

The Longitudinal Relationships between Symptoms
and Cognition in Schizophrenia

by

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ABSTRACT

This study investigated the relationship between cognitive impairment and symptoms in schizophrenia cross-sectionally and longitudinally during a year of outpatient rehabilitation in a sample of ninety-six individuals diagnosed with schizophrenia or schizoaffective disorder. Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) and individual item ratings were grouped into a five component model (positive, negative, disorganization, emotional distress and excitement) derived from statistical factor analysis (van der Gaag et al., 2006). Neuropsychological impairment was assessed with a standardized test battery that included measures of executive function, attention, emotional identification, working memory and processing speed. At baseline, disorganization symptoms were significantly related ($p < .01$) to working memory, sustained attention, ability to inhibit urges and emotional identification. Change in disorganization symptoms and change in emotional distress symptoms were significantly related to change in working memory after a year of outpatient behavioral treatment. These results are consistent with previous studies which have depicted a cross-sectional relationship between disorganization symptoms and a variety of cognitive deficits. These results are also consistent with studies supporting a relationship between change in symptoms and change in working memory over time.

1. INTRODUCTION

Schizophrenia is a mental disorder with several characteristic symptoms such as psychotic symptoms, blunted affect and disorganized speech. Cognitive impairments are now regarded as a core feature of the disorder (Bleuler, 1950).

Schizophrenia has a life time prevalence (the amount of people in the population who have been diagnosed with schizophrenia at some point in their life) of about 1% (Oltmanns & Emery, 2010). The incidence (the amount of new cases of an illness that appear in a given time period) of schizophrenia is .052% (McGrath, Saha, Welham, El Saadi, & MacCauley, 2004).

The onset of schizophrenia is 18 to 25 years of age in men and 25 to 35 years of age in women (Oltmanns & Emery, 2010). The more prevalent symptoms in males are negative symptoms and social withdrawal (Castle, Wessely, & Murray, 1993; Hafner, 2003; Oltmanns & Emery, 2010). These negative symptoms are associated with worse prognosis. This is supported by studies that show that schizophrenia in males is often more chronic and does not respond as well to treatment (American Psychological Association [APA], 2001; Leung & Chue, 2000). Even though onset is earlier and the disease is more severe in males, studies have shown no difference in the prevalence rates between the two sexes (Leung & Chue, 2004; McGrath et al., 2004).

1.1 Symptoms

Two sets of symptoms are traditionally noted: positive and negative. Positive symptoms include hallucinations and delusions and are theorized to represent an “excess” of activity (Andreasen, 2000). Hallucinations are sensory experiences in the absence of an actual environmental stimulus. In schizophrenia, hallucinations are more often auditory and not visual. Delusions, by definition, are irrational beliefs that are maintained even when the person is presented with clearly conflicting evidence. The delusions are often grandiose or paranoid and are quite personal. People of the patient’s community do not share these beliefs (Gutierrez-Lobos, Schmid-Siegal, Bankier, & Walter, 2001). Other positive symptoms include grandiosity, conceptual disorganization, excitement, suspiciousness and hostility (Kay, Flszbein, & Opher, 1987). Grandiosity is represented by a sustained, unique view of oneself during conversation that is often bizarre and supported by lavish ideas (Kay, 1991). Conceptual disorganization is reflected by an inability to organize thoughts (Kay, 1991). This is commonly assessed during the opening part of the administration of the Positive and Negative Syndrome Scale (PANSS) where the patient is able to freely talk about themselves. Excitement is identified by signs of hyper-vigilance and motor acceleration by patients while suspiciousness is rated by a state of distrust towards the interviewer by the subject (Kay, 1991).

In contrast, negative symptoms represent the “absence” of something. The most common negative symptoms are blunted affect, anhedonia, social withdrawal, alogia and avolition. Blunted affect characterizes patients who do

not show any emotion or feelings through facial expressions or body language and is reflected in observable behavior. Anhedonia, on the other hand, describes the inability to feel pleasure from activities that were once pleasurable and is reported as part of subjective experience. Blunted affect is outwardly visible to people while anhedonia is subjectively reported. Alogia, by definition, is the disruption of speech. In This is illustrated by the reduction of speech in the schizophrenia patients. Avolition describes a lack of will to complete goals.

1.2 – Diagnosis

According to the DSM-IV-TR, there are three different criteria which serve to characterize the disorder: symptoms, social and occupational impairment and duration of illness. To meet the symptom criteria patients must display or report at least two of the following: delusions, hallucinations, disorganized speech, disorganized behavior or negative symptoms (APA, 2001). These symptoms must be present for at least a month. Furthermore, the duration of illness criteria specifies that these symptoms must have been present in some sort of reduced form for at least six months. In order to meet the social and occupational dysfunction criteria, social or occupational functioning must have been significantly reduced since the onset of the disorder (APA, 2001).

1.3 – Neuropsychological deficits

Over the past twenty years, neuropsychological deficits have been identified as a core feature of the illness. Neuropsychological deficits are

disruptions in cognitive processes such as attention, language and problem solving. Initially, it was thought that these impairments were simply an artifact of other features of the illness and not clinically significant. Several studies have now shown that the majority of schizophrenia patients and even relatives of those with schizophrenia may exhibit these impairments (Faraone et al., 2000; Gottesman & Gould, 2003; Wittorf, Klingberg, & Wiedermann, 2003). These deficits are hypothesized to serve as markers of the disease, appearing as early as 4 years of age in patients at-risk for the illness (Cannon et al., 2000; Fuller et al., 2002; Gottesman & Gould, 2003; Keefe et al., 2006).

Attention is a common neuropsychological deficit in schizophrenia. A three domain system of attention has been proposed (Fan, McCandliss, Sommer, Raz, & Posner, 2002). According to this system, attention consists of focusing on a particular stimulus (orienting), sustaining an alert state (alerting) and the adjusting of attention by the executive control center. The Continuous Performance Test (CPT) has been commonly used to test the alternating component, though other reaction time tests are also considered to capture the dimension. In a recent meta-analytic study, Harvey and Reichenberg (2007) found impairments to be above moderate level in the alerting system.

