Neurocognitive Deficits and Functional Outcome in Schizophrenia: Are We Measuring the "Right Stuff"?

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Abstract

There has been a surge of interest in the functional consequences of neurocognitive deficits in schizophrenia. The published literature in this area has doubled in the last few years. In this paper, we will attempt to confirm the conclusions from a previous review that certain neurocognitive domains (secondary verbal memory, immediate memory, executive functioning as measured by card sorting, and vigilance) are associated with functional outcome. In addition to surveying the number of replicated findings and tallying box scores of results, we will approach the review of the studies in a more thorough and empirical manner by applying a meta-analysis. Lastly, we will discuss what we see as a key limitation of this literature, specifically, the relatively narrow selection of predictor measures. This limitation has constrained identification of mediating variables that may explain the mechanisms for these relationships.

Keywords: Schizophrenia, neurocognition, functional outcome, social cognition, learning potential.

***Schizophrenia Bulletin*, 26(1):119–136, 2000.**

In a previous review of the literature, we concluded that specific domains of neurocognition were significantly related to functional outcome (Green 1996). The neurocognitive domains most consistently related to functional outcome included secondary verbal memory, immediate or working verbal memory, executive functioning measured with card sorting, and vigilance. Functional outcome was divided into the distinct domains of (1) community outcome, (2) social problem solving, and (3) psychosocial skill acquisition. Only 16 studies were included in the review, and the studies were generally underpowered and exploratory. Hence, our confidence in the conclusions was not strong, and the need for future studies in this area of research was clear. Almost all of the studies in the review were published in 1990 or later, which demonstrates the recency of interest in the relationships of neurocognition to functional outcome. Nonetheless, Heaton and colleagues anticipated this line of investigation (Heaton and Pendleton 1981) and examined the functional consequences of neurocognitive deficits in mixed psychiatric and neurological patients.

Reflecting the surge of interest in this area of inquiry, the cumulative published literature on neurocognitive and functional outcome in schizophrenia has doubled in the few years since the Green (1996) review. In this paper, we will address several issues. First, with a substantially larger data base, we will attempt to confirm the conclusions from the previous review. Second, we will approach the review of the studies in a more thorough and empirical manner by applying a meta-analysis. Third, we will evaluate the literature critically and discuss what we see as its key limitation, specifically, the restricted selection of appropriate predictor measures.

Literature Review

The relevant literature on neurocognitive deficits and functional outcome in schizophrenia is summarized in table 1. In this table, we selected peer-reviewed studies with well-defined neurocognitive and functional outcome measures, and a primary interest in patients with schizophrenia or schizoaffective disorder, or both. We included both cross-sectional and longitudinal studies.

The table includes 37 studies that are divided into three functional outcome domains, described below. Some of the studies ($n = 4$) examined the relationships between neurocognitive constructs and two of the functional outcome domains. When this occurred, we listed the study

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Table 1. Neurocognition and functional outcome in schizophrenia

A. Studies of community outcome and daily activities

Study	Sample[1] (Power[2])	Predictor/correlative measures	Outcome measures	Major findings
Addington and Addington 1999	80 S outpatients (0.78)	Neurocognitive Battery including measures of verbal ability, verbal and visual memory, executive functioning, visual-spatial organization, vigilance and early information processing Symptom PANSS	Social Functioning Scale, Quality of Life Scale	Mainly negative findings with Social Functioning Scale; poor cognitive flexibility associated with low scores on Quality of Life Scale.
Addington et al. 1998	30 S outpatients (0.37)	Battery including measures of verbal ability, memory, executive functioning, visual-spatial ability, and attention/vigilance	Social Dysfunction Index, Social Adjustment Scale II	No significant associations between cognitive measures and social functioning.
Bartels et al. 1997	129 S or SA geriatric, nursing home, and community (0.93)	Neurocognitive Clinical Dementia Rating Scale, MMSE Symptom BPRS	Community living skills and activities of daily living from the Specific Level of Function Scale	MMSE correlated with activities of daily living and community functioning more strongly than symptoms.
Bellack et al. 1999	22 vs. 84 S outpatients (0.54)	DS CPT, Span, WAIS–R subtests, verbal fluency, WCST, secondary memory (verbal and visual), Trails A and B, Stroop	Good vs. poor vocational outcome	Secondary memory (verbal and visual), Stroop, card sorting, verbal fluency, and IQ subtests correlated with vocational outcome; variables that best classified GVO differed from those that best classified PVO.
Breier et al. 1991	58 S or SA patients followed from index hospitalization (0.64)	Neurocognitive WCST, Trails A and B, verbal fluency Symptom BPRS, SANS	Levels of Functioning Scale, GAS	Symptoms, particularly negative symptoms, were related to functional outcome; WCST, Trails A and B, and verbal fluency related to poor social functioning; positive symptoms at index hospitalization significantly predicted social and work function at followup, while negative symptoms predicted work only.

