**	**.22**	**.87**	**-.16**	**1.15**	**.29**	**-.14**	**.18**

Note: STROOP = Stroop Test, TMT A= Trail Making Test A, TMT B= Trail Making Test B, DSF= Digit Span Forward, DSB= Digit Span Backward, WCSTCC= Wisconsin Card Sort; Categories Completed, CPD D = Conners' Performance Test Detectability, CPT HRT= Conners' Performance Test Hit Reaction Time

Meta-Analysis Comparing Error Rates Between Schizophrenic Patients and Healthy Controls

A final, exploratory analysis was made of the error rates during the neurocognitive testing of schizophrenic patients and healthy controls. Using the studies from Table 1, nine studies were identified that provided error rates for the Wisconsin Card Sorting Test and the Conners' Continuous Performance Test. Effect sizes were calculated for Wisconsin Card Sorting Test for the errors made in perseverations, or repeating the prior rule despite clinician instructions. In addition, effect sizes were also

computed for the number of incorrect responses on the Wisconsin Card Sorting Test that did not involve perseverations. Effect sizes were also calculated for omission errors on the CPT, the number of missed targets. Such errors indicate an individual was not responding to target stimuli, due to factors such as inattentiveness or a difficulty with focusing. Effect sizes were also calculated for commission errors on the CPT, which are incorrect responses to non-targets -- errors that can indicate inattention or impulsivity.

Effect sizes for errors on cognitive tests between schizophrenic patients and normal controls are found in Table 7. Positive effect sizes indicate that healthy controls performed better (fewer errors) than schizophrenic patients. Across the studies, all effect sizes, except one, were positive, indicating that healthy controls had fewer errors.

Table 7

Studies Comparing Schizophrenics with Non-Patients, Errors and Overall Effect Sizes.

Study	WCST PE	WCST NONPE	CPT OM	CPT COM
Breton et al. 2011	.89	.61		
Egan et al. 2011	.30	-.05		
Ekerholm et al. 2012	.72			
Hughes et al. 2002	.36		.69	.31
Kalwa et al. 2012	1.34	1.93		
Lopez-Luengo, 2016			.93	.32
Martino et al. 2007	1.05			
Nestor et al. 2014	.76	.30		
Sanz et al. 2012			1.20	.61
Grand *d*:	**.77**	**.70**	**.94**	**.41**

Note: WCSTPE: Wisconsin Card Sorting, Perseverative Errors; WCSTNON, Wisconsin Card Sorting, Non-Perseverative Errors; CPTOM, Conners' Continuous Performance Test, Omissions; CPTCOM, Conners' Continuous Performance Test, Commissions

CHAPTER IV

DISCUSSION

Schizophrenia effects more than 21 million people worldwide (World Health Organization, 2019) and continues to elude clinicians and researchers for a cure. Schizophrenia can be considered a brain disease with a chronic course and stable neurocognitive deficits (National Institute of Mental Health, 2016). Studies over the years have examined the relationship between schizophrenia and healthy controls on neurological functioning, and the goal of this meta-analysis was to contribute to that literature. Overall, 19 studies were identified that met inclusion criteria comparing a schizophrenic sample and healthy controls on some measure of neurological functioning. Across these studies, a total of 861 schizophrenia patients and 858 healthy controls were included. The overall effect size was .79, indicating that the average healthy control performed better than 78.52% of the schizophrenic patients. When broken down by neurological function, the greatest deficits were observed in the areas of processing speed and executive functioning. Overall, the meta-analysis was consistent with the findings that there are persistent neurological deficits associated with schizophrenia.

The second goal of the study was to conduct a meta-analysis looking at positive and negative symptomatology and neuropsychological functioning. For generations, clinicians and researchers have noted the complex presentation of schizophrenia symptoms. Schizophrenic patients presenting with negative symptoms display symptoms such as: blunt/flat affect, anhedonia, alogia, and avolition (National Institute of Mental

Health, 2016). Positive symptoms, by contrast, involve hallucinations and delusions (National Institute of Mental Health, 2016). Clinicians and researchers have noted a more disabling course for the disorder when negative symptoms are the primary presentation (Rabinowitz, 2012). Thus, a goal of this study was to look at the cognitive functioning of positive and negative schizophrenia. Based upon the inclusion criteria, 10 studies were identified involving 1,263 patients. Overall, the effect size between the symptom types calculated to .51, indicating that positive symptomatology performed better than 69.35% of the schizophrenics with primary negative symptoms with the most profound neuropsychological functioning deficit being memory.

