The Temporal Relationship Between Change in Cognition and Change in Adaptive Functioning in Schizophrenia: Implications for Therapies Focused on Improving Cognitive Deficits

by

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ABSTRACT

Background: Neurocognitive deficits remain a core feature of schizophrenia. This has led to the development and refinement of therapies for schizophrenia that target improvements in cognition. Many of these therapies are prescribed with the assumption that improvements in cognition may translate to improvements in real-world functioning, yet the majority of studies assessing the relationship between neurocognition and functioning have been cross-sectional, failing to evaluate the relationship between change in these two domains. In this study, the relationship between change in cognition and change in functioning was assessed in the context of a psychosocial treatment trial.

Methods: In the present study, 96 community-dwelling individuals diagnosed with schizophrenia or schizoaffective disorder were evaluated on measures of neurocognition and adaptive functioning at the beginning and on cessation, one year later, of computer-skills training or cognitive remediation therapy. The cross-sectional relationship between cognition and functioning and the amount of improvement or decline on these measures across the one-year treatment trial was assessed. A multiple linear regression analysis was used to assess the relationship between cognitive and functional change.

Results: A cross-sectional relationship between baseline cognition (working memory, processing speed, attention, and verbal intelligence) and adaptive functioning was confirmed and significant improvement was observed on select measures of cognition as well. Improvements in working memory and processing speed predicted improvements in adaptive functioning, however only
working memory was a specific predictor as premorbid verbal intelligence explained the relationship between improvements in processing speed and functioning.

**Conclusions:** The observed relationship between neurocognitive and functional change in this study adds to a growing body of longitudinal studies reporting associations between select facets of cognition and functioning. Further studies clarifying the relationship between change in these two domains is crucial for validation of cognitive remediation therapies for schizophrenia that aim to improve functional outcome in patients by identifying cognition as a core treatment target.
1. INTRODUCTION

1.1 – An overview

Schizophrenia is a debilitating psychiatric disorder that affects approximately 1% of the world’s population at one time. In the United States, similar prevalence for the disorder exists (Mueser & Jeste, 2011). The first modern description of schizophrenia was proposed by German psychiatrist Émil Kraepelin (1856–1927) in his late 19th century text *Lehrbuch der Psychiatrie*, however there is evidence that reports of schizophrenia-like illness date to ancient times. Descriptions of “madness” appear throughout the Bible and in Mesopotamiam, classical Greek, and Latin literature (Jeste, del Carmen, Lohr, & Wyatt, 1985). For example, many cite the prophet Ezekiel as one of the finest examples of schizophrenia in biblical times (Stein, 2010; Torrey & Miller, 2001).

Throughout history, schizophrenia has been defined as a syndrome and described as a heterogeneous disorder with different patterns of symptoms appearing in different individuals. In recent years, however, strides have been made in the reliability and accuracy of diagnostic tools for schizophrenia. In the United States, these advancements can be attributed to the development and refinement of more narrow criteria for schizophrenia, beginning with the Diagnostic and Statistical Manual of Mental Disorders-III (DSM-III; American Psychiatric Association, 1980). While a “cure” for schizophrenia remains elusive, there has been a dramatic shift in how the treatment, course, and outcome of schizophrenia have been conceptualized over the past twenty years. Traditional notions about poor outcome have been challenged and have given way to more
meaningful definitions that emphasize improved functioning, client self-direction, empowerment, and hope (Bellack, 2006; Deegan, 1988).

1.2 – Past and current definitions of schizophrenia

Despite the heterogeneous nature of schizophrenia, research demonstrates that a few symptoms appear frequently across a range of manifestations of the disorder. In 1966, the World Health Organization sponsored the International Pilot Study of Schizophrenia (Sartorius, Shapiro, & Jablensky, 1974) to investigate the illness in several centers around the world. The study found a high degree of consistency in the clinical features of schizophrenia when strict diagnostic criteria were used. This finding led to the critical revision of diagnostic categories during the 1970s in the United States, with a narrowing of its definitions and development of the core symptoms criteria. Through further revisions of the DSM (American Psychiatric Association, 2013) and the International Classification of Diseases (ICD; World Health Organization, 1992), the field has elucidated what are understood to be the core features of schizophrenia. This increased clarity and consistency of diagnosis has advanced research on the disorder tremendously over the past 25 years.

Positive symptoms are a hallmark of schizophrenia and refer to the presence of perceptual experiences, thoughts, and behaviors that are ordinarily absent in individuals without a psychiatric illness. Hallucinations (primarily auditory, but also tactile, visual, gustatory, or olfactory sensations in the absence
of environmental stimuli), delusions (false or absurd beliefs that are not shared by others in the individual’s environment), and disorganization of thought and behavior (disconnected thoughts and abnormal behavior) are all common experiences linked to positive symptoms. Negative symptoms, another clinical component of the disorder, refer to absence of behaviors, cognitions, and emotions typically present in individuals without psychiatric disorders. Common examples of negative symptoms include flat affect, avolition (lack of motivation to perform tasks), and alogia (diminished amount or content of speech). While great focus is placed on the abnormal perceptual experiences in schizophrenia, negative symptoms tend to be most debilitating because of their stability over time and ability to greatly impair social interactions (Mueser & Jeste, 2011).

The definition of schizophrenia has evolved through the six previous editions of the DSM (American Psychiatric Association, 1952, 1968, 1980, 1987, 1994, 2000). Yet, three core factors of the disorder are reflected in all definitions: a) the Kraepelinian emphasis on avolition, chronicity, and poor outcome (Kraepelin, 1971); b) pathology fundamental to negative symptoms; and c) the reality distortion intrinsic to positive symptoms.

Delusions, hallucinations, disorganized speech and behavior, and negative symptoms are all featured in Criterion A of the DSM diagnosis for schizophrenia. In the newest edition of the manual, DSM-5 (American Psychiatric Association, 2013), an individual must exhibit at least two of these specified symptoms for a period of six months with at least one month of sustained symptoms. Individuals must also demonstrate social or occupational dysfunction
since the onset of symptoms, and must not match criterion for other psychiatric disorders, most notably schizoaffective disorder, mood disorders, substance use disorders, and common developmental disorders.

Cognitive impairment is another core symptom existing across various disease profiles. The addition of cognitive impairment as a diagnostic criterion in DSM-5 was considered but was not added because it does not distinguish schizophrenia from other boundary disorders (Reichenberg et al., 2009). Still, the most sensitive instruments estimate that over 75% of the patient population presents with some form of cognitive impairment (Harvey, 2013). Additionally, cognitive impairment appears very early in the disease course. Good et al. (2004) reported that individuals with schizophrenia show cognitive deficits at the onset of psychotic symptoms. Cognitive impairment has been demonstrated even in the prodromal period (Simon et al., 2007) or well before any kind of symptomology appears (Reichenberg et al., 2006), and in first-degree relatives without a diagnosis of schizophrenia (Cannon, Huttunen, et al., 2000; Cannon et al., 1994).