Executive function is hypothesized to function as a moderator between different systems of attention thereby serving to balance our reactions toward external stimuli. Executive function is believed to play a role in a wide range of activities which include planning, decision-making, inhibition, retrieval from long-term memory and planning (Reichenberg & Harvey, 2007). One commonly

used measure of executive function is verbal fluency. Verbal fluency is the ability to retrieve verbal information from long-term memory and semantic memory. Fluency tasks assess either semantic or phonemic based information retrieval. Semantic retrieval requires the participant to generate words from a particular category such as sports or animals. On the other hand, phonemic retrieval would require the participant to retrieve information from a phonemic category such as something starting with the letter "a." The patients typically have deficits in both tasks though greater deficits are seen in the semantic fluency task (Reichenberg & Harvey, 2007). Working memory, defined as a cognitive process by which information is temporarily stored and manipulated, is likewise impaired in schizophrenia (Baddeley, 1992). The digit span task has been used to assess working memory by assessing phonological store and rehearsal aptitude (Reichenberg & Harvey, 2007). Studies have shown that this impairment is not due to attentional impairments. Aside from working memory, deficits have also been revealed in declarative memory, in particular, verbal memory. There are four different stages to memory acquisition: encoding, storing, retaining and retrieving. Most recent work suggests that the deficits are the result of problems in encoding the information (Reichenberg & Harvey, 2007). Though not as widely investigated, many aspects of learning and memory, namely classical conditioning and many examples of procedural memory, appear to be spared in schizophrenia (Kern, Hartzell, Izaguirre, & Hamilton, 2010).

It has been demonstrated that patients with schizophrenia also have deficits in motor speed. However, these deficits are not as severe as those found

in executive function and memory (Reichenberg & Harvey, 2007). Studies have shown that the attentional abnormalities do not significantly account for the deficits in neuropsychological domains.

Several studies have revealed processing speed deficits (deficits in how fast the thinker can execute mental operations) in patients with schizophrenia (Brebion, Amador, Smith, & Gorman, 1998; Egeland et al., 2003; Nuechterlein et al., 2004). It has been suggested that these deficits in processing speed may partially explain the various memory deficits in schizophrenia (Brebion et al., 1998).

1.4 Cross-sectional relationships between symptoms and cognitive deficits

Dominguez et al. (2009) performed a meta-analytic review of fifty-eight cross-sectional studies on the relationship between symptom dimensions and neuropsychological impairment. They selected four components: positive, negative, disorganized and depressive symptoms and found that the negative and disorganized factors were correlated with a majority of the nine tested cognitive domains which included executive control, verbal fluency, attention, verbal learning and memory. The largest effect sizes were found between verbal fluency, verbal learning, memory and the negative symptom dimension. With regard to the disorganized dimension only attention was linked. Positive and depressive symptom dimensions did not show any relationships with any of the measured neuropsychological domains.

1.5 Naturalistic studies of the longitudinal relationship between symptoms and cognitive deficits

Several studies have investigated the relationship between change in symptoms and a change in cognitive deficits over time in schizophrenia. For example, Hoff et al. (1999) investigated change in cognitive function and symptoms in forty-two first-episode schizophrenia patients and 16 controls over five years. Patients were assessed with the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS).

Cognitive impairment was measured using a range of different neuropsychological tests assessing areas of language, executive function, verbal memory, logical memory, spatial memory, concentration/speed, sensory-perceptual and global cognition. These test scores were then standardized using z-scores and averaged to form summary scales. The summary scores were formed on the basis of internal consistency.

When the authors looked at the change in symptoms over time they found a reduction in positive symptoms while negative symptoms minimally changed over the five year period. The investigators then compared these decreases in symptoms with the neuropsychological scale scores. They found that a decrease in positive symptoms related significantly with improvements in executive function, spatial memory, concentration/speed and global cognition. Negative symptoms were not related to neuropsychological scale scores.

Gold, Arndt, Nopoulos, O'Leary and Andreasen (1999) investigated the relationship between cognition and symptoms over a period of five years in a sample of fifty-four patients. The sample consisted of first-episode patients or patients with recent onset schizophrenia.

Symptoms were assessed using the Comprehensive Assessment of Symptoms and History (CASH). The investigators rearranged the SANS and SAPS items into a three factor model by factor analysis: positive, negative and disorganization symptoms. The patients were then reevaluated every 6 months for the five year period. There were significant improvements from baseline to the five year reassessment in all three symptom factors.

Cognitive impairment was assessed at baseline and at the five year mark. Various tests were used to assess verbal IQ, performance IQ, overall IQ, delayed visual memory, motor speed, logical memory free recall and visual search and attention. Aspects of executive function were also investigated including: speeded visual motor scanning and mental set shifting, verbal associative fluency and flexibility of the cognitive set. There was significant improvement in performance IQ, overall IQ, visual search and attention, flexibility of the cognitive set and logical memory. There was a worsening of finger-tapping speed (a test of motor speed). All other tests showed no significant change.

In contrast to Hoff et al. (1999), Gold et al. (1999) only found significant relationships between the negative symptom factor and cognitive scores. Specifically, they found that when negative symptoms improved, verbal IQ and

overall IQ also improved. There were no other significant relationships between symptoms and cognition.

They found no difference between the groups. There were no medication effects on scores of cognition or symptoms. It is also worth noting that, while all patients were on some form of antipsychotic medication, treatment was not controlled for in this study. Almost all patients were on typical antipsychotics.

In a sample of forty subjects diagnosed with schizoaffective disorder or schizophrenia, Brekke, Raine and Thomson (1995) evaluated symptoms and cognition over a period of six months. Symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS). The BPRS was rearranged into a three factor model by factor analysis: positive, negative and disorganized symptoms. The researchers administered five neuropsychological tests at baseline: three tests of visuomotor processing and two tests of auditory attentional processing. In their sample, a change in symptoms and cognition were not related to each other over time.