Study	Sample[1] (Power[2])	Predictor/correlative measures	Outcome measures	Major findings
Brekke et al. 1997	40 S or SA outpatients (0.48)	Neurocognitive Stroop, verbal fluency, WAIS–R subtests (DS, DSym, BD, arithmetic) Symptom BPRS	Strauss Carpenter, role functioning	Stroop, digit symbol, verbal fluency, and BD correlated with independent living and work.
Buchanan et al. 1994	29 treatment-resistant S patients (0.36)	WMS–R, verbal fluency, BD, visual-spatial measures, WCST, Trails, Stroop	Level of functioning, quality of life	Secondary verbal memory, visual memory, and verbal fluency predicted quality of life; visual memory predicted level of functioning.
Dickerson et al. 1996	88 S or SA outpatients (0.82)	Neurocognitive WAIS–R subtests, logical memory, Rey-O, WCST, Trails, aphasia, verbal fluency Symptom PANSS	Social Functioning Scale	Visual motor, spatial organization, and aphasia correlated with social functioning. Composite neuropsych correlated with social functioning more strongly than composite symptoms.
Goldman et al. 1993	19 S patients (0.24)	Neurocognitive BD, Trails, vocabulary, selective reminding, DS Symptom Psychotic from BPRS, negative from SANS	Strauss Carpenter Scale	Secondary verbal memory predicted community functioning; symptoms did not predict outcome.
Harvey et al. 1997	208 elderly S inpatients (0.99)	MMSE, CERAD Cognitive Battery[3]	SAFE	Composite measure of cognitive functioning correlated significantly with all 17 items of the SAFE; regression analysis using three SAFE factor scores indicated that cognitive impairment was more strongly correlated with skills deficits than behavioral undercontrol.
Harvey et al. 1998	Sample 1: 97 chronic inpatients (0.85) Sample 2: 37 nursing home (0.45) Sample 3: 31 acute inpatients (0.38) All geriatrics	Neurocognitive MMSE, CERAD Cognitive Battery[3] Symptom PANSS	SAFE	For each sample, composite cognitive score correlated with social-adaptive functioning more strongly than positive or negative symptoms.

Table 1. Neurocognition and functional outcome in schizophrenia—Continued

Study	Sample[1] (Power[2])	Predictor/correlative measures	Outcome measures	Major findings
Heslegrave et al. 1997	42 stable outpatients (0.50)	Neurocognitive COGLAB Symptom PANSS	Quality of life measured by the Sickness Impact Profile, two global subjective items	Span/CPT, iconic memory, positive, negative, and general symptoms correlated with the Sickness Impact Profile. Negative and general symptoms, but not neurocognition, correlated with the subjective items.
Jaeger and Douglas 1992	19 first episode S patients (0.24)	WCST	Social Adjustment Scale	Perseveration predicted social adjustment.
Johnstone et al. 1990	137 first episode S patients (0.95)	Neurocognitive PPVT, DSym Symptom Behavioral ratings	Occupational functioning	Neurocognitive measures did not predict outcome. Psychotic behaviors did not predict occupational outcome, but ratings of social withdrawal (negative symptom) did.
Lysaker et al. 1995	89 S and SA patients (0.82)	WCST	Occupational functioning, WPP	Card sorting predicted task orientation and social skills at work.
Meltzer et al. 1996	Sample 1: 48 treatment-resistant patients with S (0.55) Sample 2: 82 S patients (0.79)	Neurocognitive WCST, FAS, verbal list learning, mazes, DSym Symptom BPRS	GAS, Quality of Life Scale, work status	WCST correlated with GAS; mazes and VLL correlated with both GAS and Quality of Life Scale. All measures discriminated work outcome in separate sample (sample 2)—WCST was best.
Mueser et al. 1996	28 S or SA inpatients (0.35)	Emotion and face recognition	Social Behavior Scale	Facial emotion identification, discrimination, and recognition were associated with social competence as measured by the Social Behavior Scale.
Penn et al. 1996	27 S or SA chronic inpatients (0.34)	Neurocognitive COGLAB, affect recognition, empathy, social scripts Symptom PANSS	NOSIE-30	Card sorting and social cognition were related to adaptive unit behavior. Relationships with social cognition (especially affect recognition) were generally stronger than with COGLAB.
Wykes et al. 1990	28 S patients (0.35)	Neurocognitive Complex RT Symptom Psychotic, negative items from Present State Examination	Independent living	Complex RT predicted degree of independent living; symptoms did not.

B. Studies of laboratory assessment of instrumental skills and social problem solving

Study	Sample[1] (Power[2])	Predictor/correlative measures	Outcome measures	Major findings
Addington and Addington 1999	80 S outpatients (0.78)	Battery including measures of verbal ability, verbal and visual memory, executive functioning, visual-spatial organization, vigilance, and early information processing	AIPSS	Verbal ability, verbal memory, and poor cognitive flexibility were associated with AIPSS; visual-spatial ability and vigilance were associated with the sending skills subscale.
Addington et al. 1998	30 S outpatients (0.37)	Battery including measures of verbal ability, memory, executive functioning, visual-spatial ability, and attention	AIPSS	CPT, a measure of attention, was a significant predictor of processing and sending skills as assessed by the AIPSS.
Bellack et al. 1994	27 S inpatients (0.34)	Neurocognitive Verbal IQ, WMS–R Symptom Psychotic from BPRS, negative from SANS	Social Problem Solving Assessment Battery	Verbal IQ, secondary memory, negative symptoms correlated with some outcome measures. Immediate memory, psychotic symptoms did not.
Bowen et al. 1994	30 S inpatients (0.37)	CPT, Span, DSDT	AIPSS	Vigilance correlated with overall problem solving; immediate verbal memory, early visual processing did not.
Corrigan and Toomey 1995	26 S or SA chronic inpatients (0.33)	Neurocognitive CPT, RAVLT, WCST, DSDT, social perception Symptom BPRS	AIPSS	Social cue recognition and verbal memory were related to AIPSS. Social cue recognition was more strongly associated than most neurocognitive measures, and this correlation held after controlling for positive symptoms.
Corrigan et al. 1994	26 S inpatients (0.33)	Neurocognitive CPT, