Examining Attentional Control and Processing Speed Deficits as Underlying Mechanisms of Neuropsychological Impairment in Schizophrenia

Mayte Forte
University of Massachusetts Boston

EXAMINING ATTENTIONAL CONTROL AND PROCESSING SPEED DEFICITS

AS UNDERLYING MECHANISMS OF NEUROPSYCHOLOGICAL IMPAIRMENT

IN SCHIZOPHRENIA

A Thesis Presented

by

Mayte Forte

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MAYTE FORTE

Approved as to style and content by:

_____
Paul G. Nestor, Professor
Chairperson of Committee

_____
Alice Carter, Professor
Member

_____
Laurel Wainwright, Professor
Member

_____
David Pantalone, Program Director
Clinical Psychology Program

_____
Jane Adams, Chairperson
Psychology Department

ABSTRACT

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Mayte Forte, B.A. Wellesley College
M.A. University of Massachusetts Boston

Directed by Professor Paul G. Nestor

Neuropsychological impairment is a key characteristic of schizophrenia (SZ), but its

cognitive profile and underlying information processing mechanisms are not yet well

understood. We compare patterns of neuropsychological functioning in 85 persons with SZ

and 76 healthy controls across measures of intelligence, memory, and executive function. We

then test the hypothesis that neuropsychological impairment in SZ is related to dual deficits

in two related but distinct information processes: processing speed and attentional control.

All research participants completed Wechsler Adult Intelligence Scale-Third Edition (WAIS-

III), Wechsler Memory Scale Third Edition (WMS-III), and Wisconsin Card Sorting Test

(WCST), all of which provided measures of overall neuropsychological functioning. In

addition, the neuropsychological battery included Trails B as a measure of attentional control

and the WAIS-III Processing Speed Index (PSI). We hypothesized that a) patients with SZ

will show a distinct pattern within and across measures of intelligence, memory, and

executive functioning and b) attentional control and processing speed will each uniquely

account for a significant portion of the variance in neuropsychological functioning across

these measures. Our findings showed that WAIS-III Verbal Comprehension Index performance was primarily predicted by a slower Processing Speed Index (PSI), accounting for 12.25 % of the variance, and to a lesser extent by higher perseverative errors in the WCST(PE), accounting for 6.76% of the variance in the Verbal Comprehension Index. Perceptual Organization Performance was similarly primarily predicted by WAIS-III- PSI, which uniquely accounted for 30.25% of the variance and to a lesser extent by WCST PE, uniquely accounting for 15.21% of the variance. WMS-III Immediate General Memory Index was primarily predicted by the WAIS-III (PSI), accounting for 7.29 % unique of the variance, followed by WCST PE, accounting for 5.76 %. WMS-III Delayed General Memory performance was primarily predicted by WCST PE, uniquely accounting for 6.76% of the variance, yet PSI was not a significant predictor of the model in this domain. Overall, our study suggests that processing speed and secondarily attentional control mechanisms using the above proxy measures seem to account for unique portions of the variance in broad measures of overall intellectual functioning and declarative memory in SZ.

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CHAPTER 1

BACKGROUND AND SIGNIFICANCE

Introduction

Cognitive impairment is a hallmark of schizophrenia. In fact, a key quantitative

review consistently cited in the literature conducted by Heinrichs and Zakzanis (1998) found

the largest mean effect sizes for cognitive deficits in SZ to be reflected in full scale IQ, verbal

episodic memory, and executive performance. There seems to be variability in the magnitude

of deficit across domains, yet deficits have been found to be long-standing and relatively

stable, and do not seem to be affected by patient age or length of disease course (Li, 2004). In

addition, studies have shown that deficits in declarative verbal memory are robust and stable

across SZ samples, and are seen at different phases of the illness (Stone & Hsi, 2011).

Unaffected, first, and second-degree relatives of SZ have been found to perform less well

than controls on multiple tests of verbal and non-verbal declarative memory (Whyte,

McIntosh, Johnstone, & Lawrie, 2005) which suggests that these impairments may, in part,

be genetically influenced (Ragland et al., 2009) or represent a possible endophenotype of the

illness (Gottesman & Gould, 2003).

Impairment in general intellectual ability in schizophrenia seems to be as severe as

that observed in other neuropsychological functions, suggesting that specific impairment

occurs in the context of a general intellectual impairment (Reichenberg & Harvey, 2007).

Furthermore, as indicated by meta-analytic studies, the impairment in performance IQ is at

least 50% larger than that observed for verbal IQ in schizophrenia. Relatedly, a study by

MacCabe et al. (2012) examining premorbid IQ and its relation to working memory, provides

meaningful insights into the role of premorbid IQ in memory declines in SZ. Essentially, the

results suggest that among patients with high premorbid IQ scores, working memory may be

a good predictor of post-onset decline, in which individuals with better working memory usually show less evidence of decline. Consequently, it is suggested that individuals with schizophrenia showing superior premorbid intellectual functioning show less decline than those with lower cognitive reserve, although a similar pattern of decline in cognition is observed in control samples, which tend to decline to a point similar to those of typical schizophrenia patients, but to a lesser extent. Relatedly, McCabe and colleagues (2012) further suggest that some of these patients seem to remain indistinguishable from healthy controls in most cognitive tests. In contrast, Miyake et al. (2000) have argued that only the updating functions, which are encompassed by broader executive functions, predict intelligence in healthy controls.

Executive function deficits are also among the most prominent cognitive impairments in SZ. Executive function deficits are seen through most stages of the disease (Orellana & Slachevsky, 2013) and include deficits in shifting mental sets, inhibition of the dominant responses, and updating working memory representations (Wongupparaj, Kumari, & Morris, 2015). Mild to moderate impairments in executive functions has been found in patients with first-episode SZ, as well as their first-degree relatives and adolescents at risk (Orellana & Slachevsky, 2013). Executive function is mostly associated with the dorsolateral prefrontal cortex (PFC) and involved with voluntary control of behavioral responses (Orellana & Slachevsky, 2013).

Declarative memory deficits have also been reported in schizophrenia. Specifically, meta-analytic findings examining the results of 110 studies found evidence of severe impairments in immediate and delayed verbal and nonverbal memory in schizophrenia (Cirillo & Seidman, 2003). Of note, the most severe impairments have been found in episodic memory. By closely examining neuropsychological evidence of schizophrenia in their meta-analysis, Cirillo and Seidman (2003) concluded that recall deficits in schizophrenia are likely due to impaired initial acquisition of information and not due to

retrieval. By comparing affected and normal control subjects, this review proposed 10% to 20% less information retained by schizophrenia patients, although there is no evidence of an abnormal rate of forgetting, characteristic of frontal lobes dysfunction (Wheeler, Stuss, & Tulving, 1995). On the other hand, non-declarative memory and procedural (habit) learning have been found to be preserved in schizophrenia (Reichenberg & Harvey, 2007).

Differential versus Generalized Impairment

While neuropsychological deficits are a robust characteristic of schizophrenia, the debate is ongoing regarding whether the impairment is mostly driven by selective characteristics or a generalized impairment. One of the caveats of neuropsychological schizophrenia research as mentioned in Chapman & Chapman (1973) is that it remains unclear whether differential deficit in performance translates into differential deficit in ability. Supporting this line of reasoning, research has shown that various factors such as floor and ceiling effects may impact the effect sizes that have been reported (Heinrichs & Zakzanis, 1998). Likewise, Chapman & Chapman (1973) have argued that in order to measure differential deficits in ability, tasks should be matched psychometrically.

Meta-analytic findings have shown that despite the magnitude of deficits, no specific neuropsychological impairment seems to be able to separate a schizophrenia sample from healthy controls, but rather, deficits in schizophrenia occur in the context of a general impairment continuum (Heinrichs, 2003; Heinrichs & Zakzanis, 1998). For example, meta-analytic reviews focusing on the WCST studies in schizophrenia have argued in favor of a generalized impairment, specifically refuting the hypothesis that SZ performance failure on this task reflects evidence of a differential deficit in attentional perseveration, as measured by perseverative errors. As such, these findings call for caution in interpreting poor performance on the WCST as reflecting set-shifting or inhibitory function deficits related to a specific impairment in attentional perseveration (Li, 2004). However, it is still not clear whether inhibition/shifting sets dominance response is selectively impaired or not in SZ.

In support of the selective impairments hypothesis of schizophrenia, imaging data from a diffusion tensor imaging (DTI) study suggested that the generalized schizophrenic neuropsychological impairment may reflect an underlying abnormality in DTI measures of integrity of discrete neural networks. More specifically, these data pointed to a double dissociation between reduced DTI measures of the left uncinate fasiculus (UF) and poorer declarative memory, and reduced DTI measures of the left cingulum bundle (CB) and poorer executive functions in patients as compared to healthy controls (Nestor et al., 2004).

Heinrichs and Zakzani (1998) discussed consistent differences in their meta-analytic review between schizophrenia patients and healthy controls in visual and auditory attention, expressive language, reasoning, and language. Although many may interpret their findings as evidence of a generalized deficit, others such as Lee and Park (2005) have interpreted these findings as a reflection of working memory deficits underlying some of the other affected cognitive domains reported by Heinrichs and Zakzani (1998).

Further, models of central executive function propose that cognitive control involves a network of brain structures rather than a particular area (Baddeley, 2003), suggesting that we should be looking at cognitive operations such as set-shifting in the context of networks, given that distributed networks of brain regions rather than localized areas tend to be involved (Nyhus & Barcelo, 2009). Importantly, previous research has found instances of frontal damage without executive dysfunction (Andres 2003; Baddeley & Hitch ,1974) suggesting a broadly expanding network.

Working Memory and Schizophrenia: Underlying Mechanisms

Working memory is defined as a cognitive system that allows for on-line mental computations ('to be able to keep things in mind') essential for performing complex tasks such as learning and reasoning. Baddeley and Hitch (1974) proposed a working memory multicomponent model composed of three major constituent parts, including a limited attentional capacity component known as the central executive, and two storage systems, the

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phonological loop, and visuospatial sketchpad (Baddeley, 2003, 2010). Of key importance to our study, the components in Baddeley's model are separate, but interactive. Specifically, this model is unique in that it emphasizes a combined processing and storage system capacity that facilitates a range of cognitive tasks such as reasoning, comprehension, and learning. That is, information processing in this model is understood as parallel processing across subsystems while two short-term storage systems, one for visual material, and one for acoustic material make up the storage component. The fourth component of this system is known as the episodic buffer, which is assumed to have a capacity of about four chunks or episodes, which can be accessed through conscious awareness. That is, this part of the system provides a temporary store in which various components of working memory can interact with information from both perception as well as long-term memory. The episodic buffer is assumed to have a capacity of about four chunks per episode, and be accessible through conscious awareness (Baddeley, 2010). Overall, large and stable effect sizes have been indicated for global and selective verbal and nonverbal working memory impairments in SZ (Heinrichs, 2001).

A meta-analytic review examining 124 schizophrenia studies suggested that working memory (WM) deficits found in schizophrenia are robust and are not stimulus-driven (Lee & Park, 2005). Specifically, the study found that working memory deficits in schizophrenia are independent of specific modalities, as measured by different tasks (e.g., verbal, visuo-spatial tasks etc.,). This critical review also provided evidence for the hypothesis that working memory impairments are reliably found across diverse methods and approaches. Although it is possible to argue that some tasks do not have enough discriminating power many studies have used control tasks to rule out other cognitive, perceptual, and motor deficits not inherent in working memory, still finding working memory deficits when other cognitive and perceptual functions were intact (Lee & Park, 2005) and when controls were matched for IQ and education (Park & Holzman, 1992). Substantial research has also found working memory

deficits in psychometric schizotypal undergraduates matched with controls in IQ and education (Park, Lenzenweger, & Holman, 1995).