In addition to clinical features and cognitive impairment, poor functional status is a third core component of the disorder. In Criterion B of the DSM, social or occupational dysfunction for a significant portion of the time warrants diagnosis. Specific functional deficits include poor self-care, difficulty managing interpersonal relationships, and trouble sustaining work. One of the most consistent correlates and determinates of functional outcome in schizophrenia has been cognition (Green, 1996). An important step for developing new and
effective targeted treatments in schizophrenia is discovering the determinants of poor functional status that make it so difficult for individuals with schizophrenia to successfully integrate back into the community. Assessing whether and to what degree cognitive improvement or decline may serve as a determinant of functional status will be the focus of this report.

1.3 – Etiology: Genes and environmental factors conferring risk

The etiology of schizophrenia still remains unknown though nearly a century of research has yielded insights into possible causal links. Genetic studies have revealed specific gene loci conferring a risk of disease, and a host of environmental risk factors have been elucidated as well. Decades of research into the relationship between genes and risk for schizophrenia have confirmed a complex relationship exists. Early studies reported that the disorder could not be tied to a single genetic locus (O’Rourke, Gottesman, Suarez, Rice, & Reich, 1982). Confirming these early reports, a meta-analytic study by Badner and Gershon (2002) of whole-genome linkage scans of schizophrenia reported that the strongest evidence for susceptibility resided on multiple loci: 8p, 13q, and 22q. Most recently, a wealth of convergent genetic data for schizophrenia has revealed that there is an even larger polygenic component underlying risk of developing the disorder where thousands of alleles in aggregate are linked with high risk (Purcell et al., 2009).

Environmental risk factors for schizophrenia range from cannabis use in early adolescence (Smit, Bolier, & Cuijpers, 2004) to birth in winter months
(Mortensen et al., 1999). In a 1999 study published in the New England Journal of Medicine, Mortensen et al. reported that the relative risks of schizophrenia for individuals with a mother, father, or sibling who has or had the disorder were 9.31, 7.20, and 6.99 respectively, as compared to individuals with no affected parents or siblings. Additionally, in this study, the risk of schizophrenia was associated with birth in urban areas (relative risk of 2.40 compared to rural areas) and birth in winter months (highest for February and March).

The following reports demonstrate clear causal links between the individual’s environment, familial history, and genetic makeup and the risk for schizophrenia. While etiology still remains incompletely understood, pieces of these causal links are coming together to provide a sense of how nature and nurture interact to give rise to this heterogeneous disorder.

1.4 – Neurobiology of individuals with the disorder

A dopaminergic model of schizophrenia was proposed over 50 years ago. Although original descriptions made claims that many components of the disorder could be attributed to disruptions in dopamine transmission in the brain, more recent neurobiological studies have demonstrated that the neuropathology underlying schizophrenia is far more complex. Neurobiological studies of schizophrenia have yielded insights into the macroscopic and microscopic neuropathology of schizophrenia.

Common macroscopic findings in the brains of individuals with schizophrenia as compared to matched, healthy controls include enlarged lateral
ventricles and reduced volumes of the hippocampus, parahippocampal gyrus, and amygdala (Bogerts et al., 1990; Weinberger, Torrey, Neophytides, & Wyatt, 1979). Wible et al. (2001) reported that reduced prefrontal volumes were associated with negative symptom severity. Additionally, Levitan, Ward, and Catts (1999) found reduced volume in the auditory cortex of the superior temporal gyrus was associated with the severity of hallucinatory experience.

The limitations of volumetric studies should be noted however. First, they do not specify the precise microscopic pathology present in regions of reduced volume. Second, there is no clear agreement on how macroscopic abnormalities of schizophrenia contribute to the positive, negative, and cognitive symptoms of schizophrenia. And most importantly, it is unclear how exposure to antipsychotic medications and differences in environment are contributing to brain pathology. Yet, this evidence leaves little doubt that schizophrenia is a “brain disorder,” though none of these abnormalities can be used as clear diagnostic markers.

In addition to macroscopic neuropathology, schizophrenia is correlated with microscopic abnormalities as well. Microscopic pathology has been observed in the hippocampus and entorhinal cortex, anterior cingulate cortex, and prefrontal cortex (Bloom, 1993; Harrison, 1999). Similar studies have also reported changes in gross neuron size (Benes, Sorensen, & Bird, 1991) and a variety of changes in neuronal organization and structure (Arnold, Hyman, Van Hoesen, & Damasio, 1991). Recent neurochemical models of schizophrenia at the microscopic level have focused on abnormalities in neurotransmission specific
to N-methyl-D-aspartate (NMDA)-type glutamate receptors. NMDA-receptor hypofunction (Mohn, Gainetdinov, Caron, & Koller, 1999) and disrupted GABAergic interneuron functioning in the cerebral cortex (Inan, Petros, & Anderson, 2013), more recently, have been demonstrated in a number of biological models of schizophrenia. The significance of these findings is important but similar to macroscopic pathology, we cannot yet use these abnormalities as definitive diagnostic markers. The importance of a better understanding of microscopic neuropathology will be critical for the advancement of pharmacotherapies for treatment of schizophrenia.

1.5 – Neurocognition

It was Eugen Bleuler, a pioneering Swiss psychiatrist in the early 20\textsuperscript{th} century to first use the term “schizophrenia” (Bleuler, 1911, 1950), who argued that impairments in associative thinking were fundamental abnormalities of the illness with delusions and hallucination occurring as “accessory” symptoms to other core deficits. While often overlooked, Kraepelin’s description of dementia praecox in 1919 included deficits in memory, attention, and general mental efficiency (Kraepelin, 1971). Still, psychotic symptoms have continued to define schizophrenia for years with cognitive impairment often viewed as secondary to other disorder manifestations. However, over the last 30 years, cognition has reemerged as a core domain of the illness.
A “global” cognitive impairment is present in schizophrenia but this impairment is multifaceted as well. Studies have demonstrated a few core facts about cognition in schizophrenia. First, cognitive impairment manifests itself as early as childhood. Cannon et al. (2000) found that children tested at age 4 and 7 years old who later developed schizophrenia performed significantly worse than healthy controls on the Stanford-Binet Intelligence Scale and Wechsler Intelligence Scale for Children. Second, in addition to global impairment in cognition, studies have also highlighted especially pronounced deficits in verbal episodic memory (Heinrichs & Zakzanis, 1998), executive function (Reichenberg & Harvey, 2007), and processing speed (Dickinson, Ramsey, & Gold, 2007). More generally, cognitive batteries assessing attention, working memory, verbal intelligence, and social cognition in addition to executive function, verbal memory, and processing speed have been developed for targeting and measuring cognitive impairment in schizophrenia (Green et al., 2004). Third, and of special relevance to this report, a number of studies have demonstrated that measures of cognition, more so than positive and negative symptomology, have a strong association with functioning in societal roles, family and case manager ratings of functional status, psychiatric rehabilitation success, and self-reported quality of life (Bowie et al., 2006; Goldberg et al., 1995; Green, Kern, & Heaton, 2004; Green, 1996).
1.6 – *Functional outcome*