In Harvey et al. (1996), the relationship between negative symptoms and cognition over a one year period was assessed. The study was motivated by several past cross-sectional studies that have found a relationship between negative symptoms and various domains of cognition (Dominguez et al., 2009; Nieuwenstein et al., 2001; Strauss, 1993). In summary, the investigators' main goal was to determine if negative symptoms and cognitive impairments could be considered independent.

In order to answer their question, the authors examined a sample of 174 chronic, geriatric schizophrenic patients diagnosed based on the DSM-III-R criteria. They examined symptoms using the Positive and Negative Syndrome Scale (PANSS). The patients were examined at baseline and again one year later. Cognitive impairments were also examined twice and were assessed using the Mini Mental State Examination (MMSE). The MMSE examines attention, memory, orientation, naming and praxis. They then ran both cross-sectional and longitudinal tests to see if there was a relationship between neuropsychological impairments and positive and negative symptoms. They also looked at each negative symptom item on the PANSS separately.

If the results showed that cognitive impairments at baseline could predict negative symptoms one year later to the same degree or better than negative symptoms at baseline then the investigators could assume that cognitive impairments and negative symptoms are not independent constructs. The researchers hypothesized that this would not be the case. Rather, they predicted correlations between negative symptoms and cognitive impairments cross-sectionally and that these associations would not hold over time.

Contrary to previously reviewed studies (Harvey et al. 1996; Hoff et al. 1999) there was a significant worsening of negative symptoms over time in this study. Though previous studies (Harvey et al., 1996; Hoff et al., 1999) had also found improvement in positive symptoms over time, this study found no change in positive symptoms (Harvey et al., 1996). These results could just reflect the sample, specifically that these were older, chronic patients used in this study. It

is possible that the patients' positive symptoms had been reduced as much possible before the study began.

Just as the investigators anticipated, cognitive impairment at the end of the follow-up period was predicted only by cognitive impairment at baseline and total negative symptoms at follow-up. It was not predicted by negative symptoms at baseline. Thus, in support of their hypothesis, negative symptoms at baseline did not predict cognitive impairment at follow up.

However, contrary to the hypothesis of the investigators, cognitive impairment was a predictor of negative symptoms at both times points. In order to gain a better understanding of this relationship the investigators looked at how cognitive impairment related to each individual negative symptom. Cross sectionally, cognitive impairment was related to each negative symptom at follow up. Nevertheless, cognitive impairment at baseline was never a better predictor of individual negative symptoms at follow up than individual negative symptoms at baseline. The authors concluded that negative symptoms and cognitive impairment are related but nonetheless distinct. It seems as though certain cognitive impairments overlapped with certain negative symptoms.

Hughes et al. (2003) sought to investigate the relationship between symptoms and cognition over a six month period in a sample of sixty-two patients who were diagnosed with schizophrenia or schizoaffective disorder according to the DSM-IV. They organized the PANSS into two-, three- and five-dimensional models and compared the results across the 3 models.

The researchers hypothesized that there would be an improvement in symptoms since many of the patients were clinically unstable at study entry. Aside from the patient sample, the investigators also acquired 25 normal controls.

The cognitive areas assessed were attention, verbal and non-verbal memory, psychomotor processing and executive functioning. Each cognitive area assessed was measured with a variety of tests.

Hughes et al (2003) found that regardless of the symptom model used there was improvement, in all areas, after six months. The patient sample also showed improvement in immediate and delayed verbal memory, parts of executive function (as assessed by the Wisconsin Card Sorting Test and the Trailing Making Test) and attention.

Lastly Hughes et al. (2003) noted the relationship between symptoms and cognition cross-sectionally at baseline. Positive symptoms were not associated with neuropsychological impairment regardless of the model chosen to display symptoms. According to the two factor model, increased negative symptoms were associated with decreased IQ, executive function and memory. Cognition was, for the most part, relatively stable over time.

The findings of Hughes et al. (2003) are consistent with those of Harvey et al. (1996) who found cross-sectional relationships between negative symptoms and cognition, but these associations did not hold longitudinally. Perhaps because of less dramatic improvement in symptoms in chronic patients the relationship between symptoms and cognition is not apparent. However,

some do not find this to be an adequate explanation (Bell & Mishara, 2006). Several studies have found correlations between symptoms and cognition in first-episode patients. It is even possible that if a longer period of time was allowed before first and second evaluations an association may have been found.

Hughes et al. (2003) concluded, in chronic schizophrenia, cognition and symptoms may be related but they are still distinct constructs.

Recently, Bell and Mishara (2006) investigated the relationship between negative symptoms and neuropsychological impairment in schizophrenia over time. In this study they examined 267 chronic, schizophrenia outpatients at baseline and six months later. All the patients were on stabilized on medication. All the patients were part of a work and cognitive rehabilitation program. They also made two subgroups, one with patients who showed greater improvement in negative symptoms and one who showed significantly less improvement. They compared these groups to see if the possible relationship between cognitive impairment and negative symptoms over time could be hidden when there was only a small improvement in negative symptoms. They hypothesized that negative symptoms would relate cross sectionally to executive function, memory and motor speed. They hypothesized that these cross-sectional relationships would co-vary at follow-up.

Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). A five factor model was applied to the ratings (Bell et al., 2006). The factors were positive, negative, cognitive, excitement and emotional discomfort.

Some of the patients also received the Scale for the Assessment of Negative Symptoms (SANS), a more detailed assessment of negative symptoms.

Cognitive areas of executive functioning, attention, working memory, processing speed, visual and verbal memory, verbal learning, visual cue identification, theory of mind, thought disorder, cognitive flexibility, motor speed and verbal fluency were also assessed.

With the exception of a link between negative symptoms and processing speed the authors found very modest cross sectional relationships between negative symptom scores from the SANS and PANSS and neuropsychological impairment. Change in negative symptoms was not related to change in cognition longitudinally.

In order to explain the presence of modest cross sectional relationships in the absence of a longitudinal relationship, the authors hypothesized that poor neurocognition and more negative symptoms may be co-occurring as a syndrome without a causal relationship between the two.

