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Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: A meta-analysis☆

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Abstract

Background—Neurocognitive functioning in schizophrenia has received considerable attention because of its robust prediction of functional outcome. Psychiatric symptoms, in particular negative symptoms, have also been shown to predict functional outcome, but have garnered much less attention. The high degree of intercorrelation among all of these variables leaves unclear whether neurocognition has a direct effect on functional outcome or whether that relationship to functional outcome is partially mediated by symptoms.

Methods—A meta-analysis of 73 published English language studies (total n = 6519) was conducted to determine the magnitude of the relationship between neurocognition and symptoms, and between symptoms and functional outcome. A model was tested in which symptoms mediate the relationship between neurocognition and functional outcome. Functional outcome involved measures of social relationships, school and work functioning, and laboratory assessments of social skill.

Results—Although negative symptoms were found to be significantly related to neurocognitive functioning ($p < .01$) positive symptoms were not ($p = .97$). The relationship was moderate for negative symptoms (r=−.24, n = 4757, 53 studies), but positive symptoms were not at all related to neurocogniton ($r = .00$, n= 1297, 25 studies). Negative symptoms were significantly correlated with

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Contributors
Joseph Ventura conceived the study design, data analysis plan, conducted literature searches, supervised the conduct of the study, and wrote the manuscript Dr. Hellemann conducted the data analysis and commented on all drafts of the manuscript. Ms. Thames performed literature searches, created tables, and commented on all drafts of the manuscript. Ms. Koeller conducted literature searches and organized study papers. Dr. Nuechterlein provided consultation of concepts we addressed and edited the final manuscript. All authors have contributed to and approved the final manuscript.

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None of the authors has a financial conflict of interest.

functional outcome (r =−.42, p<.01), and again the correlation was higher than for positive symptoms (r = −.03, p = .55). Furthermore, our findings support a model in which negative symptoms significantly mediate the relationship between neurocognition and functional outcome (Sobel test p <.01).

Conclusions—Although neurocognition and negative symptoms are both predictors of functional outcome, negative symptoms might at least partially mediate the relationship between neurocognition and outcome.

Keywords

Meta-analysis; Schizophrenia; Neurocognition; Positive symptoms; Negative symptoms; Mediation model; Sobel test; Functional outcome

1. Introduction

Perhaps one of the most contemporary and compelling issues in schizophrenia research today is the understanding of the relative contribution of neurocognitive deficits and psychiatric symptoms to functional outcome. Neurocognitive deficits continue to be widely accepted as a core feature of the disorder (Green et al., 2004; Bellack et al., 2007; Harvey et al., 2006) because they are present not only in chronic patients when they are acutely ill, but also during periods of symptom remission. Similar deficits have also been found in first episode patients (Saykin et al., 1994; Albus et al., 1996; Bilder et al., 2000; Hoff and Kremen, 2003; Hoff et al., 2005). Several literature reviews that have included cross-sectional and longitudinal data demonstrate that neurocognitive functioning is a strong predictor of community functioning, such as social functioning, work performance, and social skills (Green, 1996; Green et al., 2000). In general, these studies conclude that neurocognitive functioning more robustly predicts functional outcome than do symptoms, especially positive symptoms (reality distortion). In contrast to the recent emphasis of the impact of neurocognitive deficits on functional outcomes in schizophrenia, psychiatric symptoms have received relatively less attention as predictors but are nonetheless significantly associated with community outcomes.

Several cross-sectional studies have suggested that performance on neurocognitive tests is correlated with at least one of the three of the major symptom factors, positive, negative, or disorganization (Roy and DeVriendt, 1994; Davidson and McGlashan, 1997; Rund et al., 1997; Addington and Addington, 1999, 2000; Brazo et al., 2002, 2005). Most of the studies seem to have found a stronger cross-sectional relationship with negative symptoms than with positive symptoms, non-disorganizing type (Harvey et al., 1998; Heaton et al., 1994; Corrigan and Toomey, 1995; Harvey et al., 2006; Keefe et al., 2006a,b). A substantial body of literature suggests that symptoms of disorganization, when reported as a separate factor, are also strongly related to neurocognition and warrant a separate empirical study. In particular, attentional deficits and poor performance in verbal fluency have been linked to severity of negative symptoms (Nuechterlein et al., 1986; Kerns et al., 1999; Howanitz et al., 2000). In addition, there is some evidence to suggest that negative symptoms or deficit syndrome patients have particular impairments in reasoning and problem solving (executive functioning) and on tests of motor functions as compared to memory functions (Cuesta et al., 1995; Berman et al., 1997; Zakzanis, 1998; Bryson et al., 2001; Bozikas et al., 2004); (Brazo et al., 2005). One study linked the severity of negative symptoms to IQ (Carlsson et al., 2006) while contradictory results of other studies show that this finding is not consistent (Simon et al., 2003; Brazo et al., 2002; Bozikas et al., 2004). Some have argued that schizophrenia patients with the greatest cognitive impairments have the most prominent negative symptoms (Brazo et al., 2005; Villalta-Gil et al., 2006). Thus, at least on a cross-sectional basis, neurocognition is linked to psychiatric symptoms (Harvey et al., 2006).

Although psychiatric symptoms have received relatively less emphasis recently as predictors of functioning, they are nonetheless significantly associated with community outcomes (Addington and Addington, 1999; Dickerson et al., 1999a,b; Norman et al., 1999; Addington and Addington, 2000; Suslow et al., 2000; Smith et al., 2002; Dickinson and Coursey, 2002; Malla et al., 2002; Hoffmann et al., 2003; McGurk et al., 2003; Lysaker and Davis, 2004; Milev, 2005; Pencer et al., 2005; Hofer et al., 2006; Bowie et al., 2006; Bozikas et al., 2006). Interestingly, positive (non-disorganizing) symptoms appear to interfere less with social and work functioning than do negative symptoms, yet both symptom groups appear to make independent contributions to community functioning (Pogue-Geile and Harrow, 1984; Breier et al., 1991; Herbener and Harrow, 2004). For instance, negative symptoms have predicted deficits in community functioning for up to two years following baseline assessments (Breier et al., 1991; Beng-Choon et al., 1998; McGlashan and Fenton, 1992; Herbener and Harrow, 2004). Despite the number of theorists who conclude that neurocognitive deficits should take center stage in predicting functional outcomes, there are compelling arguments and data suggesting that the importance of symptoms, in particular negative symptoms, should not be overlooked (Brekke et al., 2005; Harvey et al., 2006). The consistency of the cross-sectional association between negative symptoms and neurocognitive functioning, combined with the results of studies that examine symptoms as predictors of functional outcome, warrants further investigation of these complex relationships. This line of research raises the question of whether negative symptoms might mediate some of the associations observed between neurocognitive performance and functional outcome in schizophrenia.

This meta-analysis was conducted to determine if the relationship between neurocognitive functioning and functional outcome is mediated by the extent of positive (non-disorganizing) or negative symptoms in patients with schizophrenia. We hypothesized that the meta-analysis would support a mediation hypothesis for negative symptoms based on the strength of the relationship between neurocognition and negative symptoms, and negative symptoms and outcome.

2. Methods

2.1. Review procedures

A literature search was conducted in scientific journals covering the period from 1977 to December 31, 2006. The following databases were used in the literature search: *PsychInfo, PsychAbstracts, EBSCOhost, PubMed,* and *Social Sciences Citation index.* Searches were restricted to articles published in the English language. The following key search terms in schizophrenia were used (some terms were combined): *neurocognition, neuropsychology, working memory, verbal learning and memory, executive functions, problem solving, attention/vigilance, symptoms, skills assessment, social functioning, work performance, and functional outcome*. The reference lists of published articles were also searched to locate additional studies that were relevant. We cannot be certain that we were able to locate all of the published English language papers that met our inclusion criteria, but we were able to obtain a sufficiently representative number of relevant papers for empirical analysis.

Using these methods, over 200 articles were identified as potentially relevant to this topic. The inclusion criteria were as follows: (1) study must have used empirical methods and been published in a peer reviewed journal; (2) contained descriptions of study measures and operational definitions of variables; (3) used structured assessments of symptoms with established scales or standardized methods of symptom assessment; (4) neurocognitive functioning was assessed using standardized batteries; (5) all participants in the study must have been diagnosed with schizophrenia or schizoaffective disorder according to DSM criteria (6) statistics reported must have been correlation coefficients or other statistics that could be converted into correlations (e.g. *F*-statistic, *t*-statistic) so that an effect size and *z* score could

be calculated, and (7) sample data from a study were not included or published previously in another paper.

One hundred and eleven articles were eliminated due to not meeting these criteria. An additional 26 were excluded because the statistics they reported could not be converted into effect sizes or correlations for statistical analyses. A total of 73 studies met all the criteria (Table 1) which included 6519 patients. There were three primary categories of studies (see Table 1), those that examined (1) the relationship between neurocognition and symptoms, (2) the relationship between symptoms and functional outcome, and (3) interrelationships of all three. Studies of both inpatients and outpatients were included. If a study included cross-sectional and longitudinal analyses, we included only the cross-sectional data into our meta-analysis. We considered an interval between observations of less than 90 days to be cross-sectional. For each of the 73 studies a record was created that included (1) a description of the neuropsychological tests, e.g., Wisconsin Card Sorting Test (WCST), California Verbal Learning Test (CVLT), (2) symptom measures, e.g., Scale for the Assessment of Positive Symptoms (SAPS), Scale for the Assessment of Negative Symptoms (SANS), (3) measures of functional outcome, e.g., QOL, (4) study statistics, e.g., correlation coefficients, and (5) study characteristics, such as gender ratio, patient status, diagnosis, location.

2.2. Defining neurocognition, positive and negative symptoms, and functional outcome

For the current study, *neurocognition* was operationally defined as cognitive processes that are measurable with structured neuropsychological tests, such as verbal learning and memory (Table 2). Selection of neurocognitive domains for analysis was guided by the MATRICS initiative (Nuechterlein et al., 2004). The current study included 6 of the 7 MATRICS domains of cognitive functioning: speed of processing, attention/vigilance, working memory, verbal learning visual learning, and reasoning and problem solving, but not social cognition. Because social cognition may itself be a mediator between neurocognition and functional outcome (Brekke et al., 2005;Sergi et al., 2006), we excluded it from this examination of symptom mediators between neurocognition and functional outcome.