The goal of every schizophrenia rehabilitation program is “recovery.” While there is no cure for schizophrenia, recovered individuals are able to live independently, sustain vocational or education pursuits, and engage in fulfilling relationships with others. Yet, poor functional status remains one of the most stubborn components of the disorder. Deficits associated with poor functional status include problematic self-care, impaired social interaction, and difficulty engaging in recreational activities and performing in the work place. According to current estimates, 70-80% of individuals with schizophrenia are unemployed at any one time, and among the portion of patients with schizophrenia who receive Social Security Insurance, only half are ever removed from these services (Rupp & Keith, 1993). This amounts to an estimated cost of illness on the order of billions of dollars when accounting for lost wages and lifelong medical care.

Over the past two decades, an association between functional outcome and various domains of neurocognition has been demonstrated in the literature, yet most studies have failed to illustrate whether the relationship is significant beyond correlation at a single point in time. Poor test performance in the areas of attention, memory, and problem solving show a moderate to strong relationship to a variety of dimensions of functional status in the disorder with estimates suggesting that neurocognition accounts for 20-60% of the variance in outcome (Green, Kern, Braff, & Mintz, 2000; Green et al., 2004). Studies that have directly compared cognitive versus clinical predictors of functional outcome have reported that cognition is a better predictor. For example, Sitzer, Twamley,
Patterson, and Jeste (2008) demonstrated that a cognitive screening measure explained 25% of variance in scores on a measure of social skills, while “clinical variables” like positive and negative symptoms, depression, and insight only explained an additional 12% of variance. From the literature, there is no question about whether neurocognition is related to functional outcome. Rather, the question has shifted to how neurocognition is related to functional outcome—specifically, how change in these two domains could be related. Research devoted to answering this question will help improve the development and implementation of targeted cognitive treatments for schizophrenia.

1.7 – Links between neurocognition, performance-based functioning, and real-world functioning

Many behavioral interventions for schizophrenia target cognition with the assumption that cognitive improvements will translate to better functioning in the community. Cognitive skills are critical for adaptive transaction in the environment and cognitive impairment serves to limit these transactions, resulting in unemployment, inadequate social and life skills, and other aspects of low functional status. Yet, few studies have examined the longitudinal relationship between neurocognition and functioning. Additionally, with different assessment tools available that measure specific dimensions of cognition and functioning, it is unclear which facets of these two domains are related.
Research studies examining the relationship between cognition and functioning have used different measures to define “functional status.” This includes functioning assessments that simulate everyday life tasks in a laboratory setting, referred to as proximal measures. These proximal assessments may include demonstrating skills in organizing a recreational trip or dialing a phone and providing relevant information to reschedule a doctor’s appointment. Other assessments, referred to as distal measures, are hypothesized to get closer to true community functioning. These distal measures include clinically-reported outcome measures, psychiatric rehabilitation success, or quality of life (Bowie et al., 2006; Goldberg et al., 1995; Green et al., 2004; Green, 1996). For example, distal measures such as the Quality of Life Scale may ask a patient to evaluate how many close friends they have or what goals they have set for themselves (Heinrichs, Hanlon, & Carpenter, 1984). Proximal and distal measures of functioning are best viewed along a continuum in relation to cognition, as detailed in Figure 1.

Cognition has been linked to both proxy and distal measures of functioning (Green et al., 2004) but the exact nature of this link is less clearly understood. Measures simulating everyday life skills, may have a closer relationship with cognitive performance measures as they require a variety of cognitive skills for successful completion, but likely do not match up exactly with measures of real-world community functioning where improvement involves access to social opportunities, work, and recreation that depend on a variety of social factors beyond skills in cognition. More proximal measures have the
advantage of allowing tighter experimental control and better utility in establishing the cause and effect relationship of a treatment trial. However, more distal measures might offer greater generalizability of findings to real-world community functioning.

Additionally, it may be that proximal measures of functioning and cognition are more closely tied because of the similar nature of these assessments. For example, in studies assessing Social Skills Training (SST) interventions in a review by Kurtz (2011), proximal measures to assess content mastery of skills taught in SST were assessed through paper-and-pencil tests. Neurocognitive measures were similarly assessed through paper-and-pencil tests. Distal measures, however, took an entirely different approach to assessment using client reported and clinician-rated community function.

![Figure 1. Links between Neurocognitive Performance and Proximal and Distal Measures of Functioning. Adapted from Green et al. (2004).](image)
Studies examining the relationship between cognition and functional status can be grouped into four categories: (1) single-time-point, cross-sectional correlations between cognitive and functional outcome variables, (2) longitudinal studies of cognition measured at one time point and level of functioning measured at a subsequent time point, (3) correlation studies of cognition measured at one time point but functioning assessed at multiple time points, and, more rarely, (4) analyses of the relationship of change in cognition to the relationship of change in functioning. As previously mentioned, studies of the first category have been relatively consistent in illustrating a cross-sectional relationship between cognition and functional outcome: individuals with schizophrenia that perform well on cognitive measures also perform well on assessments of functioning (Green et al., 2000). Longitudinal studies of the second type have demonstrated reliable results: cognitive performance on various measures at baseline is related to subsequent level of functioning at follow up (Green et al., 2004). Third, studies looking at the relationship between cognitive performance at baseline and change in functioning over time have found a link between strong cognitive performance on specific measures at baseline and improvement in quality of life (Kurtz, Bronfeld, & Rose, 2012), increased work functioning and improved levels of independent living (Brekke, Raine, Ansel, Lencz, & Bird, 1997).

Studies of the final category comparing the relationship of change in cognition to the relationship of change in functioning have been less frequent and have yielded mixed findings. As discussed in a review by Matza et al. (2006),
several studies have provided evidence that change in cognition is related to change in functional status, but these relationships are sparse, existing between select facets of cognition and functioning. Two of these studies considered the effect of a pharmacological intervention. In a study by Buchanan, Holstein, and Breier (1994), change on Wechsler Memory Scale performance over a one-year period was associated with change in quality of life for schizophrenia patients enrolled in open clozapine treatment. Similarly, Galletly, Clark, McFarlane, and Weber (1997) reported that improved performance on a digit symbol substitution task was significantly correlated with improvement in quality of life over the course of a 6-month clozapine treatment trial of 19 participants.