Other reasons for the independence of symptoms and neurocognition over time have been proposed. Gold et al. (1994) suggested that the developmental distinctiveness of symptoms and neuropsychological impairments, the difference in response to anti-psychotics and lastly, the weak cross sectional correlations all suggest that these domains of the illness are at least somewhat independent.

Bell et al. (2006) used a sample of veteran patients and thus, as they point out, these may not be a representative sample of patients with schizophrenia

since the patients were able to enlist without showing any symptoms. They noted that the veterans may have had better premorbid functioning relative to patients taken from non-military hospitals. Better premorbid functioning could suggest a different relationship between symptoms and cognition.

In a small sample of thirty-eight schizophrenia patients, Addington and Maticka-Tyndale (1991) investigated the relationship between positive and negative symptoms and cognitive functioning over a period of six months. Symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of the Positive Symptoms (SAPS). Improvement in cognitive test scores was not related to change in negative symptoms over time. However, various cognitive test scores were related to various improvements in positive symptoms.

In a related study, Addington et al. (1997) looked specifically at the relationship between symptoms and attention in seventy-two patients who were diagnosed with schizophrenia according to the DSM-III-R. The patients were assessed at study-entry and at a three-month follow-up.

Symptomology was measured using the Positive and Negative Syndrome Scale (PANSS). Attention was assessed using the Digit Span Distractibility Test. In order to get a high score on the test the participant must be able to recall information in the presence of distractors.

At the three month follow-up there was significant improvement in both positive and negative symptoms but not in the digit span task. There were also no relationships over time between symptoms and attention. Cross-sectional

analysis showed no significant relationships between positive symptoms and attention at either time. However, there was a significant relationship between negative symptoms and attention at time 2.

In a naturalistic study without a specified intervention, Wittorf, Klingberg and Wiedermann (2003) looked at symptoms, secondary verbal memory, attention, immediate and working memory and executive function over time in schizophrenia.

The sample for this study consisted of forty-four inpatients with a diagnosis of schizophrenia according to the DSM-IV criteria. 115 first degree relatives were also tested. Positive, negative and disorganization symptoms were assessed by the PANSS. Executive functioning, vigilance, psychomotor, secondary verbal memory, immediate visual-spatial memory, immediate verbal memory, working memory, processing speed and delayed visual memory were assessed by a neuropsychological test battery. Cognitive measures were organized into four factors by principal components analysis (PCA). Factor 1 consisted of vigilance, attention and psychomotor (VAP). Factor 2 consisted of secondary verbal memory (SVM). Factor 3 consisted of immediate and working memory. Lastly, factor 4 consisted of abstraction and problem solving. Patients were assessed for a second time after one year.

All symptom dimensions (positive, negative and disorganization) showed a significant improvement. The improvements in negative symptoms were associated with an improvement in secondary verbal memory. No other relationships between cognition and symptoms were evident.

1.6 Drug trials which examined the longitudinal relationship between symptoms and cognitive deficits

Four studies have investigated the relationship of change in cognition to change in symptoms in the context of evaluating antipsychotic efficacy in schizophrenia. For example, Hagger et al. (1993) examined symptoms and cognition in thirty-six patients who were started on clozapine and a control sample of twenty-two healthy participants in a trial of the atypical antipsychotic.

Symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS). The cognitive measures administered assessed executive function, recall memory, retrieval from reference memory and attention. Symptoms and cognition were assessed at baseline, after 6 weeks and after 6 months.

At six weeks only verbal fluency improved among the cognitive measures. At six months, attention, executive functioning, retrieval from reference memory and verbal recall memory, including verbal fluency, all showed improvement. There was significant improvement in positive and negative symptoms at both follow-ups.

At six months, a reduction of negative symptoms still predicted improvement in immediate verbal recall memory. Lastly, total symptom score predicted improvement in immediate verbal recall memory at both follow-ups

In a related drug trial, also using clozapine, Galletly, Clark, McFarlane, & Weber (1997) examined the relationship between symptoms and cognition. Nineteen schizophrenia patients were assessed right before the patients began

treatment with clozapine and during the clozapine treatment. The Positive and Negative Syndrome Scale (PANSS) was used to assess symptoms. Neuropsychological impairments assessed included: attention, psychomotor speed, verbal concept formation, frontal lobe function and verbal fluency.

The researchers found significant improvement in symptoms and all measured areas of cognition with drug treatment. A reduction in negative symptoms and general psychopathology was associated with an improvement in psychomotor speed.

Controlled Oral Word Association, thought to be a test of frontal lobe function, was correlated with a reduction in negative symptoms. However, the findings between negative symptoms and frontal lobe function were mixed. The Similarities Test, thought to be related to left frontal and temporal function via functional neuroimaging studies, correlated with a reduction of positive symptoms but showed no relationship with negative symptoms

A reduction of positive symptoms and total symptoms was also associated with improvement in delayed verbal memory.

Schuepbach, Keshavan, Kmiec and Sweeney (2002), in a large sample consisting of thirty-four first-episode patients and control group of twenty-four participants, looked at the relationship between symptoms and cognition. In this study patients were assessed at baseline and again after five weeks of treatment with haloperidol or risperidone.

Symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) or the Scale for the Assessment of Positive Symptoms (SAPS).

A three factor model of symptoms was employed: positive, negative and disorganized symptoms. The neuropsychological domains assessed were as follows: verbal learning and memory, verbal fluency, attention, visuospatial perception and psychomotor skills.

Analysis revealed significant improvement in positive, negative and disorganized symptoms in both the haloperidol treated group and the risperidone treated group. Since there were no significant differences between the groups the investigators combined the haloperidol group and risperidone group in the rest of their analyses.

Verbal learning and memory were found to be significantly, but slightly, decreased at the five week follow-up. Controls had higher scores at baseline and showed improvement, not deterioration, at follow-up. Language skills, attention, nonverbal learning and reasoning and motor speed did not show any significant improvement.

The only significant finding was between a reduction in negative symptoms and improvement in verbal fluency. No other cognitive tests or symptom factors showed associations over time. The authors also noted that patients who had less improvement in negative symptoms also had worse cognitive scores. They suggested that this might point to some sort of correlation between negative symptom treatment responsiveness and cognition.