The construct of *symptoms* included positive and negative symptom dimensions as measured by structured instruments (Table 2). Positive symptoms consisted of hallucinations and delusions (reality distortion) which were considered conceptually different from symptoms of disorganization (Dibben et al., 2009;Nieuwenstein et al., 2001). For the current analysis, we considered only the relationship between reality distortion and neurocognition, and reality distortion and functional outcome. We excluded a separate consideration of the relationship between symptoms of disorganization and neurocognition because this topic warrants an independent investigation. Therefore, studies or analyses were excluded that had combined disorganization with positive symptoms (reality distortion), e.g., the PANSS positive symptom factor which includes delusions, hallucinations, and conceptual disorganization, the total score from the SAPS which combined reality distortion, bizarre behavior, and formal thought disorder. For the definition of negative symptoms, we considered only those scales which measured negative symptoms, e.g., SANS, or had negative symptom items that were clustered together or were created through factor analysis, e.g., PANSS negative symptom factor.

The construct of *functional outcome* was divided into community functioning, skills assessment, and functional capacity (Table 2). Community functioning included work or school performance, social functioning, independent living, and quality of life. Social skill was measured in the laboratory using structured measures, e.g., a role-play test such as the Assessment of Interpersonal Problem-Solving Skills (AIPSS), and functional capacity, e.g., the University of San Diego Performance-Based Skills Assessment. Social skills and functional capacity are considered intermediate variables rather than direct measures functional outcome.

2.3. Data analysis procedures

For the main analysis we combined all 6 domains of neurocognitive functioning and created one composite neurocognitive variable to represent neurocognition. There were a sufficient number of studies for analysis in each of the separate domains that examined the relationship between neurocognition and symptoms, and also between symptoms with functional outcome. The relationship between neurocognition and functional outcome (estimated r =.30) was based on the meta-analysis by Green et al. (2000). Correlation matrices were constructed based on aggregated estimates of neurocognition, positive and negative symptoms, and functional outcomes. These 3 by 3 correlation matrices were derived by first transforming the observed (published) correlations in each study using Fisher's *r*-to-*z* transformation. Where indicated, multiple results were averaged from the same domain, e.g., several tests of working memory were combined into a single observation for that study. The correlation coefficients were then combined into a single estimate of the population correlation by averaging them weighted by sample size (Hedges and Olkin, 1984). Based on these combined correlation coefficients, the studies were then tested for homogeneity by calculating a *Q*-statistic. Every neurocognitive domain proved to be heterogeneous at the .05% level. Some of the studies that contained multiple measures of the same neurocognitive variables showed evidence that the measures were heterogeneous even within studies. However, there were not enough examples of each particular test from different studies to conduct a random effects model controlling for both study and within-study measurement effects. As heterogeneity of measures is a known problem in the field, and because of the fact that the question of the adequate multivariate alpha level of a multi-*Z* study is not yet solved (Hafdahl, 2007), the decision was made to continue the analysis using all studies in our sample. Although the significance of the reported *p*-values may be exaggerated, the data presented here can at least be considered a preliminary analysis of the relationship between the variables of interest. The estimated correlation coefficients were then combined into the 3 by 3 correlation matrices of interest using the multi-*Z* method, and these combined meta-analytic correlation matrices are the basis of the reported correlations and follow-up analyses.

2.4. Testing mediation

For testing mediation, we followed the well-established procedures and conceptual understanding provided by Baron and Kenny (1986) (Fig. 1). The Sobel test (Preacher and Hayes, 2004) determines the significance of the indirect effect through the mediator by testing the hypothesis of no difference between the total effect (path c; neurocognition and functional outcome) and the indirect effect (path c′; neurocognition and symptoms, symptoms and outcome). The indirect effect of the mediator is the product of paths a and b; which is equivalent to (c–c′). As such a significant result of the Sobel test is evidence of partial mediation and does not make any claims about the absence or presence of complete mediation. The regression coefficients for the multiple regression predicting functional outcome from both neurocognitive variables and symptom ratings can be estimated from the pairwise correlation coefficients used to evaluate the strength of the indirect effect.

$$b = \frac{r_{yx_1} - r_{yx_2} r_{x_1 x_2}}{1 - r^2_{x_1 x_2}}$$

Deriving the estimate of the conditional correlations directly from the pairwise correlations makes it easier to account for different sample sizes underlying the different elements of the covariance matrix. This is done by calculating the standard error of the estimate of the regression coefficients based on the number of observations of a particular estimate. This approach is more straightforward than trying to determine the correct sample size of a structural equation model that has been fitted to data that are derived from a combined correlation matrix.

Because of the lack of homogeneity of the neuropsychological tests (described above), three neurocognitive domains were chosen with the highest correlations for tests of indirect effects. These neurocognitive domains would most likely represent true effects in the population despite the fact that the significance of test statistics for these variables is potentially exaggerated. Even under conservative assumptions, such as assuming that the significance is 10 fold increased, a number of the results are still significant.