Studies investigating psychosocial treatment for schizophrenia and the relationship between change over time in neurocognition and functional status have also found mixed results with correlation only significant between select measures of cognition and functional status (Hogarty et al., 2004; Spaulding et al., 1999; Wykes et al., 1999). These results validate conclusions made in earlier reviews (Green et al., 2000) that differential relationships exists between specific domains of cognition (working memory and executive function to name two examples) and certain measurements of functional status (proximal versus community outcome measures of functioning). Finally, many of the longitudinal studies described thus far lack long-term outcome data (e.g., > 6 month follow up) and results depend highly on the nature of the treatment trial administered.

Some of the most recent studies addressing the relationship of change in cognition to the relationship of change in functioning address some of these
limitations but still only report a sparse relationship of change between one to two cognitive domains measured and change in functioning. Reeder, Smedley, Butt, Bogner, and Wykes (2006) examined the relationship of change in executive functioning and memory domains to the relationship of change on the Social Behavior Schedule (SBS) for patients enrolled in Cognitive Remediation Therapy. Reeder et al. reported that only improvements in executive functioning predicted improvement on the SBS. Fiszdon, Choi, Goulet, and Bell (2008) found that change in verbal memory and executive function significantly predicted change in quality of life, however improvements in quality of life were associated with declines in executive function. Most recently, among schizophrenia outpatients receiving treatment and rehabilitation as usual, Miles et al. (2014) reported no relationship between change in working memory, processing speed, and verbal memory and change in functioning, as measured by the Multidimensional Scale of Independent Functioning.

1.8 – The present study

In the existing literature, the temporal relationship between change in cognitive variables and outcome variables is inconsistent, with some studies reporting no relationship between these two domains of the illness even though a cross-sectional relationship may exist. In this study, the relationship between change in cognition and change in adaptive functioning in schizophrenia in the context of two therapies for improvement of cognition and psychosocial function was investigated. A wealth of studies report modest to strong correlations
between these two domains of the illness cross-sectionally. However, only a few longitudinal studies have looked at how change in these two domains is related. Results from this analysis will help direct targeted behavioral treatment for schizophrenia and will elucidate whether cognitive change serves as a predictor of functional change in schizophrenia. The relationship between change in function and change in cognition is especially important because many of the current cognitive remediation therapies are prescribed with the understanding that improvements in cognition translate to improvements in outcome and real-world functioning.

In light of the limitations of previous studies, four hypotheses were developed for the current study. It was hypothesized (1) that, at the start of the treatment trial, all domains of neurocognition (processing speed, attention, working memory, verbal learning and memory, reasoning and problem-solving, and verbal IQ) would be significantly correlated with adaptive functioning, consistent with previous research, (2) that at cessation of the one-year treatment trial including two types of remediation therapy, significant improvement would be evident on measures of cognition and functioning, (3) that change in cognition in the treatment trial would predict change in adaptive functioning, and (4) that the relationship of change in cognition and change in adaptive functioning would be specific, and not secondary, to differences in estimated premorbid verbal intelligence.
2. METHODS

2.1 – Participants

Participants consisted of 96 community-dwelling individuals diagnosed with schizophrenia or schizoaffective disorder as assessed by the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995). All procedures met relevant institutional approval and all participants gave written informed consent to participate. Individuals were excluded from the study if they possessed: (a) uncorrected visual or auditory impairments, (b) neurological illnesses other than schizophrenia, (c) developmental disability, (d) evidence of mental retardation as evidenced by a history of services, (e) current substance abuse, or (d) lack of fluency in English. The majority of patients were recruited from the schizophrenia rehabilitation program at The Institute of Living (IOL) in Hartford, Connecticut (n=82). Other individuals were recruited from MidState Medical Center in Meriden, CT (n=4) and InterCommunity, a community mental health clinic in East Hartford, CT (n=10). This study was a re-analysis of existing data sets collected as part of two randomized controlled trials assessing the cognitive and social efficacy of cognitive remediation therapy (Kurtz, Seltzer, Shagan, Thime, & Wexler, 2007; Kurtz, Mueser, Thime, Corbera, & Wexler, 2015).

All participants were enrolled in one of two treatment groups—pre-vocational computer-skills training or cognitive remediation therapy. In addition, patients treated at The IOL were enrolled in a three-day per week program consisting of structured group therapy, life skills training, and exercise. Goals included increasing social interaction for clients who desired more social
contact or strategies for increasing medication adherence for clients who were at risk for relapse. Clients at the other two community mental health centers attended social clubs on a routine basis but participated in a more limited set of group activities (e.g., daily food preparation).

Individuals were assessed on a number of neurocognitive and functional outcome measures at two different time points—once before the start of cognitive remediation or computer skills training and a second time after completion of these interventions, a mean 11.05 months later (SD=4.78). Demographic characteristics of all participants are displayed in Table 1.

### Table 1. Demographic characteristics of the overall sample (n=96)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.65 (11.06)</td>
<td>18-59</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>71.88</td>
<td></td>
</tr>
<tr>
<td>Years of education</td>
<td>12.91 (2.15)</td>
<td>6-18</td>
</tr>
<tr>
<td>Illness duration (years)</td>
<td>9.57 (9.02)</td>
<td>0-39</td>
</tr>
<tr>
<td>Number of hospitalizations</td>
<td>4.25 (3.98)</td>
<td>0-20</td>
</tr>
</tbody>
</table>

### 2.2 – Neurocognitive measures and assessment of adaptive functioning

To assess neurocognitive functioning, all participants were administered a neuropsychological test battery with measures selected on the basis of criteria outlined in the NIMH study to develop a consensus for a reliable and valid cognitive battery for use in clinical trials (Green et al., 2004). From review of factor-analytic studies, seven separable domains underlying cognitive
impairment in schizophrenia have been identified: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, Reasoning and Problem Solving, and Social Cognition.

The neurocognitive test battery used in this study was representative of five of these seven separable factors underlying cognition (Nuechterlein et al., 2004).

The neurocognitive and functional assessments selected are detailed in Table 2.

The vocabulary subtest from the Wechsler Adult Intelligence Scale-IV (WAIS-IV; Wechsler, 2008) was administered at baseline as an assessment of premorbid verbal IQ at the start of computer skills or cognitive remediation therapy. The brief version of the UCSD Performance-based Skills Assessment (UPSA-B; Mausbach, Harvey, Goldman, Jeste, & Patterson, 2007; Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001) was used as a performance-based, proximal measure of adaptive functioning. The UPSA is designed to measure everyday functioning skills using standardized role-plays.