In a sample of fifty-nine disabled, treatment-resistant patients diagnosed with schizophrenia, according to the DSM-III-R, Green et al. (1997) performed a double-blind experiment analyzing the effects of haloperidol versus risperidone

on verbal memory. Patients treated with risperidone showed a significant improvement in verbal working memory while patients in the haloperidol group did not. Neurocognition was assessed at baseline and at the one and two month marks of treatment. Positive and negative symptoms were assessed using a modified version of the Brief Psychiatric Rating Scale (BPRS). The results of this showed that positive and negative symptoms were not related to the change in verbal working memory over the course of the drug trial (Green et al., 1997).

Table 1 and Table 2 provide a summary of the findings from previously longitudinal studies. Table 1 includes past findings from studies that were not drug trials. Table 2 presents the findings from the past drug-trials. In summary, the past findings were quite mixed but the drug trials suggest a stronger relationship between changes in symptoms and cognition than in studies focusing on stabilized outpatients with presumably low-levels of baseline symptoms.

The current study was designed to assess the relationship of changes in symptoms to changes in cognition in an archival analysis of records from a sample of largely chronic, stabilized outpatients with schizophrenia collected from 2001 - 2011 using a “state-of-the-art” five-factor approach to categorization of psychiatric symptoms (Van der gaag, 2006). Based on our extant analysis of the literature, we hypothesized that the changes in the disorganization factor would relate to changes on measures of executive function. We also predicted a relationship between the negative symptom factor and a wide range of cognitive domains. This was supported by past research that

found relationships between negative symptoms and executive function, memory, verbal fluency, overall IQ and verbal IQ (Galletly et al., 1997; Gold et al., 1999; Hagger et al., 1997; Harvey et al., 1996; Hughes et al., 2002; Schuepach et al., 2002; Wittorf et al., 2003). The one study that used a five factor model to investigate the relationship between symptoms and cognition found no relationships between symptoms and cognition over time (Bell and Mishara, 2006).

1.7 Possible underlying variables

Past studies have examined the effect of possible confounding variables on the evaluation of neuropsychological impairment and symptoms. As discussed above, there does not seem to be a significant effect of attention deficits on other cognitive domains. The effects of medication and illness duration have often been quite limited (Reichenberg & Harvey, 2007).

Table 1

Summary of the longitudinal studies of symptoms versus cognitive deficits in non-drug trial related studies

Paper	Sample Characterization	Conclusions
Addington et al., 1991	hospitalized patients	<ul style="list-style-type: none"> • positive symptoms related to memory, executive function, IQ and performance IQ, attention and working memory • negative symptoms were

		not related to cognitive impairments
Addington et al., 1997	stabilized outpatients	<ul style="list-style-type: none"> no relationships between symptoms and attention
Bell & Mishara, 2006	stabilized outpatients	<ul style="list-style-type: none"> no relationships between symptoms and neuropsychological impairments over time.
Brekke et al., 1995	first-episode patients and recent onset patients	<ul style="list-style-type: none"> no relationships between symptoms and cognitive impairments
Gold et al., 1999	first-episode patients and recent onset patients	<ul style="list-style-type: none"> negative symptoms were related to verbal IQ and overall IQ
Harvey et al., 1996	chronic, geriatric patients	<ul style="list-style-type: none"> negative symptoms were predicted by baseline and follow-up cognitive impairments
Hoff et al., 1999	First-episode patients	<ul style="list-style-type: none"> positive symptoms were related to executive function, spatial memory, concentration/speed and global cognition negative symptoms were not related to anything
Hughes et al., 2003	chronic, stabilized on medication outpatients	<ul style="list-style-type: none"> negative symptoms were related to IQ,

Wittorf et al., 2003	hospitalized patients	<p>executive function and memory</p> <ul style="list-style-type: none"> • negative symptoms were related to verbal memory
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Table 2

Summary of the longitudinal studies of symptoms versus cognitive deficits in drug trials

Paper	Sample Characterization	Conclusions
Galletly et al., 1997	n/a	<ul style="list-style-type: none"> • general psychopathology and negative symptoms were related to psychomotor speed • positive and negative symptoms were related to frontal lobe function
Green et al., 1997	n/a	<ul style="list-style-type: none"> • positive and negative symptoms were not related to changes in verbal working memory
Hagger et al., 1993	treatment-resistant patients	<ul style="list-style-type: none"> • negative symptoms and total symptoms were related to immediate verbal recall
Schuepbach, 2002	first-episode patients	<ul style="list-style-type: none"> • negative symptoms were related to verbal fluency

2. METHODS

2.1 – Participants

Ninety-six consenting participants diagnosed with schizophrenia or schizoaffective disorder according to the DSM-IV (American Psychiatric Association 1994) as assessed by the Structured Clinical Interview for DSM-IV (First et al., 1995) participated. Data for this study was collected as part of an ongoing study of cognitive remediation (Kurtz et al., 2007). Patients were excluded who had visual or auditory impairments, neurological illnesses other than schizophrenia, traumatic brain injury, evidence of mental disability, substance abuse or lack of proficiency in English. Most patients were recruited from the Institute of Living in Hartford, Connecticut (n=84) as part of an outpatient program, other patients were recruited from community mental health centers in Meriden, Connecticut (n=8) and East Hartford, Connecticut (n=4). Additional exclusion criteria for this study included patients who did not have PANSS scores at both assessment periods. Patients who did not have CVLT scores at both time periods were also excluded. Demographic variables are displayed in Table 3.

Table 3
Demographics for the overall sample (n=96).

Variable	Mean (SD)	Range
Age	33.82 (11.585)	19 – 59
Sex % (M/F)	71.9 / 28.1	
Education	12.89 (2.307)	6 – 18
Duration of Illness	10.47 (10.282)	0 – 40

Number of Hospitalizations	4.15 (3.567)	0 – 20
Age of Onset	23.4484 (7.46266)	13 – 46

Additional: SD: standard deviation

2.2 – Symptom assessment

Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The PANSS is a semi-structured interview that assesses symptoms on 30 different items on a clinician rated 7-point Likert scale.