Similarly, meta-analytic findings looking at 70 studies suggest that the magnitude of working memory impairment in SZ is not affected by potential moderators (or clinical variables) including age, medication, duration of illness, patient status, severity of psychopathology, or positive symptoms. Similarly, negative symptoms have shown a small significant correlation with working memory impairment (Aleman, Hijman, Haan, & Kahn, 1999). Overall, several different measures have been used throughout studies, suggesting that findings are not an artifact of specific task characteristics, and further suggesting working memory deficits in SZ are robust and modality independent.

Common neural mechanisms between working memory and fluid intelligence have been found in healthy participants, with a shared variance significantly explained by interference control (Duncan et al., 2000). That is, both intelligence and attentional control processes of working memory have been found to depend on neural circuitry of the prefrontal lobe. In support of the above findings, functional neuroimaging studies support modality-independent working memory deficits, showing abnormal activation of the prefrontal cortex during tasks of working memory (Henseler, Falkai, & Gruber, 2010) along with dysregulation of networks supporting verbal and visuospatial working memory functions in schizophrenia (Henseler, Failkai, & Grueber, 2010).

Attentional Control and Working Memory

Overall, working memory capacity appears to significantly influence psychometric intelligence in healthy controls by mediating underlying attentional control processes (Nestor et al., 2015). We seek to further explore whether the same mechanisms are evident in SZ patients.

Executive functions and attentional control processes point to higher cognitive functions, sometimes referred to as frontal lobe functions (Reichenberg & Harvey, 2007).

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However, double dissociation studies have posed that not all executive processes are uniquely sustained by the frontal cortex (Miyake et al., 2000) and in fact, some executive processes seem to be sustained by distributed cortical networks (Andres, 2003; Baddeley & Hitch, 1974).

Nestor et al. (2015) examined attentional control deficits in healthy controls, and found that there is notable variability in higher cognitive abilities, as psychometrically measured by the full-scaled IQ of the WAIS-III which may be influenced by unique attentional control capacities, specifically related to shifting mental sets and response inhibition abilities. Nestor and colleagues (2015) found that the strongest relationship of attentional control capacity and IQ occurred independently of any differences in processing speed. That is, Trail B response times uniquely accounted for 15.13% to 19.18% of the variance in full-scale IQ, while WCST perseverative error rate uniquely accounted for 8.12% to 11.29% of the variance in full-scale IQ. Tasks such as the Wisconsin Card Sorting Test (WCST) and the Trail Making Test (TMT) require successful engagement of some form of executive control in addition to basic cognitive processes (Heaton et al., 2001). The WCST measures the ability to shift strategies efficiently, while Trails B requires mental flexibility to switch between two sets (Palmer & Heaton, 2000). Both of these measures have been reported to be severely impaired in schizophrenia samples (Heinrichs & Zakzanis, 1998; Heaton et al., 2001; Reichenberg, Harvey, Bowie, Mojtabai, Rabinowitz, Heaton, & Bromet, E. (2008). More recently, and in support of these findings, Wongupparaj and colleagues (2015) have established that in a sample of patients diagnosed with schizophrenia the relation between working memory and intelligence is mediated by executive functions including inhibition, updating, and shifting, suggesting a key role of attentional control in working memory. Therefore, it follows that higher levels of intellectual functioning may heavily depend on executive attentional control processes related to inhibition and shifting mental

sets, making these target domains for cognitive remediation interventions. We seek to replicate these findings in our study.

Processing Speed and Working Memory

Debate in the literature still exists as to whether aspects of working memory other than attentional control, set shifting, and inhibition also play a key role in the neuropsychological deficits seen in schizophrenia. Although schizophrenic patients show sensorimotor and cognitive slowing, these two processes are seemingly unrelated and only the cognitive slowing has been associated with cognitive deficits in schizophrenia (Morrens, Hulstijn, Hecke, Peuskens, & Sabbe, 2006). Cognitive slowing is affected by processing speed, or the speed with which different cognitive operations can be executed (Dickinson, 2008) and is psychometrically defined as the number of trials completed in a task given a specific amount of time, usually 60-120 seconds.

Studies on cognitive deficits in aging were some of the first to highlight slowing in motor and mental functions as a normal by-product of aging. Initially, it was hypothesized that cognitive performance in the elderly was constricted by the slowing of performance of basic cognitive operations and accounting for variance for measures of processing speed significantly reduced differences between young and older subjects on memory measures (Salthouse, 1993). Following this line of research, Brébion and colleagues (1998) were some of the first to suggest that dysfunction in processing speed in schizophrenia could similarly represent an alternative explanation to the previously established idea of a deficit in working memory, and highlighted its resemblance with slowing seen in bradykinesia in Parkinson's disease, psychomotor retardation in depression, and cognitive slowing in normal aging (Brébion, Amador, Smith, Gorman, 1998). Similarly, bradyphrenia, or slowness in mental processing in schizophrenia and Parkinson's disease (Perry, Light, Davis, & Braff, 2000) has been suggested to reflect striatal pathology in both conditions.

Later studies (Nestor et al., 2007) have supported these findings by pointing to reduced DTI derived cingulum bundle (CB), measures of connectivity associated with overall slower reaction times in schizophrenia.

Processing speed abilities have historically been overlooked when studying cognitive deficits in schizophrenia. Some of the most highly researched tasks believed to tap into information processing impairment in schizophrenia include the Coding Substitution tasks, Symbol Digits Modalities Task (SDMT), and Trails A (Dickinson, 2008). Slow information processing has been identified as the largest cognitive impairment in SZ (Dickinson, 2008). However, meta-analytic findings (Knowles et al., 2015) have identified moderator variables that impact processing speed impairment evident in SZ, primarily involving antipsychotic medication dosage.

Given this gap in the literature, we will examine the unique contributions of processing speed and its influence in working memory capacity, independent of attentional control processes in a schizophrenia sample. Processing speed measures are an integral aspect of cognitive testing, and are usually seen as subtests in measures of intelligence (Dickinson, 2008). To date, the idea that processing speed deficits, or cognitive processing inefficiency might account for a significant proportion of the deficit in working memory capacity in schizophrenia has not been substantially explored.

Despite the existence of moderating variables, processing speed indexes have been shown to be the most sensitive to neuropsychological impairment in schizophrenia (Dickinson, 2008). Predominantly, Digit Symbol Coding subtests of the WAIS-III, have been reported to be the most sensitive indicator of processing speed deficits in schizophrenia with an effect size of 1.57, even when present at the onset of psychosis, and in the context of intact general intellectual ability. Others have extended this research to suggest that processing speed deficits, as measured by digit symbol coding tests represent behavioral markers of schizophrenia's pathophysiology (Bachman et al., 2010), and may also be

pointing to endophenotypes (Dickinson, 2008) of the disease. With respect to endophenotypes, processing speed scores have been shown to be sensitive to cognitive impairment in non-affected high-risk relatives of patients with schizophrenia, who later became psychotic (Dickinson, Ramsey & Gold, 2007). Generally, coding tasks show a graded relationship with symptom risk, severity, and disability or functional outcome in schizophrenia (Dickinson et al., 2007).

A different meta-analytic investigation by Leeson et al (2010) matched patients to controls using IQ measures and found processing speed to be attenuated in recent-onset schizophrenia. By measurement of a processing speed index (Digit Symbol Coding, Symbol Search, Trails A) deficits were found to contribute significantly to episodic memory deficits, and after a one year follow-up it remained a good prognostic factor for poor outcomes in the schizophrenia sample. Further, Leeson and colleagues (2010) posed that the sensitivity of this domain to impairment is unaffected by practice effects or antipsychotic medications over the first year of the illness, but showed sensitivity to the effects of symptom severity. In contrast, different researchers have suggested moderating effects of antipsychotic medication on overall processing speed deficits (Knowles et al., 2010).

In support of these findings, Andersen and colleagues (2013) have examined cognitive impairment in antipsychotic-naive schizophrenia and have found these patients to display moderate/severe impairment in all cognitive domains assessed including processing speed during the first stage of the illness. Notably, scores on processing speed and attention tend to be lower when drug-naïve patients are characterized by a deficit syndrome (a schizophrenia pathophysiological subtype primarily characterized by negative symptoms) rather than non-deficit syndrome (Chen et al., 2014).

Attentional Control versus Processing Speed

Critical to our discussion, is the proposition that processing speed and attentional control can be distinguished and each may make a unique contribution to neuropsychological

impairment in SZ. To date, however, research has typically looked at each of these cognitive processes separately, seldom if ever examining the relative contributions of processing speed and attentional control to neuropsychological disturbance in SZ. For example, Bryson and colleagues (2002) have pointed to an overlap between WCST measures of attentional control and processing speed (Digit Symbol Coding), yet also highlighting the difference in level of improvement, despite general stability over time. This overlap can be interpreted as common cognitive process underlying processing speed (as measured by digit symbol coding) and attentional control (as measured by perseverative errors).

Further research supporting our hypothesis of dual deficits in related but distinct information processing components, Kane and colleagues (2005) showed that working memory capacities primarily, but not uniquely, reflect variance that can be attributed to attentional-control capabilities (Kane, Hambrick, & Conway, 2005). Kim and colleagues (2004) add to these findings describing a disproportionate deficit in the central executive component of working memory (responsible for switching of attention and mental manipulations), and finding a general trend in the schizophrenic patients as compared to controls, showing diminished performance in maintaining information or manipulating internal representations across a brief delay (Kim, Glahn, & Nuechterlein, & Cannon, 2004).

Relatedly, Brebion and colleagues (2014) have found that the association between working memory span and negative symptoms in schizophrenia seem to be mediated by processing speed but not by verbal IQ. Specifically, this research team proposed differential associations between working memory and short-term memory, as differences in a letter-number span assessment was eliminated between patients and controls when a Digit Symbol Substitution Test (DSST) was co-varied. Similar findings in first-episode schizophrenia patients have been found using the DSST (Rodriguez-Sanchez, Crespo-Facorro, Gonzalez-Blanch, Perez-Inglesias & Vazquez-Barquero, 2007). This line of study has concluded that the executive center of working memory is related to cognitive speed, yet short-term memory

storage processes aren't. These findings have been supported, at least partially, by DTI studies which have suggested abnormal DTI patterns linking declarative–episodic verbal memory deficits to the left UF and executive function deficits to the left CB among patients with schizophrenia but not in healthy control groups (Nestor et al., 2010, 2004). Following the dual deficit supportive findings, attentional control has been conceptualized as both executive functioning and as working memory capacity (MacCabe et al., 2010). Supporting this evidence in SZ, healthy control studies (Kane, Bleckley, Conway, & Engle, 2001) have suggested that although the maintenance and central executive aspects of attention seem to be impaired, central executive impairment frequently presents as more severe (Kim et al., 2004).

Relationship between Attentional Control, Processing Speed and Outcome Measures: Intelligence (fluid and crystallized), Declarative Memory, and Executive Functions

Fluid and Crystallized Intelligence. Tests of fluid intelligence call for novel problem-solving using verbal or visual content (Roca et al., 2012). Several lines of research have proposed that working memory and general intelligence or fluid intelligence (gf) constitute the same construct, or a nearly identical one (Martin et al., 2015). However, different meta-analytic findings have explored correlations between working memory and gf factor of intelligence and have found a non-isomorphic relation between the two (Ackerman et al., 2005). Of interest, Ackerman's argument has the underlying premise that working memory capacity (WMC) measures do not show significant discriminant validity- or that they correlate significantly with many different abilities. In support of the same construct hypothesis, Burgess and colleagues (2012) have also found a common neural mechanism between working memory and fluid intelligence in healthy control groups, in which the shared variance was significantly explained by interference control. That is, when looking at the healthy control literature, Kane and colleagues (2005) proposed a latent-variable approach which leads to findings suggesting that executive attention processes mediate the WMC-Gf association. Mainly, attentional control is conceptualized as largely responsible for

the shared variance between WMC and Gf in this model. One of the implications of this study is that attentional control processes are driving some of the overlap as well as the variability between working memory capacity and fluid intelligence scores. We seek to examine whether this extends to schizophrenia populations.

In sharp contrast, studies with SZ patients have argued that fluid intelligence and related cognitive control processes only explain a proportion of the variance in executive abilities between patients and control groups and suggest part of the variance can be explained using other measures assessing a more general cognitive loss (Martin et al., 2015). Similarly, when fluid intelligence is partialled-out as a covariate, group differences between SZ and controls become obsolete (Roca et al., 2012).

In general, verbal performance scores of the Wechsler Adult Intelligence Scale have been used as a robust psychometric construct believed to reflect crystallized intelligence capacity (Nestor et al., 2010) When looking at crystallized intelligence in schizophrenia samples, neurocognitive deficits are different for superior, medium, and very low crystallized verbal skills groups, as measured after adjusting for education and illness duration. Of note, crystallized verbal skills in the average to very low average range have been found to be correlated with diffused impairment across domains and particularly correlated with processing speed and verbal memory impairment (Nestor et al., 2010).

Similar studies have found crystallized verbal skill to be positively related to cognitive flexibility and abstraction (stronger for abstraction) on a sample of community dwelling adults (Savla,Twamley, Delis, Roesch, Jeste, & Palmer, 2012). Functional capacity, or everyday functioning abilities on the other hand, have been positively correlated to abstraction abilities and cognitive flexibility in community dwelling adults diagnosed with schizophrenia (Savla et al., 2012).

Further, recent studies expanded on Heinrichs et al (200), suggesting that measures of working memory, verbal learning and memory, processing speed scores, and adaptive life

skills, were all stronger in verbally superior participants with SZ and not different from healthy control performance. This study confirmed no difference in symptom severity across groups as previously established by Heinrichs (Kurts, Donato, & Rose, 2011).

Declarative Memory. Deficits in declarative verbal memory are similarly robust and stable across schizophrenia samples, and are seen at different phases of the illness (Stone & Hsi, 2011). Deficits in verbal declarative memory are mostly independent of clinical state (Cirillo & Seidman, 2003), are largest in the learning encoding stage (Leavitt & Goldberg, 2009), and expressed as mild deficits in rates of forgetting and in recognition (Cirillo & Seidman, 2003). Likewise, unaffected relatives of schizophrenic patients perform less well than controls on multiple tests of verbal and non-verbal declarative memory (Whyte et al., 2005) and deficits in unaffected, first, and second-degree relatives suggest that these impairments are genetically mediated and overall smaller than in control groups (Ragland et al., 2009).

It has been suggested that declines in declarative memory, may, along with IQ, be indicative of premorbid levels of ability in SZ (Potter & Nestor, 2010). Critically, clinical variables have not been found to moderate this type of memory impairment in SZ, including decline with illness duration, suggesting this may be a potential trait characteristic of the illness (Aleman et al., 1999). Relatedly, studies examining cognitive deficits in subjects with early onset SZ have suggested that verbal declarative memory deficits are dissociable from overall cognitive ability (Tuulio-Henriksson, Partonen, Suvisaari, Haukka, & Lönnqvist, 2004) and scores continue to represent impairment after controlling for IQ scores (Reinchenberg et al., 2009).

Performance on declarative verbal memory has been found to be most sensitive as a heritability measure (0.34) in a sample of first episode, drug-naïve patients with schizophrenia, as well as their siblings and parents in relation to controls (Wang, Chan, Xin Yu, Shi, Cui, & Deng, 2008). More specifically, declines in auditory immediate memory

scores have significantly been correlated with higher severity of both overall negative and general symptoms of the PANSS, flat affect, attention, and overall negative symptoms for the SANS. For the patient group, greater decline in auditory delayed memory correlated with SANS attention and decline in visual delayed memory correlated with severity of SAPS hallucinations (Nestor et al., 2013). Declarative memory deficits in healthy controls have similarly been found to be moderately heritable (Finkel, Pedersen, & McGue, & MCclearn, 1995) pointing to immediate recall on the WMS Logical Memory Test as one of the most sensitive assessment tools (0.40-0.49) to detect impairment in this area.

Executive Functions. Executive function impairments are prominent in schizophrenia and include deficits in shifting mental sets, inhibition of the dominant responses, and updating working memory representations (Wongupparaj et al., 2015). Mild to moderate impairments in executive functions are evident in patients with a first-episode of SZ and are also seen in first degree relatives, and adolescents at risk (Orellana et al., 2013). Executive function is mostly associated with the dorsolateral prefrontal cortex (DLPFC) and involved with voluntary control of behavioral responses (Orellana et al., 2013). Activation in specific regions of DLPFC in patients fully or partially resistant to antipsychotic medication prior to receiving psychosis treatment has predicted responsiveness to treatment (Wongupparaj et al., 2015).

As Wongupparaj and colleagues (2015) have recently highlighted, investigators pursuing different lines of research have proposed similar models of conceptualization around executive functions and working memory. Baddeley and Hitch's working memory model contains elements similar to the key executive functions investigated by Miyake et al (2006) in which Baddeley's attentional control mechanisms are paralleled by Miyake and colleagues's (2006) specified shifting functions. Specifically, Miyake et al. (2006) have proposed an alternate framework in which executive functions are described as supporting and being correlated with working memory, yet representing separable components, such as

inhibition, updating, and shifting between mental sets. Taken together, WM-Ef-g covariation is indicated by both frameworks, and further supported by neuroimaging findings pointing to working memory and intelligence as sharing common neural processes in the network of brain regions spanning parietal- frontal areas, including the dorsolateral prefrontal cortex (DLPFC), lateral prefrontal cortex (LPFC), and parietal brain regions (Wongupparaj et al., 2015). Wongupparaj and colleagues further (2015) suggest a model where executive functions mediate the connection between working memory and the g factor, and specify that the association is stronger for crystallized than fluid intelligence. Although the association is explained by all three functions, the inhibition function shows the strongest effect, followed by abilities in updating and shifting. Similarly, Weiss and colleagues have suggested impairments in control mechanisms being responsible for the reduction found in working memory (Weiss et al., 2003).

Wisconsin Card Sorting Test, Trails B Test, and Executive Functions

       Wisconsin Card Sorting Test. The WCST is a neuropsychological measure that has been long used to examine executive functions (Heaton et al., 1993) including mental flexibility and set-shifting (Polgár, Réthelyi, Bálint, Komlósi, Czobor, & Bitter, 2010). During completion of the task, subjects are required to sort cards according to different rule dimensions (number, form, or color) and after a certain number of correct answers, the rule is changed by the examiner without warning, which participants have to deduce following the examiner's verbal feedback.

       The WCST literature has been marred by inconsistent findings, and there is still a debate on whether this measure can tap into selective deficits in executive functions, or a generalized cognitive impairment in schizophrenia. For example, recent meta-analytic data (Cohen & Minor, 2008) have not confirmed the specificity of a cognitive performance deficit, and instead suggest a non-specific deficit in all cognitive domains. Similarly, studies using imaging techniques have yielded varied findings. For example, perseverative errors

(PE) in the WCST have been partially associated with the dorsolateral prefrontal cortex (Demakis, 2003). Overall, it is important to consider how studying PE can bring us closer to possible rehabilitation targets in SZ. An important area of work with WCST and SZ is related to insight, which can be conceptualized as an awareness of illness severity and a need for treatment (Stratton et al., 2013). Insight has been found to be cross-sectionally associated with perseverative errors on the WCST, although meta-analytic reviews have found PE fail to predict changes in insight over time (Aleman, 2014; Stratton et al., 2013).

Several studies examining the psychometric properties of the WCST using exploratory and confirmatory factor analytic techniques have found a 3-factor solution, with factor 1 accounting for 48-71% of the total variance, primarily loading scores of perseverative errors, conceptual responses, and categories completed (Polgár et al., 2010; Greve et al., 2004). Both perseverative (PE) and non-perseverative errors (nPE) have been found to underlie overall WCST deficit in close to equal proportions in patients with frontal lobe lesions, supporting the multiple domain deficit view that has also been proposed in the SZ literature (Chiang-Shan & Li, 2004). Perseverative errors occur when a patient continues to sort cards according to the same rule, despite negative feedback from the examiner (Li, 2004).

Trail Making Test (Trails B Test). Trails B of the Trail Making Test (TMT) is a speeded, paper-and-pencil task, which involves connecting alternating numbered and lettered circles (Nestor et al., 2015) tapping into attentional control processes, including response inhibition, task switching, and shifting mental sets (Arbuthnott & Frank, 2000). Trails B differs from Trails A in terms of attentional demands and perceptual complexity. Correlational findings have suggested that performance on the Trails B relative to Trails A reflects attentional control processes necessary to manage rapid alternation of two tasks, which may be related to the efficiency of resolving suppression of a previously-abandoned task or a task-set inhibition effect that can be attributed to cognitive task-set management and

not to control of perceptual and motor processes (Arbuthnott & Frank, 2000). By looking at candidate endophenotypes of schizophrenia in comparison to control groups, studies have found Trails B scores to be amongst the measures that showed the largest effect sizes (d=0.50) along with simple and complex performance measures (CPT-X) between relatives and controls (Snitz, MacDonald, Carter, 2005). Overall, Trails B has been used to tap into executive control functions in first-degree relatives of patients with schizophrenia (Snitz et al., 2005). Supporting the construct validity of the trails test, several studies examining Trails A and B have not found any significant differences in effect sizes between the two tasks, challenging the argument that task difficulty and complexity, rather than specific cognitive deficits might be elicited by these tasks, as Trails A is a less demanding version of the task than Trails B (Heinrichs & Zakzanis, 1998).

Specific Aims and Hypotheses

The neuropsychological profile of schizophrenia has been consistently characterized by widespread impairments in working memory, executive functions, attention, and processing speed that give rise to a generalized cognitive deficit (Reichenberg et al., 2009) expressed in difficulties with reasoning, concentration, perceiving, and remembering (Nestor et al., 2010). Recent studies suggest that the enduring neuropsychological disturbance in schizophrenia may figure prominently in disease-related functional outcomes and recovery (Reichenberg et al., 2009). In fact, ongoing research suggests that specific cognitive mechanisms related to working memory, namely attentional control and processing speed, may play a key role in both neuropsychological disturbance and symptom expression in schizophrenia, and as such may represent potential targets for cognitive training and rehabilitation programs aimed to improve the functional outcomes of this patient population. To address these research questions this study proposes the following specific aims:

Specific Aim 1: To examine the nature of neuropsychological functioning in schizophrenia (SZ) in relation to healthy controls on broad measures of intelligence and declarative memory.

All research participants completed a comprehensive neuropsychological battery which included measures of intelligence (WAIS-III), declarative memory (WMS-III) and executive functions (WCST). To examine group differences in patterns of neuropsychological performance, test results were submitted to a series of mixed-models ANOVAs with one between-subjects factor of diagnostic group (control/SZ) and a within-subjects factor of neuropsychological measure (i.e., intelligence, memory, or executive function). It is predicted that SZ and control groups will show different patterns of performance across each of these neuropsychological measures, as reflected in statistically significant interactions of group x neuropsychological measure.