<table>
<thead>
<tr>
<th>Table 2. Measures used for neurocognitive and functional assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Domain being measured</strong></td>
</tr>
<tr>
<td>Speed of Processing</td>
</tr>
<tr>
<td>Attention/Vigilance</td>
</tr>
<tr>
<td>Working Memory</td>
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<tr>
<td>Verbal Learning and Memory</td>
</tr>
</tbody>
</table>
Reasoning and Problem-Solving: Penn Conditional Exclusion Test (PCET; Kurtz, Ragland, Moberg, & Gur, 2004; Kurtz, Wexler, & Bell, 2004)

Premorbid Intellectual Functioning (Verbal Intelligence): Vocabulary subtest of the Wechsler Adult Intelligence Scale-IV (WAIS-IV; Wechsler, 2008)

Adaptive functioning: UCSD Performance-based Skills Assessment-Brief version (UPSA-B; Mausbach et al., 2007; Patterson et al., 2001)

### 2.3 – Assessment of Cognitive Domain 1: Speed of processing

The Processing Speed Index (PSI; Wechsler, 2008) was used to assess the individual’s ability to rapidly process and respond to routine visual material without making errors. It is one of the four factor scores of the Wechsler Adult Intelligence Scale and consists of two tasks, a symbol search and coding task. In the symbol search task, the participant must decide if a target symbol appears in a row of other symbols. The accuracy and speed at which the participant completes the test allows the investigator to gauge visual perception and psychomotor speed. In the coding task, the individual copies symbols that are paired with numbers within a time limit. Under each digit the individual must write down the corresponding symbol as fast as possible. The age-corrected scaled scores for the symbol search and coding subtests were used to measure processing speed in this study.
2.4 – Assessment of Cognitive Domain 2: Attention and vigilance

The Penn Continuous Performance Test (PCPT; Kurtz et al., 2001) was selected to measure sustained visual attention. During the PCPT, the individual is shown vertical and horizontal lines on a computer screen and is asked to respond whenever the lines are arranged to visually represent a digit 1 though 9. During distractor trials, the lines are rearranged to form nonsense configurations, which the participant must ignore. Stimuli are presented at a rate of one per second and are exposed for 300 milliseconds each. The scaled z-score of true positives was used to measure the domain of attention and vigilance in this study.

2.5 – Assessment of Cognitive Domain 3: Working memory

The Working Memory Index (WMI; Wechsler, 2008) is another factor from the Wechsler Adult Intelligence Scale and was used to assess working memory in participants. It consists of a digit span task and a letter-number sequencing task. In the digit span task, the individual is asked to repeat a list of numbers back to the investigator both forward and backward. The letter-number sequencing task requires the individual to order a mixed list of numbers and letters, repeating the series first with numbers in ascending order followed by letters in alphabetical order. The age-corrected scaled scores for the digit span and letter-number sequencing subtests were used to measure working memory in this study.
2.6 – Assessment of Cognitive Domain 4: Verbal learning and memory

The California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) was selected as a comprehensive assessment of verbal learning and memory. The CVLT-II is administered to understand the patient’s verbal learning, verbal memory, and semantic organization. The test consists of an oral presentation of a list of 16 words followed by five, immediate-recall trials after the list is read each time. The test measures how many words the patient is able to recall and also how that number improves across trials. The age-corrected overall recall score for the five immediate-recall trials was selected to measure verbal learning and memory.

2.7 – Assessment of Cognitive Domain 5: Reasoning and problem solving

The Penn Conditional Exclusion Test (PCET; Kurtz, Ragland, et al., 2004; Kurtz, Wexler, et al., 2004) was used to assess reasoning and problem solving. The assessment functions similarly to the well-known Wisconsin Card Sort Task (Heaton, 1993). For each trial, participants must select which of four shapes does not belong based on one of three sorting rules (line thickness, shape, and size are examples). Participants are given immediate feedback on-screen, reading “correct” or “incorrect” for each trial. If the participant makes the correct choice 10 times, the sorting rules changes and the participant must discover the new rule. The age-matched scaled z-score score for the number of errors on the PCET was selected to measure reasoning and problem solving.
2.8 – Assessment of premorbid intellectual function

The vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2008) assesses the individual’s word knowledge. During the assessment, the individual is presented words visually and orally and must name the object presented or give a definition of the word. The age-corrected scaled score for the vocabulary subtest was used as a measure of baseline IQ in this study.

2.9 – Assessment of adaptive functioning

The brief version of the UCSD Performance-based Skills Assessment (UPSA-B; Mausbach et al., 2007; Patterson et al., 2001) was selected to assess the individual’s ability to perform certain tasks of everyday living. The original version of the UPSA is made up of five domains of functioning. In this brief form of the assessment, participants are asked to role-play skills in finances, through tasks such as writing a check, and skills in communication, through tasks such as dialing for help in an emergency and rescheduling an appointment with a doctor. Participants receive a score ranging from 0 to 20, with higher scores representing better functional capacity. Performance on the UPSA-B is effective at predicting whether persons with schizophrenia are living independently in the community and employed (Brent T Mausbach et al., 2011) and was similarly used in this study for assessing functional capacity at the beginning and end of the treatment trial.
2.10 – Statistical analyses

The Statistical Package for the Social Sciences (SPSS 21.0) was used for statistical analyses. All data were evaluated for normality. In no cases did data violate the assumptions underlying the use of parametric statistical procedures.

A statistical analysis plan was developed to test whether changes in cognition over time were related to change in functioning. To test hypothesis 1 that cognition and functioning were related cross-sectionally, Pearson bivariate correlation coefficients were calculated between baseline measures of cognition and baseline scores on the UPSA-B. To test hypothesis 2 and to ensure that rehabilitation produced expected effects on cognition and functioning over the course of the one-year treatment trial, change scores were calculated and paired sample t-tests were conducted to assess the change that took place in the sample.

To test hypothesis 3 that change in specific cognitive domains would be related to changes in adaptive function, a multiple linear regression analysis was conducted. UPSA-B scores at follow-up were entered as the dependent variable while UPSA-B scores at baseline, changes scores for all measures of neurocognition, treatment group, and recruitment site were entered as independent variables. Variables were entered in a series of three hierarchical blocks: (1) UPSA-B performance at baseline, treatment group and site; (2) all neurocognitive change scores; and (3) premorbid verbal IQ.
Changes scores were calculated as the difference between neurocognitive scores at time point one and two. Treatment group membership (pre-vocational computer-skills training versus cognitive remediation) and recruitment site (The IOL, MidState, or InterCommunity) were included in the model to account for any variability associated with treatment group membership or differences in treatment site. Baseline measures of the UPSA-B were included in the model in order to remove any variance from follow-up UPSA-B scores that could be attributable to UPSA-B variability at baseline.

To test hypothesis 4 that the temporal relationship between cognitive and functioning measures were specific, and not explained by individual differences in premorbid IQ, baseline scores on the WAIS-IV vocabulary subtest were entered into the regression equation in the final step (block 3). This type of regression analysis used to assess hypotheses 3 and 4 is more powerful for evaluating the predictive relationship between change in neurocognition and functioning than alternatives such as correlation of change scores (Everitt & Pickles, 2004; Senn, 2008).