3. Results

To provide a foundation for examining the variables of interest, we examined separately the relationship between neurocognition and symptoms, and the relationship between symptoms and functional outcomes. As the severity of illness might influence the functional relationship between these variables, we tested if these relationships differ between inpatient samples and out-patient samples. We considered the patient status as a proxy for severity of illness because we assume in-patient samples are in an acute phase of illness, while outpatients in general are stable. The results were identical for both types of patients in that negative symptoms were a significant mediator for both inpatients and outpatients. Therefore, all of the following results are presented for the combined sample which included both types of patients.

The cross-sectional relationship between neurocognition and positive symptoms (reality distortion) was not statistically significant (r=−.00, p = .97) as was the relationship between positive symptoms and community functioning (r =−.03, p = .55). Therefore, no test of mediation was performed (Table 3). In contrast, the effect size of the correlation between neurocognition and negative symptoms was moderate (r=−.24, p <.01) (Table 3). Negative symptoms were significantly related to functional outcome (r=−.42, p<.01) defined as community functioning and with skills assessment (r = −.28, p<.01)(Table 4). These significant relationships between neurocognition and negative symptoms, and between negative symptoms and functional outcome formed the basis for examining the mediation hypothesis.

Using the Sobel test for indirect effects, we examined the estimated strength of the indirect effect from independent variable to the dependent variable through the mediator, and the p-value to determine the level of significance (Table 4). We found support for the hypothesis that the relationship between neurocognition and community functioning and skills assessment was partially mediated by negative symptoms (Sobel test for indirect effects: z= 133.20, p<.01 and z = 4.33, p<.01, respectively). The relationship between neurocognitive domains and functional outcome (i.e., community functioning and skill assessment) was also partially mediated by negative symptoms (Table 4). As expected, and despite using the same methodology in calculating effect sizes, the estimated effect of negative symptoms on community functioning (estimated r=−.42) is much stronger than the estimated effect of positive symptoms (estimated r=−.03).

4. Discussion

We examined models that included neurocognition, positive symptoms, and negative symptoms as predictors of community-based functional outcomes and social skills in schizophrenia. Our meta-analyses showed there was strong cross-sectional evidence indicating that negative symptoms are related to community-based functional outcome and skill assessment. Using meta-analytic techniques, such as the Sobel test of mediation, yielded fairly strong evidence indicating that the relationship between neurocognition and functional outcome is at least partially mediated by negative symptoms. In this model, neurocognition is still a primary causal variable that influences outcome. However, we found that the total effects of neurocognition on outcome were at least partially mediated via an indirect path through

negative symptoms. Therefore, neurocognition is proposed to have both direct and indirect effects on functional outcome.

Previous research has linked neurocognition to symptoms and symptoms to functional outcome, but in separate studies. In fact, there is a consistent and moderately strong relationship between neurocognition and negative symptoms. Harvey et al. (2006) suggested that cognitive deficits and negative symptoms share many features in common and are correlated, at least cross-sectionally. They point out that cognitive deficits and negative symptoms can have a similar type of onset, course, and are correlated with other aspects of schizophrenia, e.g., functional outcome. However, as far as we are aware, no prior meta-analysis has empirically tested a mediation model using the Sobel test to examine whether negative symptoms mediate between neurocognition and functional domains. The current results indicate that the relationship of negative symptoms to community-based functioning is relatively strong, but the relationship of positive symptoms to community-based functioning is relatively weak. Thus, positive symptoms (non-disorganizing type), such as hallucinations and delusions, do not consistently interfere with a person's ability to socialize or to perform at work. Patients might learn to compensate for positive symptom deficits in various ways, e.g., ignoring beliefs about aliens while working in retail clothing store. However, the data suggest that negative symptoms might be more closely linked to impairments in daily performance or skill acquisition. This relationship seems to hold for both inpatients and outpatients with schizophrenia.

Heterogeneity in the measurement of neurocognition was very evident in the studies included in this meta-analysis. Some neurocognitive tests were used very frequently, e.g., WCST. The constructs of executive functions, working memory, and attentional processes appeared to be oversampled as compared to constructs such as visual and spatial learning and memory. In addition, even within one domain of neurocognition, such as working memory, several tests were used, e.g., digit span measured auditory processing of working memory while spatial span tests measured visual working memory. In some cases, the same tests were classified in different studies as assessing different domains, probably because the tests demanded several different cognitive processes. For the current meta-analysis, we used the MATRICS classification scheme and definitions of domains (Nuechterlein et al., 2004) to place measures in domains based on the predominant cognitive process required.

There are several limitations to this study that warrant mention, some of which are common to all meta-analytic investigations (for a discussion, see: Rosenthal, 1991; Lipsey and Wilson, 2001). First, the study sample was not randomly selected. Additionally, neurocognition is not a homogenous concept and its measurement was influenced by how common a particular set of neurocognitive tests appear in the published literature. Therefore, the *p*-values that were averaged across studies are certainly not precise. The relationships in the studies in this meta-analysis are cross-sectional rather than longitudinal in design. For all of these reasons, and more, one cannot use meta-analysis or any correlational data, to infer causality. Further, the selection of which variables to place as predictors and which to test as a mediator was somewhat arbitrary. A theory driven approach was used to decide the direction that neurocognition is likely an underlying “causal” factor for the severity of negative symptoms. We do not believe that there is strong evidence suggesting that negative symptoms cause neurocognitive deficits. Similarly, the severity of symptoms most likely contributes to poor outcomes, but poor outcomes could conceivably contribute to a worsening of symptoms. In addition, we note the possibility of measurement overlap resulting in an inflated correlation between negative symptoms and outcome. With the SANS, there are definitions and anchor points for rating domains such as avolition at work or school that overlap with definitions of functional outcome. Despite the fact that each of these study limitations suggest that caution should be used in interpreting the results of the current study, our findings still provide some direction for future

research on potential contributors to outcome. While we believe that this study can inform future outcomes research, we want to emphasize that a meta-analysis cannot replace focused empirical research.

The model of mediation that was tested in this study would benefit from further examination because it would, if validated through longitudinal observational and experimental designs, have implications for intervention. Considering the central role that neurocognitive deficits play in relationship to daily functioning in schizophrenia, it is not surprising that cognitive deficits have emerged as important targets for new treatments (Green and Nuechterlein, 1999; Carpenter and Gold, 2002; Carpenter, 2004; Gold, 2004). If the relationship between neurocognition and functional outcome is partially mediated by negative symptoms, then perhaps negative symptoms should be an additional treatment target as a means to improve functional outcome.

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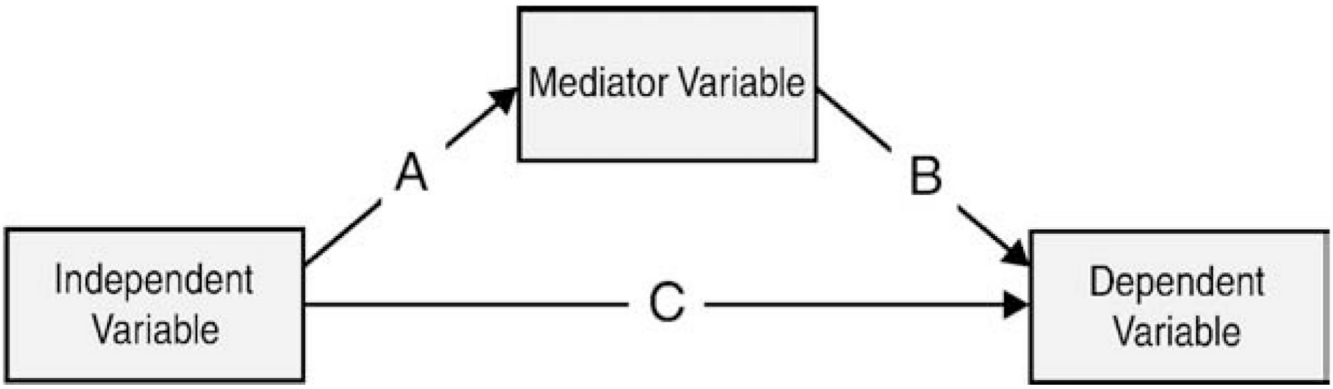

Fig. 1.
Typical mediation model.

Table 1

Studies included in meta-analysis, domains of interest, and number and type of subjects.

Author(s)	Domains investigated	Number and type of subjects
Bell and Mishara (2006)	Neurocognition, symptoms	267 outpatients
Bowie et al. (2006)	Neurocognition, symptoms, outcome	78 outpatients
Bozikas et al. (2006)	Symptoms, outcome	40 outpatients
Hofer et al. (2006)	Symptoms, outcome	60 outpatients
Keefe et al. (2006a)	Neurocognition, symptoms	1493 inpatients
Klingberg et al. (2006)	Neurocognition, symptoms	135 outpatients
Moore et al. (2006)	Neurocognition, symptoms	138 inpatients
Rocca et al. (2006)	Neurocognition, symptoms	70 outpatients
Villalta-Gil et al. (2006)	Neurocognition, symptoms, outcome	113 outpatients
Caligiuri et al. (2005)	Neurocognition, symptoms	43 outpatients
Pencer et al. (2005)	Symptoms, outcome	138 outpatients
Rhinewine et al. (2005)	Neurocognition, symptoms	45 inpatients
Rocca et al. (2005)	Neurocognition, symptoms	78 outpatients
Wegener et al. (2005)	Symptoms, outcome	24 inpatients
Bowie et al. (2004)	Neurocognition, symptoms, outcome	392 inpatients
Bozikas et al. (2004)	Neurocognition, symptoms	58 outpatients
Evans et al. (2004)	Neurocognition, symptoms, outcome	112 outpatients
Gooding and Tallent (2004)	Neurocognition, symptoms	36 outpatients
Müller et al. (2004)	Neurocognition, symptoms	100 inpatients
Pantelis et al. (2004)	Neurocognition, symptoms	97 inpatients
Rund et al. (2004)	Neurocognition, symptoms	207 outpatients
Addington et al. (2003)	Symptoms, outcome	177 outpatients
Aghevli et al. (2003)	Symptoms, outcome	33 outpatients
Hoffmann et al. (2003)	Neurocognition, symptoms, outcome	53 inpatients
McGurk et al. (2003)	Symptoms, outcome	30 outpatients
Minzenberg et al. (2003)	Neurocognition, symptoms	57 outpatients
Simon et al. (2003)	Neurocognition, symptoms	38 inpatients
Cameron et al. (2002)	Neurocognition, symptoms	52 outpatients
Daban et al. (2002)	Neurocognition, symptoms	51 inpatients
Friedman et al. (2002)	Neurocognition, symptoms, outcome	124 inpatients
Malla et al. (2002)	Neurocognition, symptoms, outcome	66 outpatients
Park et al. (2002)	Neurocognition, symptoms	28 outpatients
Schuepbach et al. (2002)	Neurocognition, symptoms	34 outpatients
Shean et al. (2002)	Neurocognition, symptoms	92 outpatients
Smith et al. (2002)	Neurocognition, symptoms, outcome	46 inpatients
Startup et al. (2002)	Symptoms, outcome	64 inpatients
Guillem et al. (2001)	Neurocognition, symptoms	27 outpatients
Moritz et al. (2001a)	Neurocognition, symptoms	25 inpatients
Moritz et al. (2001b)	Neurocognition, symptoms	47 inpatients
Silver and Shlomo (2001)	Neurocognition, symptoms, outcome	36 outpatients