Specific Aim 2: To examine and compare performance on specific measures of attentional control and processing speed in SZ and healthy controls

All research participants completed Trails B of Trail Making Test (TMT), which provides a valid measure of attentional control (Arbuthnott & Frank, 2000), and processing speed measures, specifically TMT Trails A and WAIS-III subtests of Digit Symbol Coding and Symbol Search. We predicted that SZ and controls would show different patterns of performance across these measures of attentional control and processing speed as reflected in statistically significant interactions of group by measures. Several lines of research suggest attentional control to be confounded by underlying information processing speed processes. Given the ambiguity of the literature in this area, I tested attentional control and processing speed separately to examine the contribution of each to neuropsychological disturbance in SZ.

Specific Aim 3. To examine the relative and distinct contributions of attentional control and processing speed to neuropsychological functioning in SZ and healthy controls.

Attentional control allows us to actively maintain stimulus representations on-line in the context of distraction or interference (Baddeley, 2003; Kane et al., 2001; Nestor et al., 2015). Attentional control is therefore, a component of an executive system that helps us organize and plan goal-directed behavior and thoughts (Nestor et al., 2015). Processing speed measures are also an integral aspect of intelligence (Dickinson et al., 2008). Recent findings by Leeson et al. (2010) showed that processing speed was attenuated in recent-onset schizophrenia, and contributed significantly to working and episodic memory deficits. Therefore, it is hypothesized that attention control and processing speed each make unique contributions to neuropsychological impairment in SZ. To test this hypothesis, a series of hierarchical regression analyses were performed with attentional control (Trails B) and processing speed (WAIS-III PSI) as independent variables, with intellectual abilities (e.g., WAIS-III Perceptual Reasoning Index), declarative memory (e.g., WMS-III Immediate and Delayed General Memory Indexes) or executive functions (e.g., WCST perseverative (PE) and non-perseverative (non-PE) errors) as the dependent variable.

CHAPTER 2

RESEARCH DESIGN AND METHODS

Participants

Eighty-five patients (72 (84.7%) males, 13 (15.3%) females) with a diagnosis of schizophrenia and 76 healthy comparison participants (53 (69.7%) males, 23 (30.3%) females) who were part of an ongoing comprehensive, longitudinal study of schizophrenia at the Boston VA Health Care System – Brockton Division were included in this report. Patient mean age mean age was 41.81 (SD=9.4), mean duration of illness of 15.9 years (SD=10.33), mean years of education 13.01 (SD= 2.09), mean parental SES of 2.94 (SD= 1.13), and HC mean age of 41.55 (SD= 7.9), mean years of education 15.13 (SD= 2.02), and mean parental SES of 2.48 (SD= 1.11). All patients were receiving antipsychotic medication, with a mean daily dose equivalent to 436.10 mg (369.56) of chlorpromazine (Woods, 2003). All participants were right-handed, native speakers of English, without any history of neurological illness, ECT, and without alcohol or drug abuse in the past five years.

Procedures

Assessment of Psychopathology. All patients were diagnosed with schizophrenia based on the DSM-IV criteria, using information from the Structured Clinical Interview for DSM-III-R (Spitzer et al., 1990b) by trained interviewers. Patients were recruited from the VA Boston Healthcare System, Brockton Division. This study was approved by the Veterans Administration Medical Center – Brockton Institutional Review Board (IRB).

Healthy control participants were recruited through newspaper advertisements and screened using the Structured Clinical Interview for DSM-IV Axis I Disorders-non-patient Edition (SCID-NP) criteria of no past or current Axis 1 and/or Axis II disorder (First, Spitzer, Gibbon, & Williams, 2002; First, Gibbon, Spitzer, Williams, J.B.W., & Benjamin, 1997) along with chart review.

Measures

  Wechsler Adult Intelligence Scale-Third Edition (WAIS-III). The WAIS-III provides a measure of psychometric intelligence. It yields summary measures of verbal IQ, performance IQ, full-scale IQ, along with four summary index scores: Verbal Comprehension (VC), Perceptual Organization (PO), Working Memory (WM), and Processing Speed (PS).

  Wechsler Memory Scale- Third Edition (WMS-III). The Wechsler Memory Scale-Third Edition (WMS-III) (Wechsler, 1997b) provides a valid standardized test of declarative episodic memory. Among the WMS-III indexes are Auditory Immediate Memory, Visual Immediate Memory, Auditory Delayed Memory, Visual Delayed Memory, General-Delayed Memory, and Delayed Auditory Recognition**.**

  Wisconsin Card Sorting Test (WCST). The Wisconsin Card Sorting Test (WCST) provides a measure executive functions of planning, self-monitoring, and response inhibition. The WCST perseverative errors (PE) will serve as a proxy index of attentional control and are believed to reflect an inability to inhibit a dominant previously correct sorting rule in the face of real-time performance feedback (Heaton, 1981).

  Trail Making Test (TMT) Parts A & B. The Trail Making Test (Arbuthnnott & Frank, 2000) provides a measure of visual attention, sequencing and shifting, psychomotor speed, abstraction, mental flexibility, and executive functions. In condition A, the participant is to draw lines to connect circled numbers in a numerical sequence (i.e., 1-2-3, etc.) as quickly as possible. In condition B, the participant is to draw lines to connect circled numbers and letters in an alternating numbering and alphabetic sequence (i.e., 1-A-2-B, etc.) as rapidly as possible.

  Attentional Control. Trails B response time will serve as a proxy index for attentional control. Trails B is a speeded paper-and-pencil task, which involves connecting

alternating numbered circles and lettered circles, placing heavy demands on attentional control processes, particularly related to shifting mental set, response inhibition, and task switching (Arbuthnnott & Frank, 2000).

Processing Speed. Trails A will serve as a proxy measure for response speed. The WAIS-III PSI will serve as our second proxy measure for mental and graphomotor processing speed and includes the Coding, Symbol Search.

Statistical Analysis

Independent sample t-tests were ran to compare the means of the patients and control groups on relevant demographic variables including sex, age, education, SES, and parental SES. The effect size associated with educational attainment differences across the two groups was assessed.

Group comparisons on neuropsychological tests were examined with analysis of covariance (ANCOVA), controlling for years of education. For each group (patients and controls), correlational analyses were ran to examine inter-test relationships on all of the neuropsychological measures. Hierarchical regression analyses were used to test the relationship of attention control, as measured by Trails B performance time and WCS PE, with neuropsychological measures of intelligence and memory. Likewise, hierarchical regression analyses were used to test the relationship of processing speed, as measured by WAIS-III PSI and Trails A performance time, with neuropsychological measures of intelligence and memory. Last, hierarchical regression were used to examine the relative and unique contributions of attentional control and processing speed to performance on tests on intelligence and memory.

Before testing the study's specific aims, Pearson product correlational analysis were ran between TMT and WCST and psychometric measures of intellectual functioning (WAIS-III full scale IQ and summary indexes) and memory (WMS-III- Logical Memory I, II scores). WAIS indexes included Verbal Comprehension, Perceptual Organization, Working Memory,

and Processing Speed. We also looked at Verbal and Performance IQ's measures of the WAIS-III.

We then explored partial correlations as a test for the specificity between Trails B and WAIS-III scores, covarying for scores on information processing on the Trails A. Likewise we tested the relationship of WCST perseverative errors and non-perseverative errors, and WAIS-III scores covarying for either PE or NPE respectively.

Parametric hierarchical regression analyses were used to partition the total variance of the dependent variables test score (WAIS-III FSIQ score and subtest index scores) as well as WMS-III Logical Memory Immediate and Delayed scores among independent variables (Trails B, WCS PE) (Cohen and Cohen, 1983).

To examine the unique contribution of attentional control and processing speed measures scores to the outcome variables (WAIS III, WMS-III) test scores partial (rp) and semi-partial (rsp) correlations were obtained by using a series of hierarchical regression analyses, in order to evaluate the significant univariate relationships by partitioning the total variance of the dependent variables (WAIS-III full scale IQ and subtests, WMS-III logical memory I and II Immediate and Delayed) among independent variables (Trails B-attentional control, WCST PE/nPE- attentional control, Trails A, Symbol Search, Coding-processing speed) (Cohen and Cohen, 1983). The partial correlation squared (rp2) represents the proportion of variance of a particular test score (e.g. Trails B IV) shared by the outcome measures (WAIS-III FSIQ) after the effects of other independent variables (e.g. Trails A IV) have been removed from the test score (Cohen and Cohen, 1983).

By running these analyses, we sought to explore what proportion of the remaining test score variance, not estimated by other IVs was uniquely estimated by each test mostly reflecting attentional control or processing speed deficits contributing to WAIS-III and WMS-III impairments (DVs).

We then calculated the semi-partial correlation (rsp2) to estimate the amount of intelligence or memory test score variance that was uniquely shared with a particular test of processing speed or attentional control, after all other test scores (IVs) had been removed; therefore, removing the effects of other independent variables from the independent variable, but not from the dependent variables.

CHAPTER 3

RESULTS

Descriptive Statistics and Preliminary Analyses

Table 1 presents the key demographic characteristics of participants with complete

neuropsychological testing (N= 161). As seen in Table 1, mean age in years did not differ

for patient (M = 41.81, S.D = 7.99) and control (M = 41.55, S.D. = 7.99) groups, nor did

parental socioeconomic status differ for patient (M = 2.94, S.D. = 1.13) and control (M =

2.48, S.D. = 1.11) groups. By contrast, patients reported significantly fewer years of

completed education (M = 13.00, S.D = 2.08) than controls (M= 15.13, S.D = 2.02), t (1,181)

=, p<.001.

Table 1. Demographics of Research Participants (N = 161)

Variable	Schizophrenia *n* = 85	Controls *n* = 76
Age	41.81 years (SD = 9.41)	41.55 years (SD = 7.99)
Gender Identity		
Female	13 (15.3%)	23 (30.3%)
Male	72 (84.7 %)	53 (69.7%)
Education level	M = 13.01 (SD = 2.09)	15.13 (SD= 2.02)
Parental Socioeconomic Status	2.94 (SD = 1.13)	2.48 (SD = 1.11)

Table 2 presents neuropsychological test scores for both groups. A series of mixed-

model ANCOVAs with group (patient, control) as the between-subjects effect, co-varying for

education examined group differences on each of these neuropsychological measures. For

WAIS-III measures of verbal and performance IQ scores, ANCOVA revealed only a highly significant group effect, F (1, 158) = 35.04, p<.001, Partial Eta Squared = .182.

As shown, in Table 2 patients had significantly lower scores across full-scale, verbal, and performance IQ measures. For WAIS-III indices of verbal comprehension, perceptual organization, working memory, and processing speed, ANCOVA revealed a highly significant group effect, F (1,158) = 41.83, p <. 001, Partial Eta Squared =.209 as well as a significant interaction effect of group x index measure, F (3,474) = 11.05, p<.001, Partial Eta Squared = .065 specifically for the Processing Speed Index. That is, a different pattern of scores was seen among the different index measures, with the most pronounced difference seen in the Processing Speed Index scores. More specifically, patients again showed overall lower scores across WAIS-III indexes, with group differences especially pronounced for the Processing Speed index.