3. RESULTS

3.1 – Cross-sectional associations between cognition and adaptive functioning at study entry

As displayed in Table 3, Pearson correlations conducted on variables collected upon study entry revealed a cross-sectional link between cognition and adaptive functioning. UPSA-B performance was correlated with the Working
Memory index \( r=0.61, p<0.01 \), Processing Speed index \( r=0.32, p<0.01 \), PCPT scores \( r=0.30, p<0.01 \), and WAIS-IV vocabulary subtest scores \( r=0.49, p<0.01 \). PCET and CVLT performance were not significantly correlated with UPSA-B performance at the \( p<.01 \) level.

| Table 3. Correlations of study variables at the start of the treatment trial (n=96) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 | WMI             | PSI             | PCET            | PCPT            | CVLT            |
| UPSA-B                          | \( r=0.61^{**} \) | \( r=0.32^{**} \) | \( r=0.03 \)    | \( r=0.30^{**} \) | \( r=0.24 \)    |
|                                 | \( p<0.01 \)    | \( p<0.01 \)    | \( p=0.75 \)    | \( p<0.01 \)    | \( p=0.02 \)    |
|                                 |                 |                 |                 |                 |                 |

**. Correlation is significant at the 0.01 level (2-tailed).


### 3.2 – Improvement on measures of cognition and adaptive functioning during the treatment trial

As can be seen in Table 4, over the course of the one-year treatment trial, participants showed significant improvements in performance on select study measures. Changes scores displayed whether change over time was positive, thus signifying improvement, or negative, thus signifying decline. Paired t-tests demonstrated significant improvement on the Working Memory \( \Delta=+4.13; p<0.01 \) and Processing speed indices \( \Delta=+4.16; p<0.01 \) and on CVLT \( \Delta=+4.21; p<0.01 \) and PCPT performance \( \Delta=+0.34; p<0.01 \). PCET and UPSA performance also improved but this improvement was not significant at the \( p<0.01 \) level.
Table 4. Mean performance and significance of change in study variables across the one-year treatment trial (n=96)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean score (SD)</th>
<th>T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow up</td>
</tr>
<tr>
<td>WMI</td>
<td>88.10 (15.45)</td>
<td>92.23 (16.65)</td>
</tr>
<tr>
<td>PSI</td>
<td>82.15 (11.59)</td>
<td>86.30 (14.36)</td>
</tr>
<tr>
<td>PCET</td>
<td>-0.30 (1.54)</td>
<td>0.16 (1.53)</td>
</tr>
<tr>
<td>PCPT</td>
<td>-0.99 (2.58)</td>
<td>-0.65 (1.88)</td>
</tr>
<tr>
<td>CVLT</td>
<td>37.34 (12.21)</td>
<td>41.55 (14.23)</td>
</tr>
<tr>
<td>UPSA-B</td>
<td>14.86 (3.18)</td>
<td>15.22 (3.10)</td>
</tr>
<tr>
<td>VOCAB</td>
<td>9.74 (4.02)</td>
<td></td>
</tr>
</tbody>
</table>

**. Correlation is significant at the 0.01 level (2-tailed).

3.3 – Improvement in cognition as a predictor of improvement in adaptive functioning during the treatment trial

The results of a hierarchical block regression calculated to predict total UPSA change based on change in various neurocognitive measures are found in Table 5. Controlling for baseline UPSA-B performance, group membership, and treatment site (block 1) and including all neurocognitive changes scores (block 2) explained 57% of the variance in UPSA-B scores at the end of the one-year treatment trial (R²=.57, F[8,87]=14.10; p<.01). Improvement on the Working Memory (t=2.14; p<.05) and Processing Speed indices (t=2.10; p<.05) significantly predicted improvement on the UPSA. Higher scores on the UPSA at the beginning of treatment (t=8.80; p<.05) also predicted higher scores on the UPSA at the completion of treatment.
3.4 – Premorbid verbal IQ explains the relationship between improvement in processing speed and improvement in adaptive functioning

With the addition of the premorbid verbal IQ measure (block 3), an added 4% of variance was explained. In this last step, baseline premorbid IQ (t=2.82; p=.01) and working memory improvement (t=2.70; p=.01) predicted improvement on the UPSA. However, improvement on the Processing Speed Index no longer predicted improvement on the UPSA, suggesting that premorbid IQ explains the relationship between the Processing Speed Index and the UPSA.
Table 5. Results of stepwise block entry linear regression predicting improvement on the UPSA (dependent variable: UPSA performance at treatment trial completion)

<table>
<thead>
<tr>
<th></th>
<th>Beta</th>
<th>t</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline UPSA</td>
<td>.67</td>
<td>8.77</td>
<td>.00</td>
</tr>
<tr>
<td>Group</td>
<td>.01</td>
<td>.16</td>
<td>.87</td>
</tr>
<tr>
<td>Facility</td>
<td>.05</td>
<td>.63</td>
<td>.53</td>
</tr>
<tr>
<td>Block 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline UPSA</td>
<td>.64</td>
<td>8.79</td>
<td>.00</td>
</tr>
<tr>
<td>Group</td>
<td>.03</td>
<td>.43</td>
<td>.67</td>
</tr>
<tr>
<td>Facility</td>
<td>.03</td>
<td>.44</td>
<td>.66</td>
</tr>
<tr>
<td>WMI Change</td>
<td>.16</td>
<td>2.14</td>
<td>.04</td>
</tr>
<tr>
<td>PSI Change</td>
<td>.16</td>
<td>2.10</td>
<td>.04</td>
</tr>
<tr>
<td>PCET Change</td>
<td>-.01</td>
<td>-.12</td>
<td>.90</td>
</tr>
<tr>
<td>PCPT Change</td>
<td>-.02</td>
<td>-.26</td>
<td>.79</td>
</tr>
<tr>
<td>CVLT Change</td>
<td>.15</td>
<td>1.94</td>
<td>.06</td>
</tr>
<tr>
<td>Block 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline UPSA</td>
<td>.54</td>
<td>6.75</td>
<td>.00</td>
</tr>
<tr>
<td>Group</td>
<td>.03</td>
<td>.40</td>
<td>.69</td>
</tr>
<tr>
<td>Facility</td>
<td>.00</td>
<td>.01</td>
<td>.99</td>
</tr>
<tr>
<td>WMI Change</td>
<td>.20</td>
<td>2.70</td>
<td>.01</td>
</tr>
<tr>
<td>PSI Change</td>
<td>.12</td>
<td>1.60</td>
<td>.11</td>
</tr>
<tr>
<td>PCET Change</td>
<td>-.02</td>
<td>-.28</td>
<td>.78</td>
</tr>
<tr>
<td>PCPT Change</td>
<td>.00</td>
<td>.05</td>
<td>.96</td>
</tr>
<tr>
<td>CVLT Change</td>
<td>.13</td>
<td>1.77</td>
<td>.08</td>
</tr>
<tr>
<td>Vocab Change</td>
<td>.23</td>
<td>2.82</td>
<td>.01</td>
</tr>
</tbody>
</table>