Symptom scores were organized according to a five component model with the categories of positive, negative, disorganization, excitement and emotional distress (van der Gaag, 2006). Symptoms were grouped according to factor analysis. The van der Gaag model was made to be *complex* meaning that some items can be found in more than one category due to the fact that they may have multiple causes (van der Gaag et al., 2006). This allows the model to incorporate different underlying causes and recognize that the symptoms do not only apply to a particular factor. The *positive* factor consisted of items: P1, P3, G9, P6, P5, G1, G16, N5 and G12. The *negative* factor: N6, N1, N2, N4, G7, N3, G16, P2, G13 and G8. The *disorganization* factor: G9, N7, G11, G10, P2, N5, G5, G12, G13, G15. The *excitement* factor: P5, N3, G16, G14, P4, P7, G8 and G4. The *emotional distress* factor: P6, G1, G16, G15, G2, G6, G3 and G4.

2.3 – Neuropsychological measures

The participants received a neuropsychological test battery at two different occasions. Tests were chosen which we felt could accurately measure

working memory, verbal learning, reasoning and problem solving, social cognition and processing speed.

2.3.2 – California Verbal Learning Test-II (Delis et al., 2000)

The CVLT-II assesses verbal learning. This includes immediate, short and long-term recall. In this test the patient is asked to recite 16 words which are read to them. The words come from 4 different semantic categories and the same words are read to the subject in 5 consecutive trials. The test measures how many words the patient can recall and also how that number improves over the trials. This data is then compared to an average in order to understand the subject's verbal learning, verbal memory and semantic organization.

2.3.3 – Penn Conditional Exclusion Test (PCET; Kurtz et al., 2004)

The PCET assesses problem solving and reasoning. In the test participants are required to select which one out of four shapes based on a sorting rule. After several rounds, or if the participant makes the correct choice 10 times, the rule switches and participant is expected to discover the new rule. Participant errors were measured on a standardized scale

2.3.4 – Working Memory Index (WM; Wechsler, 1997)

The WMI is a score of working memory and attention that is offered as part of the Wechsler Adult Intelligence Scale. The score is composed of performance on a digit span task and a letter-number sequencing task. In the

digit span task the participant is asked to repeat a list of numbers back to the investigator who records how many numbers the subject could repeat in the same order. The subject may also be asked to repeat the numbers in the reverse order. The letter-number sequencing task requires the subject to put a mixed list of numbers and letters into numerical and alphabetical order.

2.3.5 – Processing Speed Index (PSI; Wechsler, 1997)

The PSI is used to assess processing speed through the Wechsler Adult Intelligence Scale. The index score is based on the subject's ability to perform a symbol search. In this test 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. Other tests that are part of the PSI measure visual-perceptual speed and visual-motor coordination.

2.3.6 – Penn Continuous Performance Test (PCPT; Kurtz et al., 2000)

The PCPT is a test which measures sustained attention and impulsivity. The idea is that the subject should be able to focus on one thing without being distracted by competing stimuli. In this test the subject sees vertical and horizontal lines in different positions and is asked to respond when they arrange to form a digit. The investigator then measures true positives along with the reaction time of the participant. The lines also rearrange to form distractor symbols, and the goal is for the participant to ignore these.

2.3.7 – Penn Emotional Acuity Test (PEAT)

This test is meant to assess emotional identification and emotional discrimination. In this task the subject is presented with 40 black-and-white photographs depicting various emotional states. The participant is asked to rank the face on a scale from 1-to-7 with 1 being ‘very sad’ and 7 being ‘very happy.’ The number of correct responses or responses within 1 point of the correct value on the scale is measured.

2.4 – Data Analysis

SPSS 19.0 was used to analyze the data. All scores used in the data analysis were standardized. For tests in which standardized scores were not present they were converted by subtracting the mean and dividing by the standard deviation. In order to look at the data over time the difference between follow-up and baseline between each symptom factor and neuropsychological test was taken. Pearson correlations were run between demographic variables (age, gender, illness duration, education and age of onset) and study variables in order to explore their relationships. Present relationships, with demographic variables, were controlled for in subsequent partial correlations between the various study variables.

The same process was followed for the analysis of the data at baseline. Pearson correlations were run between the demographic variables and study

variables. Significant relationships were then controlled for in the following analysis of study variables.

3. RESULTS

3.1 – Cross-sectional analysis at baseline

Cross-sectional relationships between study variables and sample demographics, at time 1, are shown in Table 4 & 5. Age was directly related to positive symptoms ($r=0.285$, $p<.01$), disorganized symptoms ($r=0.314$, $p<.01$) and emotional distress symptoms ($r=0.358$, $p<.01$). Age was inversely related to PCET ($r=-0.277$, $p<.01$) and PEAT ($r=-0.517$, $p<.01$) scores. Education was directly related to WMI ($r=0.292$, $p<.01$) and PCPT ($r=0.310$, $p<.01$) scores. Illness duration was directly related to disorganization symptoms ($r=0.319$, $p<.01$) and inversely related to PCET ($r=-0.320$, $p<.01$) and PSI ($r=-0.345$, $p<.01$) scores.

The significant results, stated above, were controlled for in the subsequent partial correlations between the symptom factors and standardized neuropsychological test scores at baseline. The disorganization symptom factor was inversely related to WMI ($r=-0.386$, $p<.01$), PEAT ($r=-0.543$, $p<.01$) and PCPT ($r=-0.288$, $p<.01$). These results are presented in Table 6.

Table 4

Demographic & symptom factor variables intercorrelations at baseline (n=96).

	Positive	Negative	Disorg	Emotional Distress	Excite
Sex	0.073	-0.105	-0.03	-0.029	-0.153
Age	0.285*	0.082	0.314*	0.358*	0.206
Education	-0.095	0.157	-0.031	0.195	0.167
Illness Duration	0.192	0.102	0.319*	0.262	0.141
Age of Onset	0.153	-0.048	0.022	0.164	0.096

Additional: * p<.01.