This study revealed that SZ patients had significantly lower scores across all measures of intelligence and declarative memory, as compared to healthy controls and differences between groups were particularly pronounced on the processing speed index. In addition, in relation to controls, patients showed pronounced slowing on Trails B as shown by the highly significant interaction of group by task. Whereas normal controls showed similar rates of perseverative and non-perseverative errors, patients showed a disproportionate higher rate of perseverative errors than non-perseverative errors,

For the WMS-III patients had significantly lower scores across immediate and delayed memory tests, F (1, 152) = 34.87, P < .001, Partial Eta Squared - .187 but no significant interaction effect, as both groups showed similar patterns across tests. For the

Trail Making Test patients had significantly lower scores across Trails A and Trails B tests F (1,158) = 43.04, p < 0.001, Partial Eta Squared = .214 as well as a significant interaction effect of group x task F (1,158) = 18.54, Partial Eta Squared =.105. While patients had significantly reduced time for both Trails A and Trails B relative to controls they

also showed greater pronounced slowing on Trails B relative to Trails A when compared to controls.

For the WCST, in relations to controls patients made more errors, both perseverative and non-perseverative errors on the WCST F (1, 158) = 18.121, p < 0.001 Partial Eta = .103. Whereas normal controls showed similar rates of perseverative and non-perseverative errors, patients showed a disproportionate higher rate of perseverative errors than non-perseverative errors, reflected in the significant interaction of error type x group F (1, 158) = 3.94, p <.049 ,Partial Eta Squared = .024.

Table 2. Means and Standard Deviations of Test Performance on Neuropsychological Measures for All Participants (N = 161)

Group	Schizophrenia (n = 85)		Controls (n = 76)	
WAIS-III				
Full-Scale IQ	M = 90.27	SD = 13.84	M= 109.20	SD = 13.70
Verbal IQ	M = 92.66	SD = 14.94	M = 109.67	SD = 13.33
Performance IQ	M = 87.45	SD = 13.21	M = 106.72	SD =14.50
Verbal Comprehension	M = 95.79	SD = 17.53	M = 108.01	SD =12.90
Perceptual Organization	M = 90.25	SD = 15.82	M= 107.67	SD = 14.91
Working Memory	M = 89.15	SD = 16.87	M = 108.92	SD = 14.74
Processing Speed	M = 82.11	SD = 14.48	M = 105.55	SD = 15.10
WMS-III				
Auditory Immediate	M = 86.19	SD = 18.36	M= 104.50	SD =13.18
Auditory Delayed	M = 90.59	SD = 18.84	M= 107.80	SD = 12.52
Visual Immediate	M = 83.12	SD = 16.94	M= 101.22	SD= 15.31
Visual Delayed	M = 84.22	SD = 17.24	M= 103.93	SD= 13.78
Immediate Memory Index	M = 81.45	SD = 18.29	M= 103.84	SD= 15.09
Delayed Memory Index	M = 85.58	SD = 16.20	M= 106.03	SD= 13.30
TMT (sec)				
Trails A (sec)	M = 49.11	SD =19.77	M = 30.42	SD =10.98
Trails B (sec)	M = 126.38	SD = 67.55	M = 63.61	SD = 19.65
WCST				
Perseverative Errors	M = 25.89	SD = 21.57	M = 10.75	SD = 7.17
Non-perseverative Errors	M = 18.58	SD = 11.33	M = 12.36	SD =12.24
Categories Completed	M = 3.61	SD = 2.33	M = 5.45	SD = 1.31

Table 3 presents correlations of WCST and Trail Making Test with WAIS-III measures for the patient group. As can be seen in Table 3, faster response times on Trails A correlated very significantly with higher scores on WAIS-III measures of performance IQ ($r = -.29$, $p<.05$), as well as for three of the four WAIS-III index measures of perceptual organization ($r = -.30$, $p<.05$), working memory ($r = -.40$, $p<.001$), and processing speed ($r=-.34$, $p<.05$).

For Trails B, faster response times similarly correlated very significantly with higher scores on WAIS-III measures of performance IQ ($r = -.44$, $p < .001$), as well as with three out of four of the WAIS-II index measures of perceptual organization ($r = -.39$, $p <.001$), working memory ($r = -.45$, $p < .001$), and processing speed ($r = -.40$, $p <.001$). Further, a higher number of perseverative errors on the WCST correlated very significantly with scores on WAIS-III measure of full scale IQ ($r = -.47$, $p<.001$), measures of performance IQ ($r = -.48$, $P<.001$), and verbal IQ ($r = -.42$, $p<. .001$), as well as for two of the four WAIS-III index measures of verbal comprehension ($r = -.35$, $p<.05$) and perceptual organization ($r = -.45$, $p< .001$).

WCST Non-perseverative errors correlated significantly with higher scores on WAIS-III measures of verbal IQ ($r = -.34$, $p< .05$), as well as for two of the four WAIS-III indices of verbal comprehension ($r = -.38$, $p< .001$), and perceptual organization ($r = -.28$, $p< .05$).

As can be observed in Table 3, higher numbers of categories completed on the WCST correlated very significantly with full scale IQ ($r= -.35$, $p< .05$) and measures of performance IQ ($r = .36$, $p< 0.05$), verbal IQ ($r= .38$, $p<0.001$ as well as on WAIS-III index measures of verbal comprehension ($r=.39$, $p< 0.001$) and perceptual organization ($r=.39$, $p< 001$).

Table 3. Correlations of Trail Making and Wisconsin Card Sort with Wechsler Intelligence Test subscales for Schizophrenia Group Participants (n=81)

Measures	Trail Making Test		Wisconsin Card Sorting Test		
	Trails A	Trails B	CC	PE	NPE
WAIS_III					
IQ score	*-.25**	*-.44***	*.35***	*-.47***	*-.25**
Verbal	*-.24**	*-.39***	*.38**	*-.42***	*-.34***
Performance	*-.29***	*-.44***	*.36***	*-.48***	*-.20*
WAIS-III Index					
Verbal Comprehension	*-.16*	*-.27**	*.39***	*-.35***	*-.38***
Perceptual Organization	*-.30***	*-.39***	*.39***	*-.45***	*-.28***
Working Memory Index	*-.40***	*-.45***	*.23**	*-.25**	*-.19*
Processing Speed Index	*-.34***	*-.40***	*.11*	*-.19*	*-.02*

 * Indicates statistical significance at p <.05
** Indicates statistical significance at p < 0.001

Table 4 presents the correlations WMS-III scores with Trail Making, WCST and WAIS-III PSI performance measures for the patient group. As can be seen in Table 4, there were moderate associations between faster response time on Trails B correlated vscores on four of the WMS-III measures including a measure of auditory immediate memory (r = -.44, p < .001), visual immediate memory (r = -.40, P< 0.001), auditory delayed memory (r = -.31, p < .05), and visual delayed memory (r = -.41, p< .001). Similarly, there were moderate associations between Trails B and the Immediate General Memory Index (r= -.46, p < .001), as well as with the Delayed General Memory index (r = -.35, p <. 05).

Similarly, there were small to moderate associations between higher number of perseverative errors on the WCST and higher scores on auditory immediate memory (r= -.31, p< .05), visual immediate memory (r= -.36, p = .001), auditory delayed memory (r = -.24, p < .05), and visual delayed memory (r = -.31, p < .05). Likewise, there were moderate associations between higher perseverative errors on the WCST and the Immediate General

Memory Index (r = -.40, p<.001) and the Delayed General Memory Index (r = -.37, p<.05).

Categories completed only showed a moderate association with the immediate general

memory index (r = .31, p <.05), while non-perseverative errors did not correlate significantly

with any measure from the WMS-III.

Table 4. Correlations of Trail Making and Wisconsin Card Sort with Wechsler Memory Test subscales for Schizophrenia Group Participants (n=81)

Measures	Trails Making Test		Wisconsin Card Sorting Test		
	Trails A	Trails B	PE	NPE	CC
WMS_III					
Auditory Immediate	*-.26**	*-.44***	*-.31***	*-.15*	*.24*
Auditory Delayed	*-.22**	*-.31***	*-.24**	*-.14*	*.16*
Visual Immediate	*-.21*	*33333*	*-.36***	*-.20*	*.23*
Visual Delayed	*-.20*	*-.42***	*-.31***	*-.08*	*.11*
Immediate Memory Index	*-.24**	*-.46***	*-.40***	*-.20*	*.31***
Delayed Memory Index	*-.18*	*-.35***	*-.37***	*-.15*	*.22**

* Indicates statistical significance at p <.05
** Indicates statistical significance at p < 0.001

Hierarchical Regressions Examining Attentional Control and Processing Speed Variables on General Intellectual Functioning and Memory Performance

Hierarchical regression analyses (Tables 1a-4a, Expanded in Appendix) were used to

examine relative and unique contributions of attentional control (i.e., Trails B, WCST PE) and

processing speed variables (i.e., Trails A, WAIS-III PSI index) to performance of intellectual

functioning and memory functioning (WAIS-III and WMS-III outcome measures) in the

schizophrenia and control groups. In order to conserve statistical, power the model was built based

on significant correlational analyses.

Verbal Comprehension Index

In the first step of the regression analysis examining predictors of the general Verbal

Comprehension Index, Trails A was entered in the model. As shown in Appendix Table 1a, Trails A

uniquely accounted for 2.5 % of the variance in the Verbal Comprehension Index, as reflected in

semi-partial and partial correlation value of -.16 (model not significant). The second model included both Trails A and Trails B time spent in seconds. Here as shown in Appendix Table 1a, the data showed that Trails B uniquely accounted for 4.8 % of the variance in the Verbal Comprehension Index, as reflected by the partial correlation of -.22. The third model included Trails A, Trails B, and WCST perseverative errors. In this model, as shown in Appendix Table 1a, the data showed that WCST perseverative errors uniquely accounted for 6.25-6.76% of the variance in Verbal Comprehension performance, as reflected in a semi-partial correlation of -.25 and a partial correlation of -.26.

The fourth and final model included Trails A, Processing Speed Index from the WAIS-III, perseverative errors from the Wisconsin Card Sorting Test, and Trails B. The results of the final prediction model (Model 4) as show on Table 5 was statistically significant $F_{(1, 80)} = 6.47$, $p = .001$ and accounted for approximately 25 % of the variance of the Verbal Comprehension Index of the WAIS-III ($R^2 = .25$, Adjusted $R^2 = .21$). WAIS-III Verbal Comprehension Index performance was primarily predicted by a slower Processing Speed Index (PSI) and to a lesser extent by higher perseverative errors in the WCST (att. control). In the final model, Trails A and Trails B were no longer significant predictors of Verbal Comprehension Index performance.

The PSI index received the strongest weight in the model, accounting for a unique variance of 12.25 % in the Verbal comprehension index, followed by WCST perseverative errors, accounting for a unique variance of 6.76 % in the Verbal Comprehension Index score. The raw and standardized regression coefficients, partial and semi partial correlations, and R^2 change are shown in Table 5 below.

	Model 4				
Variables	B	*SEB*	β	Partial	Part
Trails A	.03	.11	.03	.03	.02
Trails B	-.00	.04	-.01	-.01	-.01
WCST_ PE	-.22	.09	-.28	-.27*	-.24
PSI	.44	.13	.36	.35	.32
R^2			.25		
F for change in R^2			6.47		

Table 5. Summary of Hierarchical Regression Analysis (Model 4) for Variables Predicting Performance on **Verbal Comprehension Index** on SZ sample (*n* = 85)
*Indicates statistical significance at p <.05

The same regression analysis was used to examine the relative and unique contributions of attentional control processes and processing speed scores to performance of intellectual functioning and general memory function in a comparison control group. The results of the final prediction model (model 4) approached but did not attain significance F(1, 71) = 10.01, p = .052. WCST perseverative errors received the strongest weight in the model, accounting for a unique variance of 9.61-13.69 % in the verbal comprehension index score.