Implications

Clinical Implications

From the time of diagnosis, the course of schizophrenia has deleterious effects on the individual, the family, and the community (Miller, 1996). Managing symptoms within the day-to-day function can be very difficult for those struggling with disease. When considering treatment of schizophrenia, it is in the best interest of the individual to have family support. Family therapy may be of benefit to both the patient and the support system (Dixon & Lehman, 1995; Jewell, Downing, & McFarlane, 2009). In light of the current review, beyond the need for psychopharmacological intervention cognitive remediation and other forms of skills-based therapies may be helpful for the individual (Lopez-Luengo et al., 2016; Sanz et al., 2012). Many researchers have noticed a better outcome and improved cognitive functioning with early diagnosis and intervention, such as psychopharmacology, cognitive remediation, psychotherapy, occupational therapy, and ongoing case management services (Herold et al., 2019; Hughes et al., 2003).

Treatment compliance has been a long-standing concern and challenge for some individuals with schizophrenia (Fenton et al., 1997). Mental illness stigma, insight, substance use, medication side effects and lack of support, for example, can contribute to treatment non-compliance for those struggling with the diagnosis (Fenton et al., 1997). This can also raise clinical implications for neurocognitive functioning and treatment noncompliance. Cognitive functioning should be considered as early as diagnosis, and the discussion of selecting a caretaker or adult protective agency to assist when symptoms may impair adequate treatment could be a viable resource to treatment planning and compliance.

Currently, the *Diagnostic and Statistical Manual of Mental Disorder (DSM)*, 5th edition (American Psychiatric Association, 2013) places cognitive impairment related to schizophrenia in the 'Associated Features' section, and states that cognitive impairment is linked to vocational or functional impairment (American Psychological Association, 2013). In light of the current review, it may be beneficial to add the cognitive criteria to the diagnostic section in the *DSM*. In addition, based upon the present research, these cognitive criteria should be evaluated quantitatively (e.g., neuropsychological tests) rather than qualitatively (i.e., clinical impression).

Lastly, antipsychotic medication should be considered. A majority of schizophrenic patients are prescribed second generation medications, with some individuals requiring first-generation medications (treatment resistance schizophrenia; TRS). It is important to understand the role that antipsychotics may have on cognitive deficits and if the side effects may worsen the deficits. Literature indicates that cognitive deficits are present in drug-naïve schizophrenic patients (Fatourous-Bergman et al., 2014;

Zhang et al., 2013), indicating that cognitive deficits are present in early stages of schizophrenia and continue with the progression of the disease.

Further, treatment of negative symptomatology can be more difficult for clinicians compared to positive symptoms (Ellenbroek & Cools, 2000; Sarkar, Hillner, & Velligan, 2015). Sensory gating deficits in schizophrenia expressed as difficulty tuning out irrelevant stimuli thus posing a challenge to maintaining attention (Freedman et al., 1987; Judd et al., 1992; Lijffijt et al., 2009). Nicotine improves sensory gating in schizophrenia, and schizophrenic patients are at high-risk for smoking (Featherstone & Siegel, 2015). Examining the role of nicotine and the improvement of sensory gating could lead to treatments for improving cognitive functions without creating additional problems with the medication effects (Hoffer et al., 1957; Levin & Rezvani, 2002). Specifically, some medications have interactive effects when used with nicotine, however, studies have shown that smoking can alleviate some side effects of anti-psychotics (Matthews, Wilson, & Mitchell, 2011). The impact, however, is that smoking impacts the metabolism of medications (Lyon, 1999; Ziedonis et al., 2006).

Neuropsychological Implications

Neuropsychological advancements have had a great impact on uncovering the cognitive abilities of individuals across a variety of diagnoses. The biggest implication of the neuropsychological assessment's role when testing cognitive functioning for specific diagnoses is the wide range of testing available and the need for a standardized measurement that allows for more concise data and interpretation. During the course of the study, it was difficult to pool data on several studies due to varying scores, procedures, and modifications being used. Studies ranged in interpretation procedures

with some studies using the scores set forth by the manuals and others using alternative scoring.

Neuropsychological testing provides substantial information for research in the schizophrenic population, and pairing this data with neuroimaging can improve the data being used for treatment and research. These findings could assist with determining the prognosis at a more discrete level, potentially from the prodromal phase throughout the duration of the disease. Literature supports that cognitive functioning may be useful as a vulnerability marker (Cornblatt, 2002; Davidson et al., 1999; Reichenberg, 2010). This proves the need for continued research on neuropsychological measures and schizophrenia from the early stages (prodromal) and into the depths of the disease, into the lifespan.

Conclusion

In conclusion, this study gives evidence that schizophrenic patients experience distinct and significant cognitive decline. In addition, negative symptomatology was associated with greater cognitive impairment. Consequently, the assessment of positive, negative, and cognitive symptoms when diagnosing and treating schizophrenia must become routine in clinical practice. Regarding treatment recommendations based upon these findings, the implementation of skill-oriented therapies along with family involvement may lead to more successful treatments.

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[i] Effect sizes can be translated into z-scores on either sample distribution. For example, a d=.50 suggests that the average of one samples distrubtion falls .50 standard deviations away from the mean on the second sample, which would translate to a z of .50. Using that, z-score percentiles under the curve can be computed.