Table 5

Demographic & standardized neuropsychological variables intercorrelations at time 1(n=96).

	CVLT	WMI	PCET	PEAT	PCPT	PSI
Sex	0.198	-0.194	-0.083	-0.207	-0.012	0.116
Age	-0.239	-0.142	-0.277*	-0.517*	-0.161	-0.239
Education	0.131	0.292*	-0.022	-0.153	0.310*	0.131
Illness Duration	-0.053	-0.112	-0.320*	-0.344	-0.102	-0.345*
Age of Onset	0.114	-0.115	0.003	-0.307	-0.161	0.045

Additional: * p<.01. CVLT: California Verbal Learning Test-II; WMI: Working Memory Index; PCET: Penn Conditional Exclusion Test; PEAT: Penn Emotional Acuity Test; PCPT: Penn Continuous Performance Test; PSI: Processing Speed Index.

Table 6

Correlations between study variables at baseline (n=96).

	Positive	Negative	Disorg	Emotional Distress	Excite
CVLT	0.080	-0.024	0.209	-0.128	0.147
WMI	-0.048	-0.069	-0.386*	0.075	-0.024
PCET	-0.064	-0.068	-0.255	-0.186	0.386
PEAT	-0.122	-0.253	-0.543*	0.037	-0.116
PCPT	-0.053	-0.391	-0.288*	-0.072	-0.201
PSI	-0.127	-0.117	-0.152	0.085	-0.005

Additional: *p<.01. CVLT: California Verbal Learning Test-II; WMI: Working Memory Index; PCET: Penn Conditional Exclusion Test; PEAT: Penn Emotional Acuity Test; PCPT: Penn Continuous Performance Test; PSI: Processing Speed Index.

3.2 – Relationship between sample characteristics and longitudinal study variables

Correlations between gender, age at testing, education, illness duration and age of onset with the study variables are shown in Table 7 and Table 8. Age was inversely related to positive symptom change ($r=-.202$, $p < .05$) age of onset was directly related to PSI change ($r= .294$, $p<.01$).

Table 7

Demographic & symptom study variables intercorrelations for variables (n=96).

	Positive	Negative	Disorg	Emotional Distress	Excite
Sex	-.088	-.080	.075	-.084	.029
Age	-.202*	.115	-.128	-.126	-.057
Education	.014	.071	-.081	-.058	-.058
Illness Duration	-.113	.145	-.130	-.085	-.009
Age of Onset	-.128	.040	.023	-.030	-.035

Additional: * $p<.01$.

Table 8

Demographic & neuropsychological study variables intercorrelations for variables (n=96).

	CVLT	WMI	PCET	PEAT	PCPT	PSI
Sex	-.039	.000	.056	.231	.112	-.052
Age	.014	.171	-.092	.021	.012	-.111
Education	-.061	.025	-.025	.17	-.14	.132
Illness Duration	-.084	.231	-.046	.018	.164	.055
Age of Onset	.162	-.054	-.077	-.016	-.209	-.294*

Additional: * $p < .01$. CVLT: California Verbal Learning Test-II; WMI: Working Memory Index; PCET: Penn Conditional Exclusion Test; PEAT: Penn Emotional Acuity Test; PCPT: Penn Continuous Performance Test; PSI: Processing Speed Index.

3.3 – Correlations among longitudinal study variables

Correlations among standardized neuropsychological change scores and symptom change scores are shown in Table 9. Demographic variables were controlled for where deemed appropriate according to Table 7 and Table 8. WMI score was inversely related to disorganization symptoms ($r = -.248$, $p < .01$) and emotional distress symptoms ($r = -.272$, $p < .01$) over time.

Table 9
Correlations between study variables (n=96).

	Positive	Negative	Disorg	Emotional Distress	Excite
CVLT	.082	.067	.075	-.091	-.177
WMI	-.198	.012	-.248*	-.272*	-.036
PCET	.145	.147	-.201	.027	.011
PEAT	-.049	-.054	-.088	-.096	.028
PCPT	.077	.019	-.141	.024	-.133
PSI	-.003	-.050	-.184	-.123	-.089

Additional: * $p < .01$. CVLT: California Verbal Learning Test-II; WMI: Working Memory Index; PCET: Penn Conditional Exclusion Test; PEAT: Penn Emotional Acuity Test; PCPT: Penn Continuous Performance Test; PSI: Processing Speed Index.

4. DISCUSSION

4.1 – Our hypothesis & the cross-sectional relationships

The cross-sectional relationships, for the most part, agreed with the hypotheses of this study. We hypothesized that the disorganization symptom factor would relate to all the neuropsychological tests due to its previously documented relationships with verbal learning, executive function and attention. No relationships were found between verbal learning and verbal memory, problem solving and processing speed and the symptom factors. Disorganization symptoms were related to working memory, emotion identification and sustained attention skills. This means that at baseline more disorganization symptoms were related to worse working memory, emotion discrimination and sustained attention. Many of these cross-sectional relationships disappeared over time. This is discussed in more detail in section 4.4.

4.2 – Working memory and symptoms

In this study there were several relationships between working memory and symptoms. Specifically, at the first testing, working memory was inversely related to the disorganization symptom factor. The only longitudinal relationships between cognition and symptoms included working memory. More specifically, change in working memory was found to be inversely related to change in disorganization symptoms and change in emotional distress

symptoms. That is, when disorganization symptoms and emotional distress symptoms got worse, working memory also got worse.

The results of this study are mixed with regard to past research. Carter et al. (1996) reported a relationship between working memory and negative symptoms. However, there were a few drawbacks and differences between their study and the present one. One, the relationship was found specifically between spatial working memory and negative symptoms. Second, symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) rather than the Positive and Negative Syndrome Scale (PANSS). Another difference was that symptoms were not arranged according to a five-factor model. Lastly, this study involved patients being withdrawn from antipsychotic medication before being tested. In the sample analyzed in this study, the patients were stabilized on antipsychotic medication.