<sup>a</sup>R²=.47, F=26.74, df=3, 92, p<.001  
<sup>b</sup>R²=.56, F=3.95, df=5, 87, p<.005  
<sup>c</sup>R²=.60, F=7.98, df=1, 86, p=.006

4. DISCUSSION

4.1 – Evaluating the hypotheses

While a wealth of studies have investigated the cross-sectional relationship between neurocognition and functional outcome in schizophrenia
(Green et al., 2000), or the relationship between cognition at one time and functional outcome at a subsequent time (Green et al., 2004), this is one of only a few studies, to our knowledge, to investigate how change in these two key illness domains relate to one another in the context of a psychosocial treatment trial. In the current study, we attempted to replicate previous work, by first assessing the relationship between neurocognitive measures and functional outcome measures when participants with schizophrenia entered the treatment trial. We then assessed the degree of improvement or decline on a variety of neurocognitive measures and a measure of adaptive function upon completion of the one-year treatment trial. Lastly, we assessed the relationship between observed improvements in neurocognition and improvement in adaptive functioning and determined the specificity of these relationships by controlling for estimated premorbid IQ.

4.2 – Hypothesis 1: Cross-sectional relationships between neurocognition and functioning

Because of the large number of cross-sectional studies demonstrating a relationship between neurocognition and functional outcome, it was hypothesized that measures of baseline neurocognition would be correlated with adaptive functioning performance at baseline. This hypothesis was confirmed by the results of the study. Specifically, elevated functioning in working memory, processing speed, attention, and premorbid IQ domains was significantly correlated with higher levels of adaptive functioning. However, the
relationship between verbal learning and memory and reasoning and problem-solving domains and adaptive functioning was non-significant.

Multiple cross-sectional studies have confirmed similar findings. For example, Bowie et al. (2006) used a highly similar neurocognitive battery to that selected for the current study, measuring attention, motor skills, verbal learning and memory, verbal fluency, and executive functioning, and an identical measure to assess adaptive functioning, the UPSA. Global cognition at baseline was correlated with functional capacity as measured by the UPSA (r=.63). Similarly, Kurtz, Seltzer, Fujimoto, Shagan, and Wexler (2009) found a correlation between select cognitive measures and UPSA performance. In agreement with the present study, the investigators also reported no correlation between the reasoning and problem-solving domain as measured by the PCET and adaptive functioning. Finally, in a more recent cross-sectional study, Keefe, Poe, Walker, Kang, and Harvey (2014) replicated the positive correlation between levels of global cognition and performance on the UPSA (r=0.65).

4.3 – Hypothesis 2: Degree of neurocognitive and functional improvement

Because all participants were involved in training and interventions at their respective treatment sites targeting neurocognition and functioning, it was hypothesized that all domains of neurocognition and adaptive functioning would display significant improvement at the cessation of the one-year treatment trial. Significant improvement was observed in all neurocognitive domains except for reasoning and problem solving as measured by the PCET.
While improvements in neurocognition were significant, improvements in adaptive functioning were observed but were not significant. This finding raises the question of whether adaptive functioning is harder to improve with therapy or whether the effects of cognitive training therapy did not have time to impact functioning (Wykes et al., 2012). A recent study Miles et al. (2014) reported similar findings. One hundred and twenty-eight participants with schizophrenia residing in outpatient clinics took part in the study, receiving treatment and rehabilitation as usual, but no focused cognitive interventions. Neurocognitive and functional performance were assessed at baseline and again one year later. They found, similar to the present study, that specific facets of cognition improved significantly, but all definitions of real world outcome status, as measured by the Multidimensional Scale of Independent Functioning, showed non-significant change.

4.4 – Hypothesis 3 and 4: Relationship between change in neurocognitive and adaptive functioning, controlling for premorbid IQ

Few studies have looked at the relationship between neurocognitive change and adaptive functioning change and these studies have reported mixed results with some finding a predictive relationship (Fiszdon et al., 2008; Reeder et al., 2006) while others reporting a non-significant one (Miles et al., 2014). Based on the cross-sectional link between neurocognition and functioning, it was hypothesized that improvements in neurocognition would be related to improvements in adaptive functioning. This hypothesis was confirmed in some
but not all domains of neurocognition. Improvements in working memory and processing speed, but no other neurocognitive domains, significantly predicted improvement in adaptive functioning. Additionally, when premorbid verbal intelligence was added as an additional predictor variable, processing speed improvements no longer predicted improvements in functioning, demonstrating that verbal IQ explains the relationship between improvements in processing speed and improvements in adaptive functioning.

This finding is consistent with some previous studies, but contradicts findings of others. For example, Kurtz et al. (2009) reported that baseline auditory attention and working memory predicted change in everyday life-skills when baseline life-skill scores, symptoms, and treatment process variables were controlled. A hierarchal block regression, similar to the one in the present study, was used for statistical analysis. Assessment of adaptive functioning was conducted at baseline and at one-year follow-up to provide an assessment of functional change, however neurocognitive domains were static with assessment conducted only at baseline—a limitation of this study. In a similar study comparing work therapy alone (WT) to work therapy in combination with Neurocognitive Enhancement Therapy (WT + NET) in schizophrenia outpatients, Fiszdon et al. (2008) assessed neurocognitive change and functional change at three time points, using the Quality of Life scale (QLS; Heinrichs et al., 1984) to assess functioning. These investigators reported that improvements on the Logical Memory subtest of the Weschler Memory scale were related to improvements on the QLS. The relationship between improvements of working
memory and improvements on the UPSA, reported by Fiszdon et al. (2008) and in the present study, provide early evidence of a relationship between working memory improvements and functional improvements.

However, it should also be noted that a handful of studies have also found weak, inverse, or non-significant relationships between neurocognitive change and functional change. For example, Fiszdon et al. in the same 2008 study also reported that decline in executive functioning was related to improvement in Quality of Life. Reeder et al. (2006) assessed change in neurocognition and functioning, using the Social Behavior Schedule (SBS) to assess social functioning in the context of a treatment trial assessing the effects of cognitive remediation therapy. The investigators reported that improvements in executive functioning predicted improvements on the Social Behavior Schedule. All other relationships between neurocognition and social functioning were non-significant. Most recently, Miles et al. (2014) reported that, in a large sample of schizophrenia outpatients receiving treatment as usual, improvement or decline in cognition was not related to concurrent change in community functioning. These studies in conjunction with the present one highlight that the temporal relationship between cognition and functioning remains unclear with differences in studies likely linked to sample differences, differences in psychometric characteristics of measurement instruments, and differences in intervening treatments.
4.5 - Implications for behavioral intervention in schizophrenia

The relationship between change in cognition and change in functioning in schizophrenia remains unclear, and cross-sectional associations between these two domains do not offer the best means to identify good targets for intervention. Still, cognitive interventions for schizophrenia are widely prescribed despite a lack of research addressing whether cognitive improvement is directly related to functional improvement. Miles et al. (2014) found the domains of cognitive improvement and functional improvement to be relatively independent in their sample with only 0.5% of the overall sample demonstrating a significant change on both a cognitive test and a real world outcome domain. This finding undermines the current assumptions driving development of cognitive interventions.