Perceptual Organization Index

In the first step of the regression analysis examining predictors of the perceptual organization index, Trails A was entered in the model. As shown in Appendix Table 2a, Trails A uniquely accounted for 9 % of the variance in the Perceptual Organization Index, as reflected in semi-partial and partial correlation value of -.30. The second model included both Trails A and Trails B. Here as shown in Appendix Table 2a, the data showed that Trails B uniquely accounted for 7.84 % of the variance in the Perceptual Organization Index, as reflected by the partial correlation of -.28. The third model included Trails A, Trails B, and WCST perseverative errors. In this model, as shown in Appendix Table 2a, the data showed that WCST perseverative errors uniquely accounted for 9.61- 11.56 % of the variance in the

Perceptual Organization Index, as reflected in a semi-partial correlation of -.31 and a partial

correlation of -.34.

The fourth and final model included Trails A, Trails B, WCST perseverative errors,

and Processing Speed Index from the WAIS-III. The results of the final prediction model

(Model 4) was statistically significant F (1, 80) = 18. 7, p< .05, and accounted for 48.4 % of

the variance of Perceptual Organization Index performance (R^2 = .48, Adjusted R^2 = .46).

Perceptual Organization Performance was primarily predicted by the processing speed index

of the WAIS-III, which uniquely accounted for 30.25% of the variance in the Perceptual

Organization Index and to a lesser extent by WCST perseverative errors, uniquely accounting

for 15.21% of the variance in the Perceptual Organization Index. The raw and standardized

regression coefficients, partial and semi partial correlations, and R^2 change are shown in

Table 6.

	Model 4				
Variables	B	*SEB*	β	Partial	Part
Trails a	-.05	.08	-.06	-.07	-.05
Trails b	.00	.03	.01	.01	.00
WCST_ PE	-.25	.07	-.34	-.39*	-.30
PSI	.57	.09	.53	.55*	.48
R^2				.48	
F for change in R^2				18.7	

Table 6. Summary of Hierarchical Regression Analysis (Model 4) for
Variables Predicting Performance on **Perceptual Organization Index**
on SZ sample (*n* = 85)
* Indicates statistical significance at p <.05

The same regression analysis was used to examine the relative and unique contributions of

attentional control processes and processing speed scores to the Perceptual Organization

Index performance in the comparison control group. The results of the final prediction model

(Model 4) was statistically significant F (1, 71) = 5.67, p < .05 and accounted for

approximately 24 % of the variance of the Perceptual Organization Index (R^2 =.24, Adjusted

$R^2 = .20$). The only significant predictor of Perceptual Organization Index performance was processing speed (PSI index).

Delayed General Memory Index

In the first step of the regression analysis examining predictors of the Delayed General Memory Index (WMS-III), Trails A was entered in the model and uniquely accounted for 3.24 % of the variance in the Delayed General Memory Index, as reflected by the partial correlation of -.18. The second model included both Trails A and Trails B. Here as shown in Appendix Table 3a, the data showed that Trails B uniquely accounted for accounted for 9.61 % of the variance in the Delayed General Memory Index, as reflected by the partial correlation of -.31. The third model included Trails A, Trails B, and WCST perseverative errors. In this model, as shown in Appendix Table 3a, the data showed that WCST perseverative errors uniquely accounted for 5.76 -6.76% of the variance in Delayed General Memory Index performance, as reflected in a semi-partial correlation of -.24 and a partial correlation of -.26. However, the overall model was not statistically significant F (1, 79) = 2.49, p= .12, as shown in Appendix Table 3a.

The fourth and final model included Trails A, Trails B, WCST perseverative, and processing speed index from the WAIS-III. The results of the final prediction model (model 4) approximated significance F (1, 76) = 5.45, p = 0.52 and accounted for 22.3 % of the variance in the Delayed General Memory Index ($R^2 = .22$, Adjusted $R^2 = .18$). Delayed general memory performance was primarily predicted by WCST perseverative errors, uniquely accounting for 6.76% of the variance in the Delayed General Memory Index. The raw and standardized regression coefficients, partial and semi partial correlations, and R^2 change are shown in Table 7.

	Model 4				
Variables	B	*SEB*	β	Partial	Part
Trails a	.05	.10	.06	.06	.05
Trails b	-.04	.04	-.18	-.14	-.13
WCST_PE	-.20	.09	-.27	-.26*	-.24
PSI	.24	.12	.22	.22*	.20
R^2				.22	
F for change in R^2				5.45	

Table 7. Summary of Hierarchical Regression (Model 4) Analysis for Variables Predicting Performance on **General Memory Index (Delayed)** on SZ sample (*n* = 85)
* Indicates statistical significance at p <.05

The same regression analysis was used to examine the relative and unique contributions of attentional control processes and processing speed scores to the delayed general memory index performance in the healthy control group. The results of the final prediction model (model 4) was not statistically significant F (1, 71) = 1.98, p = .34 accounting for 10 % of the delayed general memory index (R^2 =.10, Adjusted R^2 = .10). There were no significant predictors of Delayed General Memory Index performance in this model (different from SZ).

Immediate General Memory Index

In the first step of the regression analysis examining predictors of the Immediate General Memory Index (WMS-III), Trails A was entered in the model. As shown in Appendix Table 4a, the model was statistically significant F (1, 80) = 4.79, p < .05, with Trails A uniquely accounting for 5.76 % of the variance in the immediate memory index score, as reflected by the partial correlation -.24. The second model included both Trails A and Trails B. Here as shown in Appendix Table 4a, the data showed that Trails B uniquely accounted for 16.81 % of the variance in the Immediate General Memory Index score, as reflected by the partial correlation of -.41. The third model included Trails A, Trails B, and

WCST perseverative errors. As shown in Appendix Table 4a, the model was statistically significant F (1, 78) = 4.44, p < .05 and accounted for 25.8 % of the variance in the Immediate General Memory Index Score (R^2 = .26, Adjusted R^2 = .23).

In this model, as shown in Appendix Table 4a, the data showed that Immediate General Memory Index was primarily predicted by Trails B, uniquely accounting for 8.41 % of the variance while WCST perseverative errors uniquely accounted for 5.29 % of the variance in the Immediate General Memory Index score, as reflected in partial correlations of -.29 and -.23.

The fourth and final model included Trails A, Trails B, WCST PE, and Processing Speed Index from the WAIS-III. The results of the final prediction model (Model 4) was significant F (1,77) = 8.75, p <0.5 and accounted for 31.2% of the variance in the immediate general memory index score (R^2 = .31, Adjusted R^2 = .28). PSI index received the strongest weight in the model, accounting for a unique variance of 7.29 % in the Immediate General Memory Index, followed by WCST perseverative errors, accounting for a unique variance of 5.76 % in the Immediate General Memory Index. The raw and standardized regression coefficients, partial and semi partial correlations, and R^2 change are shown in Table 8 below.

	Model 4				
Variables	B	*SEB*	β	Partial	Part
Trails a	.04	.11	.05	.04	.04
Trails b	-.06	.04	-.24	-.19	-.17
WCST_ PE	-.18	.09	-.22	-.22*	-.20
PSI	.22	.13	.20	.20	.18
R^2				.23	
F for change in R^2				5.73	

Table 8. Summary of Hierarchical Regression Analysis (Model 4)
for Variables Predicting Performance on **General Memory Index
(Immediate)** on SZ sample (*n* = 85)
* Indicates statistical significance at p <.05

The same regression analysis was used to examine the relative and unique contributions of

attentional control processes and processing speed scores to the Delayed General Memory Index

performance in the healthy control group. The results of the final prediction model (Model 4) was

not statistically significant F (1, 70) = 4.123, p = .08, (R2 =.19, Adjusted R2 = .14). There were no

significant predictors of Immediate General Memory Index performance in this model (Different

from SZ). The only significant predictor was seen in Model 2, with Trails B accounting for a unique

variance of 12.25 % in Immediate General Memory scores at this step in the model.

CHAPTER 4

DISCUSSION

Schizophrenia is a highly prevalent disorder and one of the leading causes of disability among young adults around the world. Pervasive and severe neuropsychological impairment has been characterized as a key component of the disorder, and a target area for rehabilitative, educational, and vocational planning. The field, however, currently has a limited understanding of the underlying information processing mechanisms driving these deficits. As a result, it remains unclear what proportion of the disability expressed in the course of the syndrome can be targeted at the cognitive level. Promising research has turned to neuroplasticity, suggesting that intensive computerized training may positively impact overall brain function, social functioning, and reality-monitoring disturbances affecting everyday functioning. There is a great need for research assessing the underlying mechanisms beyond the robust, generalized cognitive impairment that has been previously identified to characterize the disorder.

The current study sought to understand the nature of underlying sources of variance in neuropsychological impairment in schizophrenia by testing the hypothesis that this impairment is in part driven by dual deficits in two related, but distinct information processing components: attentional control and processing speed. In doing so, we intended to contribute to the ongoing debate, by gaining a fuller appreciation of the selective characteristics involved in the neurocognitive profile of the disorder, and to add to the neurological and neuroimaging literature to improve neuropsychological assessment and cognitive remediation tools.

The specific aims of the current research study were to examine the nature of neuropsychological functioning in SZ in relation to healthy controls, to compare performance on specific measures of attentional control and processing speed in both groups, and to examine the relative and distinct contributions of these cognitive mechanisms to overall neuropsychological disturbance as assessed by broad measures of intelligence, executive functions, and declarative memory.

This study revealed that SZ patients had significantly lower scores across all measures of intelligence and declarative memory, as compared to healthy controls. Further, results indicate that differences between groups were particularly pronounced on both processing speed and attentional control measures as evidenced by pronounced slowing on Trails B as well as a significantly higher number of perseverations on the WCST (PE) in comparison to controls. Additionally, our findings suggested that processing speed and secondarily attentional control mechanisms seem to account for unique portions of the variance in broad measures of overall intellectual functioning and declarative memory in SZ groups. This work provides further evidence to suggest that, in SZ patients, overall neuropsychological impairment is related to deficits in two distinct, yet related lower-level information processing mechanisms, contributing to higher-order processes. However, these processes may still be hard to assess as selective impairments given the overlapping nature of the constructs they represent.

Performance on Measures of Attentional Control and Processing Speed

In line with our hypotheses, processing speed and attentional control measures accounted for a substantial portion of the variance in all outcome measures of intellectual functioning, including verbal comprehension and perceptual organization, as well as an index

of immediate general declarative memory. Similar to previous research (Dickinson, 2007) the processing speed index measure contributed a significant amount of the variance in deficits seen in intellectual functioning and immediate memory in the SZ sample. However, contrary to our hypothesis, our processing speed and attentional control measures did not account for a significant portion of the variance in delayed general declarative memory.