Green et al. (1997) did not find any relationship between positive and negative symptoms and working memory over time. It is reasonable to assume that our study, in which patients were stabilized on a range of anti-psychotic medications, would show different results than a drug trial where patients may be treatment resistant or clinically unstable.

Park et al. (1999) had mixed results. The results of the study supported the cross-sectional relationships between working memory and symptoms presented in this study. However, over time they did not find any relationship between working memory and symptoms. Similar to the previously discussed studies, this study had a few limitations. One, the study did not use a five-factor

model; however, symptoms were assessed by the PANSS so potentially relevant conclusions could probably be still drawn. Second, the findings related specifically to spatial working memory.

It is clear, based on the results presented in this study and the results of other investigators (Park et al., 1999; Green et al., 1997; Carter et al., 1996) that the relationship between working memory and symptoms in schizophrenia over time is still unclear. Nonetheless, it is important that these results are replicated. A future study should also incorporate relatives of schizophrenia patients and controls. This will allow for the examination of the relationship in more detail, specifically, whether or not working memory is a marker for schizophrenia. Working memory has been suggested as a marker for schizophrenia by several investigators (Keefe et al., 2006; Gottesman & Gould, 2003; Wood et al., 2003; Fuller et al., 2002; Cannon et al., 2000; Park et al., 1999).

4.3 – Our hypothesis & the other study variables

With the exception of the relationships between working memory and disorganization and emotional distress symptoms, no other relationships were found over time between study variables. This was in disagreement with our hypothesis in which we predicted that the negative symptom factor would be related to various aspects of cognition. This prediction was based on several studies (Wittorf et al., 2003; Hughes et al., 2002; Schuepach et al., 2002; Gold et al., 1999; Galletly et al., 1997; Hagger et al., 1997; Harvey et al., 1996). However,

none of these studies used a five-factor model of symptoms. It is possible that the link does not exist in this five-factor symptom model.

The findings of this study partially oppose Bell and Mishara (2006). They were the one of the few previous studies who used a similar five-factor model in their analysis of symptoms and cognition over time. They concluded that symptoms and cognition showed no relationship over time. Our relationship between working memory and disorganization/emotional distress symptoms opposes this broad conclusion.

4.4 – The disappearance of the PEAT & PCPT cross-sectional relationships over time

At baseline, the disorganization symptom factor was strongly related to PEAT score and PCPT score. This means that as there is an increase in symptoms there is a decrease in emotional identification, emotional discrimination, sustained attention and ability to control impulses. These relationships were not present longitudinally.

There are several explanations for the lack of longitudinal relationships. It is possible that this relationship was present at baseline due to confounding factors. However, this reasoning seems unlikely because this study controlled for most of the major demographic variables that showed a significant relationship with the study variables (sex, age, illness duration, education and age of onset).

Another explanation is that there is a difference in the course of attention and emotion in schizophrenia, in contrast to working memory (which showed

both a cross-sectional relationship and longitudinal relationship). This reasoning is supported by studies by Addington et al. (1997) in which attention was not found to be related to symptoms over time.

Third, the results could reflect the nature of the disorder. In schizophrenia, symptoms tend to fluctuate while cognition tends to remain more stable. This is a particularly important point because our sample consisted of young to middle-aged outpatients on stabilized medications with average illness duration of 10 years. Several studies have shown that a sample of this demographic do not show any neurocognitive deterioration over time (Kurtz, 2005; Gold, 2004; Heaton et al., 2001; Gold et al, 1999;, Hoff et al., 1999; Censits et al., 1997). However, symptoms, especially positive symptoms, will commonly experience significant change (Censits et al., 1997). This cognitive stability holds regardless of illness duration in outpatients. (Kurtz, 2005). Therefore, it is possible that the change in cognition over time is too small to show any relationship with symptoms over time even if they are related cross sectionally.

4.5 – Clinical importance of findings

Regardless of the present findings, the relationships between disorganization and emotional distress symptoms and working memory over time are of clear clinical importance. With replications of this study, one may be able to suggest a causal relationship. For example, in the specific case of the presented finding between working memory and symptoms, treatment programs could be targeted at the improvement of disorganization/emotional

distress symptoms with the goal of improving working memory or vice-versa. Any further understanding of the pattern of cognitive deficits and symptoms will help to improve patient functional outcome.

4.6 – Future Directions & Prefrontal Cortex Dysfunction

Our finding linking working memory and disorganization symptoms cross-sectionally and over time has implications for previous research on the role of the right dorsolateral prefrontal cortex (DLPFC) in schizophrenia. Lesion studies and neuropsychological testing have provided evidence for the role of the right DLPFC during working memory tasks. Functional imaging studies have also demonstrated that the right DLPFC is used during tasks involving working memory (Perlstein et al., 2001).

Several studies have suggested that there is a relationship between working memory and right DLPFC activity in people with schizophrenia. Investigators have found that when patients with schizophrenia performed tasks involving increased working memory load they performed worse and showed a decrease in activation in the right DLPFC (Perlstein et al., 2003; Manoach, 2002; Perlstein et al., 2001; Carter et al., 1998). Some researchers have gone further; they have suggested that disorganization symptoms are also implicated in this relationship. Perlstein et al. (2001) found that this relationship between working memory and decreased right DLPFC activation was also associated with disorganization symptoms. Their theory holds that disorganization symptoms are related to right DLPFC dysfunction only in cases where this right DLPFC is

related to working memory deficits. These findings have created a niche for future research. Future research should be aimed at more fully characterizing right DLPFC activity during working memory tasks because past research on the subject is still mixed. For example, recent studies have suggested that there is actually an increase of activation in the right DLPFC, not hypoactivity (Manoach, 2003).

In summary our findings demonstrate a relationship between disorganization symptoms, working memory, emotion identification and attention at baseline and disorganization and emotional distress symptoms and working memory longitudinally. The relationship between disorganization systems and working memory is particularly strong at baseline. Future studies should be aimed at fully exploring the relationship between disorganization symptoms and working memory and seeing how the relationship fits with activity in the right dorsal lateral prefrontal cortex.

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