The study by Miles et al. (2014), however, seems to be an outlier to the rest. A number of studies, many of which were discussed in this report, conducted in the last decade have demonstrated that change in specific facets of cognition and functioning are related (Fiszdon et al., 2008; Reeder et al., 2006). The current study also confirms that a relationship, though confined to specific aspects of cognition, exists. Establishing a consensus regarding the relationship between cognitive and functional change is critical for development and prescription of cognitive training therapies for schizophrenia and more studies assessing the relationship between change in these two domains is imperative.
4.6 – Limitations

In the current study, we examined cognitive and functional change over a 12-month period. Significant improvement was observed in domains of neurocognition but improvement was not significant on a measure of adaptive functioning. This one-year time frame may have been inadequate to capture the true relationship between cognitive and functional change, and it may be the case that cognitive improvements require more time to consolidate their effects on functional improvements. A third assessment at 1-3 years after completion of the cognitive intervention could help address this question.

Additionally, our choice of a functional outcome measure, the UCSD Performance-based Skills Assessment, likely played a role in the results that were obtained in this study. Functioning is a comprehensive, multi-faceted construct. A wealth of measures have been developed to assess functioning, and research demonstrates that different facets of cognition may relate to different facets of functioning. As portrayed earlier in Figure 1, functional assessments may assess more proximal, within-subject factors or more distal, interpersonal factors depending on what aspect of functioning is measured. Proximal assessments have factors that load more closely to cognition. On the other hand, functional assessments that approximate real-world functioning by assessing characteristics such as work status, or quality and number of interpersonal relationships are critical tools but may be less sensitive to cognitive change and may be impacted by factors external to the study (for example, availability of
competitive work in the region at the time and place of assessment or availability of social contacts in the participant’s living and work environment).

Caution should be observed in generalizing the reported relationships observed in this study between neurocognition improvement and functional improvement to other measures of outcome. The UCSD Performance-Based Skills Assessment, used in this study to assess functioning, is a performance-based, proximal measure of functioning different from distal measures such as the Quality of Life scale and the Social Behavior Schedule used in the majority of studies assessing the relationship of change in cognition and functioning (Fiszdon et al., 2008; Reeder et al., 2006). If a patient performs well on this measure of functional capacity it signifies the individual, if given the chance, could perform the tasks assessed in the community. It does not guarantee that he or she will actually or always perform the tasks when placed in the community or perform them to the degree that he or she did in a controlled and simulated testing environment. There are a number of external factors in the community, as well as internal, motivational factors that influence the individual’s ability to carry out tasks in everyday life. The lack of a more distal, community outcome measure in addition to the UPSA is a limitation of this study.

Furthermore, the ability of proximal measures of functioning to predict more distal, community functioning measures still needs to be validated. Proxy measures mediate the relationship between cognition and community functioning in multiple studies (Mausbach et al., 2008; McClure et al., 2007;
Twamley et al., 2002). While working memory and processing speed improvements were found to be related to improvements on a proxy measure of functioning in the present study, it cannot be assumed that this same relationship would be true for distal measures of functioning, especially if the observed effects can be explained by premorbid, verbal IQ factors.

Finally, it cannot be assumed that the neurocognitive improvements observed in this study are direct predictors of functional improvement. Premorbid verbal intelligence was found to explain the relationship between improvements in processing speed and functional improvements in this study. It is possible that other factors not addressed in this study explain the relationship of change between these two domains. For example, one cognitive factor not assessed in the study but reported to mediate the relationship between neurocognition and functioning is social cognition. Social cognition is typically defined in relation to social cognitive processes such as emotion processing, judgment of social cues, or theory of mind (Harvey, 2013). A meta-analysis by Fett, Viechtbauer, Penn, van Os, and Krabbendam (2011) examined how much variance in functioning could be explained by neurocognition and social cognition. When the explanatory strength of neurocognition and social cognition was evaluated, neurocognition accounted for 6% of variance in community functioning measures while social cognition explained 16% of variance. The following evidence demonstrates that social cognition is closely tied to functioning and may explain relationships between neurocognitive and functional change.
4.7 – Future directions

Correlations between a range of cognitive domains and a variety of functioning measures in schizophrenia have been reported and replicated in numerous cross-sectional studies. At a single time-point, neurocognitive performance in various domains is correlated with performance on proximal measures of functioning, social functioning measures, clinician-rated functioning, and work status. Yet, the temporal relationship between these two domains is less clear and of greater complexity. Improvement in specific domains of cognition has predicted improvement on select measures of functional status (Matza et al., 2006).

Future research should use a comprehensive neurocognitive battery but measure multiple facets of functioning, administering both proximal and distal measures of functioning at immediate and extended follow-up from behavioral intervention. Additionally, factors should be assessed that have the potential to mediate the relationship between cognitive and functional change. While not evaluated in the present study, negative symptoms and social cognition may both mediate the relationship between changes in cognition and functioning (Fett et al., 2011; Green et al., 2011). The following steps will further clarify the relationship between neurocognitive change and different means of assessing functional status in schizophrenia.
5. CONCLUSIONS

This study is among the first assessing the relationship between neurocognitive change and functional change in the context of a psychosocial treatment trial. A neurocognitive test battery assessing five of seven separable cognitive factors (Nuechterlein et al., 2004) and the UCSD Performance-Based Assessment was administered at the beginning and on cessation of two types of remediation therapy. When controlling for treatment site, treatment group, and baseline functioning, improvements in working memory and processing speed were found to predict improvements in functioning. However, only working memory was a specific predictor as premorbid verbal IQ explained the relationship between improvements in processing speed and functioning. The observed relationship between neurocognitive and functional change in this study adds to a growing body of longitudinal studies reporting associations between select facets of cognition and functioning. Clarifying the relationship between change in these two domains is crucial for validation of cognitive remediation therapies for schizophrenia that aim to improve functional outcome in patients by identifying cognition as a core treatment target. Further studies assessing the relationship between change in cognition and change in functioning across a greater number of time points will provide enhanced clarity on how these two domains interact over time.
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