Author(s)	Domains investigated	Number and type of subjects
Addington and Addington (2000)	Neurocognition, symptoms, outcome	65 outpatients
Howanitz et al. (2000)	Neurocognition, symptoms	35 inpatients
McDaniel et al. (2000)	Neurocognition, symptoms	37 inpatients
McGurk et al. (2000)	Symptoms, outcome	168 inpatients
Stratta et al. (2000)	Neurocognition, symptoms	20 inpatients
Addington and Addington (1999)	Neurocognition, symptoms, outcome	80 outpatients
Dickerson et al. (1999b)	Neurocognition, symptoms, outcome	72 outpatients
Kerns et al. (1999)	Neurocognition, symptoms	26 inpatients
Norman et al. (1999)	Neurocognition, symptoms, outcome	50 outpatients
Park et al. (1999)	Neurocognition, symptoms	34 inpatients; 30 outpatients
Salem and Kring (1999)	Symptoms, outcome	17 outpatients
Addington and Addington (1998a)	Neurocognition, symptoms	40 inpatients
Addington and Addington (1998b)	Neurocognition, symptoms, outcome	40 inpatients
Basso et al. (1998)	Neurocognition, symptoms	53 outpatients; 9 inpatients
Harvey et al. (1998)	Neurocognition, symptoms, outcome	97 outpatients
Robert et al. (1998)	Neurocognition, symptoms	78 patients
Zakzanis (1998)	Neurocognition, symptoms	38 inpatients
Addington et al. (1997)	Neurocognition, symptoms	72 inpatients
Berman et al. (1997)	Neurocognition, symptoms	30 inpatients
Brebion et al. (1997)	Neurocognition, symptoms	40 inpatients
Salokangas (1997)	Symptoms, outcome	227 outpatients
Carter et al. (1996)	Neurocognition, symptoms	18 outpatients
Ragland et al. (1996)	Neurocognition, symptoms	30 outpatients
Van der Does et al. (1996)	Neurocognition, symptoms, outcome	60 inpatients
Brekke et al. (1995)	Neurocognition, symptoms	40 inpatients
Cuesta and Peralta (1995)	Neurocognition, symptoms	40 inpatients
Cuesta et al. (1995)	Neurocognition, symptoms	30 inpatients
Hammer et al. (1995)	Neurocognition, symptoms	65 outpatients
Franke et al. (1992)	Neurocognition, symptoms	73 inpatients
Addington et al. (1991)	Neurocognition, symptoms	38 inpatients
Breier et al. (1991)	Neurocognition, symptoms, outcome	58 outpatients
Liddle and Morris (1991)	Neurocognition, symptoms	43 inpatients
Green and Walker (1985)	Neurocognition, symptoms	44 inpatients

Table 2

Neurocognitive domains, symptom assessments, and functional outcome measures.