Further, in partial support of our hypothesis (as some, but not all our measures accounted for a unique portion of the variance in our general outcome measures of intelligence and declarative memory), the WAIS-III Processing Speed Index and the WCST perseverative errors (PE) each made a unique and significant contribution to the WAIS-III Verbal Comprehension Index performance. However, contrary to our hypothesis, Trails A and B were not significant predictors of the verbal comprehension domain in our final model. Similar to previous research, Processing Speed Index received the strongest weight in the model and accounted for most of the variance in verbal comprehension, consistent with several meta-analyses with patients   identifying processing speed efficiency as the largest single and most sensitive domain highlighting cognitive impairment in schizophrenia (Dickinson, 2008; Heinrichs & Zakzanis,1998) despite being moderated by several factors such as antipsychotic medication dosage (Knowles, 2010) and chronicity. More recent findings suggest that the contribution of processing speed to performance in different cognitive domains tends to increase from lower order to higher order domains (Ojeda et al., 2012). This is consistent with our results, given that the Verbal Comprehension Index involves tasks of abstract reasoning (e.g. Similarities). Our findings expand on studies using verbal fluency tasks as outcome measures in schizophrenia, highlighting that better performance in verbal fluency is associated with better outcomes in community functioning, followed by verbal learning, and processing speed as predictors of success (Ojeda et al., 2010, 2012). Of interest, verbal comprehension skills tend to be resistant to change in brain structures and functioning, usually characterizing as over-learned verbal skills (Nuechterlein

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et al., 2004) or crystallized abilities. However, in our study, verbal comprehension deficits seem to be largely accounted for by deficits in processing speed and attentional control, elucidating a strong influence information processing mechanisms contributing to outcomes in crystallized intelligence performance measures.

This extends previous findings linking processing speed and attentional control with fluid intelligence performance and showing robust differences between healthy controls and schizophrenia groups (Rodriguez-Sanchez et al., 2007; Ojeda et al., 2012). This is also consistent with previous findings suggesting that processing speed deficits in schizophrenia are mediated by white matter integrity (Karbasforoushan, Blackford, & Woodward, 2015), although direct mediation has not been shown with verbal learning and executive functions (Karbasforoushan et al., 2015) shedding light on the importance of looking specifically at the impact processing speed has in higher-order domains such as verbal learning.

Verbal Comprehension and Attentional Control

Verbal comprehension involves crystallized intelligence (usually resistant to change), but also involves abstract reasoning, auditory comprehension, memory, associative and categorical thinking, learning ability and distinction between nonessential and essential features (Wechsler, 2014).

In partial support of our hypothesis, during the final regression model, one of our attentional control measures (WCST PE) also accounted for a unique significant portion of the variance in the verbal comprehension index in the schizophrenia group. Once in the model, Trails B was no longer a predictor of performance. Similar to the verbal fluency tasks, the Verbal Comprehension Index also involves executive control to a lesser extent, as well as verbal ability, concept formation, verbal reasoning, associative and categorical thinking and learning abilities, all which have been shown to be strongly supported by cognitive control (Cirillo & Seidman, 2003; Henry & Crawford, 2005). According to Baddeley's and Hitch's model of working memory, attentional control processes are involved in focusing on the

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selection of relevant information as well as inhibiting or suppressing irrelevant information. It logically follows that, in subtests from the Verbal Comprehension subtest, this lower-process mechanism could potentially account for some of the variance in tasks such as similarities and vocabulary definitions.

Contrary to our hypothesis, Trails A and Trails B did not account for a significant portion of the variance in Verbal Comprehension. Previous studies by Salthouse and colleagues (2011) have shown that the trails making test largely reflects individual differences in speed and fluid cognitive abilities, in which the relative contributions of the two abilities involved vary, according to the particular measure of performance considered. It follows that when entered in our final regression model with other measures as proxies of the same construct, potentially tapping into mental flexibility and fluid abilities to a greater extent, the Trails tasks did not predict Verbal Comprehension Index performance, a measure generally known to reflect crystallized abilities. On the other hand, these findings suggest that there are additional requirements or mechanisms involved in processing speed and attentional control measures, that may not be captured by the trails tasks and consequently do not account for a significant portion of the variance in verbal comprehension performance. We propose that this underlying mechanism may be related to learning ability, well known to be affected in schizophrenia.

Further, it is possible that some subtests of the PSI index, namely Digit Symbol and Symbol Search are placing heavier demands on associative matching, visual search and detection, encoding and decoding figures, while the Trails A may be over-representing speed over other cognitive demands, primarily involving matching numbers at a high rate. Research has found that verbal fluency tasks and verbal memory tasks seem most affected (mediated) by processing speed deficits in schizophrenia (Brebion et al., 2014). Of note, verbal fluency tasks involve executive control as well as verbal ability. Therefore, our findings are consistent with the current literature given that the Processing Speed Index accounted for

most of the variance in the Verbal Comprehension Index, which involves abstract thinking skills, concept formation skills, and verbal reasoning, some under timed conditions.

Attentional Control, Processing Speed, and Perceptual Organization Index

In line with our hypothesis, processing speed and attentional control both accounted for a unique and significant portion of the variance in the Perceptual Organization Index as one of our outcome measures. The Perceptual Organization Index of the WAIS-III involves an ability to interpret, organize, and synthesize visual information, tapping into nonverbal reasoning skills and usually associated with more fluid intelligence (Wechsler, 2014). Kane and colleagues (2001) have proposed that attentional control partly explains the shared variance between working memory capacity and fluid intelligence. It logically follows that tasks of perceptual organization would be partly accounted for by attentional control measures as seen in our study. Further, it has been shown that attentional control is largely supported by prefrontal circuitry (Nestor et al., 2015) which has been long thought to be compromised in SZ (Hartman et al., 2003; Heinrichs, 2005; Wongupparaj et al., 2015).

Processing speed deficits in schizophrenia have been shown to be mediated by white matter integrity. There are consistent findings of correlations between white matter integrity to the frontal lobe, and of executive functions and memory to the temporal lobes (Nestor et al., 2010). However, there is also evidence that processing speed deficits are correlated with white matter integrity throughout the brain, consequently affecting more broad constructs of intellectual functioning and memory (Penke et al. 2010, 2012). Emerging evidence suggests several white matter tracts have compromised integrity, including the cingulum, uncinate fasciculus, longitudinal fasciculi, internal capsule and thalamocortical connections, therefore affecting a wide-spread number of cognitive abilities including processing speed, executive functions, verbal memory and working memory (Nestor et al. 2004, 2010; Perez-Iglesias et al., 2010). More specifically, recent studies have proposed that processing speed in schizophrenia is partially mediated by white matter integrity in the corpus callosum, frontal

lobe, cingulum, anterior corona radiata, and precuneus. More importantly, they suggest the relationship between cognitive functioning and white matter integrity to be strongest for processing speed as compared to other affected domains including executive functioning, verbal learning, and working memory impairments (Karbasforoushan et al., 2015).

This newer line of research supports the previously established hypotheses of disrupted white matter integrity in schizophrenia largely accounting for individual differences in processing speed impairment and group differences persisting after accounting for impairments in executive functions and working memory. Overall, our findings add to the existing research given that we find that processing speed deficits make a unique contribution to deficits seen in higher order intellectual functioning processes including perceptual organization above and beyond deficits accounted for by attentional control processes.

Attentional Control

Our study used different measures of the same construct to establish the construct validity of attentional control and to minimize unwanted method variance and maximize the hypothesized trait variance (Nestor et al., 2015). However, our findings suggest that only one of our measures (WCST-PE) was able to capture the underlying relevant trait variance of attentional control and processing speed in a measure of perceptual organization, suggesting that the failure to inhibit or override previously correct sorting rule in the face of real-time performance feedback in WCST-PE (Egan et al., 2011; Hartman et al., 2003) might be more relevant to overall perceptual organization abilities measured in the WAIS-III than response inhibition, task switching or shifting mental sets, as measured by Trails B. Neuroimaging studies have shown that attentional control capacity can be divided into regulative and evaluative components, supported by distinct regions of the prefrontal cortex (Nestor et al., 2015). The regulative component of attentional control coordinates demands of activation, inhibition and switching, which involves orbital frontal and lateral prefrontal subdivisions, (Nestor et al, 2015), while medial frontal sectors are responsible for monitoring and signaling

adjustments in control. This suggests that the regulative components of attentional control may be the most relevant for perceptual organization in SZ.

Further evidence with healthy controls has shown that there is a strong relation between attentional control and full-scale IQ, occurring independently of variations in processing speed, and higher order cognition as measured by full-scaled IQ of WAIS-III seems to be influenced by attentional control capacities related to inhibition and shifting mental sets (Nestor et al, 2015). Similarly, recent research with schizophrenia samples have found inhibition, updating, and shifting to mediate the relationship between working memory and intellectual functioning (Wonguparraj et al., 2015). As explained by Wonguparraj and colleagues (2015), attentional control capacities are part of the central executive system which seems to involve a learning component, supporting our understanding that one of our measures of attentional control processes (WCST PE) may be tapping into a related learning ability deficit, while the other (Trails B) might not be specific or sensitive enough, driving the differences in variance they account for when put together in a model to predict perceptual organization abilities.

It is interesting to note that a category learning task such as the WCST seems to be better for tapping into the underlying mechanisms potentially liked to NMDA signaling across all neuropsychological measures, or seems to reflect NMDA-supported learning. Relatedly, Forsyth and colleagues (2015) similarly found NMDA involvement in tasks involving incremental learning but not in a task primarily involving working memory capacities (Forsyth., Bachman, Mathalon, & Asarnow, 2015). That is, they found in a probabilistic learning task (Weather Prediction Task) and a classification learning task (ITT), learning across trials was directly associated with augmenting NMDAR signaling using a partial agonist d-cycloserine (DCS) to enhance experience-dependent learning by persisting enhancement of neural potentiation.

Declarative Memory Findings, Encoding, and Forgetting rates in Schizophrenia

In partial support of our hypothesis, processing speed and attentional control processes accounted for a significant portion of the variance in an Immediate General Memory Performance Index, but not in Delayed General Memory Performance Index, supporting a previous body of knowledge suggesting that deficits in verbal declarative memory in schizophrenia are mostly accounted for by deficits at the encoding stage of information and are not necessarily due to forgetting rates over time or retrieval deficits in delayed free recall. Research by Cirillo & Seidman (2003) has previously highlighted that neither attentional control processes nor intelligence account for most of the variance in verbal memory in schizophrenia, but rather processing speed involvement has been highlighted as partially driving encoding and learning deficits theories underlying verbal declarative memory deficits in SZ (Cirillo & Seidman, 2003). Further, studies using RIF (retrieval-induced forgetting) experimental paradigms have found normal forgetting rates in SZ as compared to control groups, and also failed to establish reduced inhibition deficits as a possible mechanism underlying impaired retrieval seen in associative memory impairments (Nestor et al., 2005). However, different studies have found more subtle impairments in increased rates of forgetting (Cirillo & Seidman, 2003) in SZ. On the other hand, a growing body of literature on neuroimaging studies examining verbal declarative memory in SZ has proposed that neither deficits in semantic or perceptual encoding can fully explain deficits in verbal declarative memory (VDM) which are believed to be indicative of deficits in underlying distributed networks models. August and colleagues (2012) support this line of research and have pointed out that structural pathology in schizophrenia goes beyond medial temporal lobe and memory performance involves a broad cortical network, implicating cortical regions involved in early stimulus processing deficits (August, Kiwanuka, McMahon, & Gold, 2012). That is, successfully attending to stimuli is necessary for encoding. It then follows that attentional control processes and

information processing speed deficits play a key role in the ability of patients to encode, and consequently recall information after a short delay, affecting their learning capacity.

Further, specific studies examining WCST performance and declarative memory have found significant correlations between visual and verbal declarative memory and the WCST such that worse performance tasks have been associated with worse performance on WCST, specifically pointing out to perseverations being the most diagnostically useful indicator in WCST distinguishing patients from controls (Egan et al., 2011). Consistent with previous interpretations, we believe that given that subjects have to remember whether they were told the previous sorts were correct or incorrect and associate particular stimuli with a correct answer during the WCST task, it makes sense they will make perseverations and show impaired memory even during an immediate free recall task.

Clinical Implications

Our findings add to the existing literature by showing a significant deficit in immediate verbal memory being accounted for mostly by processing speed and secondarily by measure of attentional control involving a learning component. Our findings are consistent with a hypothesis of dysfunction in the frontal and temporal cortex, showing reduced activation of the prefrontal cortex and increased temporal activation during verbal memory tasks (Ragland et al., 2009). Nonetheless, other studies have argued that the stimulus used in certain tasks, and not the executive functioning abilities they intend to measure, may account for WCST performance in patients with schizophrenia (Kantrowitz, Revheim, Pasternak, Silipo, & Javitt, 2009).

Future Directions

Experience-Dependent Learning, NMDAR and Future Research

Consistent with our findings suggesting a possible learning deficit concurrent with deficits in attentional control and processing speed mechanisms underlying working memory functions in SZ, a substantial body of literature has shown that experience-dependent

learning is impaired in schizophrenia, underpinned by experience-dependent plasticity.

Experience-dependent plasticity is a form of plasticity that enables the brain to undergo

changes and for new behavior to develop following the brain's interaction with

environmental inputs (Forsyth et al., 2015). Experience-dependent learning (one form of

plasticity) frequently depends on long-term potentiation (LTP) or depression (LTD) of

synaptic strength and is critical for every-day function (Forsyth et al., 2015). However, in SZ,

as well as in other neuropsychiatric disorders, experience-dependent learning is usually

impaired (Forsyth et al., 2015). Recent research with healthy controls has shown that one

potential method for promoting experience-dependent plasticity in the brain is to augment

NMDAR signaling which in turn would increase long-term potentiation and facilitate

learning at a molecular level. The NMDA receptor is one of the fundamental

neurotransmitter receptors in the brain which has a high affinity for the excitatory amino acid

glutamate, and is involved in learning and memory processes (Zito & Scheuss, 2009). The

NMDA receptor acts as a coincidence detector, and is capable of signaling coincident pre-

and postsynaptic activity, strengthening the synapses through long-term potentiation or

weakening the finances through long-term depression. In turn, it has been suggested that

augmenting NMDAR signaling would enhance long-term potentiation (LTP) which would in

turn enhance acquisition and retention of information enhancing the learning process at a

molecular level. This has been shown to be the case in healthy controls, and represents a

potential area of future research for improvements in learning ability in schizophrenia.

This area of research is in line with a recently established neurobiological framework

proposing that transient plasticity underlying working memory is modulated in a

fundamentally different way than lasting plasticity changes that support learning and memory

consolidation. In turn, research using experimental paradigms with incremental learning tasks

has shown to promote long-lasting structural changes at dendritic spines, while working

memory tasks such as the n-back task only implicated transient persistent firing in the dorsolateral prefrontal cortex (dlPFC) over brief delays.

These finding have critical implications for future research, considering that cognitive processes can be targeted specifically and at an earlier stage before or during a first psychotic episode to promote learning and long-lasting structural changes in the brain associated with it. One potential method for promoting experience-dependent plasticity is to augment NMDAR signaling. NMDAR is a primary glutamate receptor and is critical for promoting LTP at multiple brain synapses. NMDAR triggers the cellular machinery that supports experience-dependent plasticity, augmenting NMDAR signaling may be used to promote LTP and learning in humans. The regulatory effect of NMDA-R dependent plasticity is consistent with the theory of schizophrenia emphasizing psychopathology can only be described by the interaction of genetic material and the environment. Consistent with our findings, the cognitive dissociation found between working memory tasks and learning tasks suggest that these two different cognitive processes may be underpinned by different neural mechanisms that could potentially be targeted using different cognitive remediation and dynamic assessment approaches. As Forsyth et al. (2015) clarify, in relation to the NMDA receptor, working memory tasks rely on reverberating activity in cortical microcircuits over short delays to maintain information in the absence of stimuli and, thus, does not rely on LTP, while incremental learning tasks, described as tasks in which stimulus -feedback associations are thought to be encoded by long-term potentiation at cortico-striatal synapses.

Relevant to our approach using the WCST task, studies exploring learning potential (LP) in a sample of individuals with serious mental illness have used the WCST as a method of dynamic assessment and have found a strong relationship between performance at baseline and follow-up (2.5 years later) for all respective WCST trials, indicating that LP performance is stable over time and that there are no practice effects accounting for post-training

performance (Rempfer et al., 2011). Similarly, studies specifically exploring performance on reinforcement learning tasks (or learning from positive and negative feedback) have shown that in an early diagnosed SZ sample, patients showed a decreased preference for avoiding the least desirable stimulus, but showed similar rates to HC groups in selecting the most rewarding stimulus (Prentice, Gold, Buchanan, 2008). Put differently, SZ patients have deficits using information to guide their decision making (Fervaha et al., 2013) and may benefit from early training promoting beneficial learning strategies. Other studies using the WCST as a primary learning measure have gone as far as suggesting that the "ability to learn" as measured by differences in responsivity to training procedures on the WCST may represent distinct subtypes of the illness with different neurocognitive characteristics. Relatedly, other studies have shown an association between impaired WCST performance but strong learning with expanded instruction and strong learning on a measure of verbal learning (CVLT-II), demonstrating shared variance between different types of dynamic assessments. Consequently, it remains unclear whether learning is most directly influenced by reward contingencies, or whether cognitive mechanisms are driving behavior in this context.

Given that LP has been shown to be an effective approach to cognitive remediation with schizophrenia samples this provides a powerful approach to compensate for working memory deficits in SZ (Rempfer et al., 2011; Fervaha et al., 2013). Essentially, given that working memory depends on learning, it is crucial that future research continues to examine the learning potential in SZ and how to best tap into these systems early on in the course of the syndrome to promote long-lasting changes in the brain. Nonetheless, the literature shows that recently LTP-processes have been induced in the human brain using high-frequency, repetitive representation of visual and auditory stimuli, which could potentially work with this sample.

Limitations

Some of the limitations of our study include placing WCST PE (tapping into categorical learning) and Trails B (representing more traditional executive functions) under the same rubric of attentional control. That is, in our study, WCST PE, which can be classified as an index of learning, reflected in the acquisition of sorting principles based on real time feedback reflected a learning process above and beyond attentional control. In this sense, unlike Trails B or any other neuropsychological measures used in our study representing the constructs of attentional control and processing speed, WCST PE has shown to be unique among the neuropsychological measures in its sensitivity as index of learning, and perhaps plasticity. Further, we did not account for medication effects in our study, representing another limitation, as antipsychotic medications have been shown to affect information processing mechanisms (Heinrichs, 2005). Nonetheless, the effect of the medications is unlikely to be a significant confound given that all patients received a stable dosage of antipsychotics for a long period of time before study recruitment, which may in fact have improved their cognitive functioning (Silver, Feldman, Bilker, Gur, 2003). However, this is an important limitation of our study given that antipsychotic drugs have been shown to have an impact of cognition and anticholinergic agents have specifically been shown to be deleterious for memory (Brebion et al., 2014). In addition, our sample represented a long average illness duration, which might have impacted our results given progressive cognitive decline with age and disease course. Further, our sample was mainly middle-aged and well-educated. However, processing speed deficits and deficits in executive functions and cognitive control have been shown to be evident at first-onset psychotic episodes, medication-naïve patients and even in non-affected relatives (Leeson et al., 2008; Andersen et al., 2013). Finally, our sample is not representative to other populations as it is primarily composed of Caucasian males.

Table 1a. Summary of Hierarchical Regression Analysis for Variables Predicting Performance on **Verbal Comprehension Index** on SZ sample (n = 85)

Variables	Model 1					Model 2					Model 3					Model 4				
	B	SEB	β	Partial	Par t	B	SEB	β	Partial	Par t	B	SEB	β	Partial	Par t	B	SEB	β	Partial	Par t
Trails a	-.14	.10	-.16	-.16	-.16	-.00	.11	-.01	-.00	-.16	-.03	.11	-.03	-.03	-.00	.03	.11	.03	.03	.02
Trails b						-.07	.03	-.27	-.22*	-.22	-.03	.03	-.13	-.10	-.22	-.00	.04	-.01	-.01	-.01
WCST_PE											-.23	.10	-.28	-.26*	-.25	-.22	.09	-.28	-.27*	-.24
PSI																.44	.13	.36	.35	.32
R^2			.03					.08					.14					.25		
F for change in R^2			2.16					3.30					4.25					6.47		

* Indicates statistical significance at p < .05, ** indicates statistical significance at p < .0001

Table 2a. Summary Hierarchical Regression Analysis for Variables Predicting Performance on **Perceptual Organization Index** on SZ sample (n = 85)

Variables	Model 1					Model 2					Model 3					Model 4				
	B	SEB	β	Partial	Part t	B	SEB	β	Partial	Part t	B	SEB	β	Partial	Part t	B	SEB	β	Partial	Part t
Trails a	-.24	.08	-.30	-.30	-.30	-.09	.09	-.12	-.10	-.09	-.12	.09	-.14	-.14	-.12	-.05	.08	-.06	-.07	-.05
Trails b						-.08	.03	-.33	-.28*	-.27	-.04	.03	-.15	-.13	-.11	.00	.03	.01	.01	.00
WCST_PE											-.26	.08	-.35	-.34*	-.31	-.25	.07	-.34	-.39*	-.30
PSI																.57	.09	.53	.55*	.48
R^2		.09					.16					.26					.48			
F for change in R^2		8.32					8.05					9.40					18.7			

* Indicates statistical significance at p<.05, ** indicates statistical significance at p<.0001

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Table 3a. Summary of Hierarchical Regression Analysis for Variables Predicting Performance on **General Memory Index (Delayed)** on *SZ* sample (n = 85)

Variables	Model 1					Model 2					Model 3					Model 4				
	B	SE B	β	Partial	Par t	B	SEB	β	Partial	Par t	B	SEB	β	Partial	Par t	B	SEB	β	Partial	Par t
Trails a	-.14	.09	-.17	-.18	-.18	.04	.11	.04	.04	.04	.02	.10	.03	.02	.02	.05	.10	.06	.06	.05
Trails b						-.09	.03	-.38	-.31*	-.31	-.06	.03	-.25	-.20	-.18	-.04	.04	-.18	-.14	-.13
WCST_PE											-.20	.09	-.27	-.26*	-.24	-.20	.09	-.27	-.26*	-.24
PSI																.24	.12	.22	.22*	.20
R^2			.03					.12					.18					.22		
F for change in R^2			2.49					5.54					5.76					5.45		

*Indicates statistical significance at p <.05, ** indicates statistical significance at p <.0001

Table 4a. Summary of Hierarchical Regression Analysis for Variables Predicting Performance on **General Memory Index (Immediate)** on SZ sample (n = 85)

Variables	Model 1					Model 2					Model 3					Model 4				
	B	SEB	β	Partial	Part	B	SEB	β	Partial	Part	B	SEB	β	Partial	Part	B	SEB	β	Partial	Part
Trails a	-.18	.09	-.21	-.21	-.21	.03	.11	.03	.03	.03	.01	.11	.01	.01	.01	.04	.11	.05	.04	.04
Trails b						-.11	.03	-.42	-.35*	-.34	-.08	.03	-.30	-.24*	-.22	-.06	.04	-.24	-.19	-.17
WCST_PE											-.18	.09	-.22	-.22	-.20	-.18	.09	-.22	-.22*	-.20
PSI																.22	.13	.20	.20	.18
R^2			.04					.16					.20					.23		
F for change in R^2			3.67					7.54					6.45					5.73		

* Indicates statistical significance at p < .05, ** indicates statistical significance at p < .001

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