Neurocognitive domain	Neurocognitive test	Description of tests
Verbal learning and memory	Logical Memory WMS-R	Subject is given two short stories and asked to recall each story immediately after presentation and again after a 30-minute delay.
	Paired Associates WMS-R	Subject is given 5 trials of paired word presentations and asked to recall the list immediately after presentation and again after a 30-minute delay.
	California Verbal Learning Test (CVLT)	Test consists of an oral presentation of a 16-word list (list A) for five immediate recall trials, followed by a single presentation and recall of a second 16-word 'interference' list (list B). Free- and category-cued recall of list A is elicited immediately after recall of list B and again 20 min later. A recognition trial is also run.
	Hopkins Verbal Learning Test (HVLT)	A list of words each belonging to one of several semantic categories is presented verbally for three trials and then after a delay that the subject must recall
	Rey Auditory Verbal Learning Test (RVLT)	The subject is given a list of 15 items and asked to recall them immediately over five trials. Subsequently, the subject is presented with an interference list. The subject is also given a story paragraph that contains the 15 words from initial list.
	Buschke-List Learning Test	Multiple-trial list-learning task.
Visual learning and memory	Rey-Osterreith Complex Figures Test (Rey-O)	The subject is asked to copy the stimulus figure. After a 3-minute and a 30-minute delay, the subject is asked to draw the figure from memory.
	Visual Reproduction WMS-R	The subject is asked to look at five figures for 10 s each. After the presentation of each figure, the stimulus is removed and the subject is asked to "draw the design" from memory. After 25 min, the subject is asked to draw as many of the designs as they can remember.
	Benton Visual Memory Test (BVMT)	Test of visual perception and visual memory using the presentation of 10 visual stimuli.
	Hooper Visual Orientation Test	Subject is required to identify common objects that have been cut into parts and arranged illogically.
Working memory	Digit Span Forward (WAIS)	Subject is instructed to repeat a string of numbers that increase in length over the task.
	Digit Span Backwards (WAIS)	Subject is instructed to repeat a string of numbers in the reverse order presented.
	Spatial Span WMS-R	Subject is instructed to point to a series of blocks in the same or reverse order that is presented by the Examiner.
	Letter-Number Sequencing (WAIS-III)	Subject is given a series of numbers and letters which must be repeated in numerical and alphabetical order.
	Digit Span Distractibility Test—Neutral	Subjects hear short strings of digits with and without distracters and are asked to recall the digits in correct order.
Reasoning and problem solving	Wisconsin Card Sorting Test (WCST)	The subject is asked to sort a series of cards to one of four key cards that vary in shape, color and number of shapes. Feedback is provided. After 10 consecutive correct sorts, the test rules shift without warning to a new sorting rule.
	Block Design (WAIS)	The subject is given a set of blocks and asked to arrange the blocks according to the stimulus picture presented
	Gorham's Proverbs—Interpretation	The subject is given 12 proverbs for which he or she must provide an interpretation.

Neurocognitive domain	Neurocognitive test	Description of tests
	Raven's Progressive Matrices	For each test item, the subject is asked to identify the missing segment required to complete a larger pattern.
Speed of processing	Trail Making Test A & B	Part A requires the subject to connect series of numbered circles arrayed randomly on a sheet of paper using a pencil. In PART B the array consists of both numbers and letters, and the subject must connect them in alternating order
	Stroop Test (Color-Word)	The subject is given words representing colors that are printed in different color ink. The subject is instructed to read the ink color as quickly as possible and later while ignoring the printed word.
	Finger Tapping Test	Test that requires that the subject tap as rapidly as possible with the index finger on a small lever, which is attached to a mechanical counter.
	Canceling Test of Zazzo	The subject is required to cancel target letters among an array of non-target letters.
	Controlled Oral World Association Test	A measure of verbal fluency requiring the ability to generate words beginning with specific letters (F, A, and S) for 1 min each.
	Chicago Word Fluency Test	Subjects are asked to generate as many words as possible that begin with an “S,” then a “C.” This is a timed task.
	Jones-Gorman Design Fluency Test	Requires production of novel (original) abstract designs under a time constraint.
	Digit Symbol –(WAIS)	The subject is provided with numbers along with corresponding symbols and is required to reproduce symbols that correspond with a number on a grid.
	Lexical Decision Task	Subjects are presented, either visually or auditorily, with a mixture of words and pseudo words. Their task is to indicate, usually with a button-press, whether the presented stimulus is a word or not.
	Hayling Sentence	The test consists of two sets of 15 sentences each having the last word missing. The examiner reads each
	Completion Test	sentence aloud and the participant has to complete the sentences.
	Purdue Pegboard	The subject is asked to place pegs into a pegboard.
Attention/vigilance	Continuous Performance Test (CPT)	Subjects are told that they will see a series of letters presented on a screen. They are told to click a button (or computer mouse) only when they see the “target” stimulus.
	Span of Apprehension (SOA)	Arrays of 3 or 12 letters are presented for 71 ms on a screen along with distracters. Subjects are instructed to report if they see a T or an F among the array of letters.
	Digit Span Distractibility Test—Interference	Subjects hear short strings of digits with and without distracters and are asked to recall the digits in correct order.

Symptom assessment scale	Description of measure
Brief Psychiatric Rating Scale (BPRS)	An 18-item rating scale designed to assess psychiatric symptoms, including positive and negative symptoms, based on a semi-structured interview.
Scale for the Assessment of Negative Symptoms (SANS)	A 29-item semi-structured scale that assesses observed and self-reported negative symptoms such as restricted affect, asociality, and amotivation
Scale for the Assessment of Positive Symptoms (SAPS)	A 35-item semi-structured scale that assesses observed and self-reported positive symptoms including formal thought disorder.

Positive and Negative Syndrome Scale (PANSS)	A 30-item semi-structured measure that assesses psychiatric symptoms in domains such as positive, negative, and general symptoms in psychiatric patients.
Comprehensive Psychopathological Rating Scale (CPRS)	A 67-item self-report measure scored from 0 (no pathology) to 3 (maximum pathology) that assesses psychiatric symptoms such as hallucinations, anxiety, and depression.
Functional outcome scale	Description of measure
Quality of Life Scale (QLS)	A measure that is based on a semi-structured interview designed to assess quality of life in various domains of living.
Social Functioning Scale (SFS)	A measure of social functioning relevant to the functioning and impairments of individuals with schizophrenia.
Multnomah Community Ability Scale (MCAS)	A 17-item instrument that assesses the community functioning of adult psychiatric patients social competence; adjustment to living; behavioral problems, and interference with daily living.
Work Behavior Inventory (WBI)	A standardized work performance assessment instrument specifically designed for patients with severe mental illness, consisting of 36 items divided into five subscales.
Global Assessment of Functioning (GAF)	A scale rated 0 through 100 used to subjectively rate symptom severity, and social and occupational functioning of psychiatric patients.
Social Behavior Scale (SBS)	A scale that rates 21 behavior areas such as hygiene, initiating conversations, etc., designed for use with long-stay patient populations or for community settings
Alzheimer's Disease Assessment Scale	Designed to evaluate cognitive, and behavioral dysfunctions; cognitive and neurocognitive subscales.
Global Assessment of Social Functioning (GAS)	A scale rated 0–100 based on the lowest level of recent functioning as determined by rater.
Life Skills Profile (LSP)	A 39-item measure designed specifically to assess general levels of function and disability in adults.
Disability Assessment Schedule (DAS)	An instrument for a clinician's assessment of difficulty maintaining personal care, performing occupational tasks, and social functioning.
Social Adaptive Functioning Scale (SAFE)	A scale that measures social-interpersonal, instrumental, and life skills functioning, rated based on observation, caregiver contact, and interaction with the patient.
Levels of Functioning Scale (LOFS)	Measures the quantity and quality of social relationships, occupational activity, and time spent in a psychiatric hospital.
WHOL-QOL Brief	A 26-item survey measuring the quality of life for a wide variety of populations.
Specific level of function (SLFS)	A 46-item clinician rated scale that documents functional deficits across psychosocial functional domains and addressing specific areas of a patient's needs.
Skills-based assessment	Description of measure
Facial Recognition Task (FRT)	This test requires matching a target face with up to three pictures of the same person presented in a six-stimuli array of faces.
Facial Discrimination Task (FDT)	This test consists of standardized black-and-white photographs of Caucasian actors exhibiting happy, sad, angry, and neutral faces that are used to measure emotion recognition skills.
Assessment of Interpersonal Problem-Solving Skills (AIPSS)	A role-played simulation test that measures an examinee's ability to describe an interpersonal problem, derive a solution to the problem, and to enact a solution.
UCSD Performance Skills Assessment (UPSA)	Performance based assessment of functional capacity in areas needed for independent living.

Table 3

The magnitude of relationships between neurocognition with symptoms, and symptoms with outcome is examined using average correlations across studies.

	Positive				Negative			
	r	***p***	***n***	**Studies**	***r***	***p***	***n***	**Studies**
Neurocognitive domains								
Working memory	−.03	= .54	357	8	−.21	<.01	2230	17
Speed of processing	.04	= .21	1040	18	−.26	<.01	3899	33
Verbal learning and memory	.00	= .93	531	10	−.21	<.01	2978	23
Reasoning problem solving	.00	= .94	797	16	−.13	<.01	3039	27
Attention/vigilance	−.10	= .15	199	4	−.17	<.01	2138	10
Visual learning and memory	−.10	= .20	179	4	−.16	<.01	454	8
Composite of domains	**.00**	**= .97**	**1297**	**25**	**−.24**	**<.01**	**4929**	**53**
Outcome domains								
Community functioning	−.03	= .55	549	9	−.42	<.01	2341	23
Skills assessment	(no studies on this topic)				−.28	<.01	269	5

Table 4

The indirect effects of neurocognition on functioning mediated through negative symptoms were examined using a Sobel test of mediation.

Neurocognition, symptom, and functioning variables examined	Sobel	*p*
Speed of processing–negative symptoms–community functioning	13.0	<.01
Verbal learning and memory–negative symptoms–community functioning	9.9	<.01
Working memory–negative symptoms–community functioning	8.5	<.01
Attention–negative symptoms–community functioning	7.1	<.01
Reasoning and problem solving–negative symptoms–community functioning	6.8	<.01
Visual learning and memory–negative symptoms–community functioning	3.1	<.01
Composite of domains–Negative symptoms–community functioning	**13.9**	**<.01**
Speed of processing–negative symptoms–skill assessment	10.1	<.01
Verbal learning and memory–negative symptoms–skill assessment	8.2	<.01
Working memory–negative symptoms–skill assessment	7.1	<.01
Reasoning and problem solving–negative symptoms–skill assessment	6.3	<.01
Attention–negative symptoms–skill assessment	6.3	<.01
Visual learning and memory–negative symptoms–skill assessment	2.8	<.01
Composite of domains–Negative symptoms–skill assessment	**11.1**	**<.01**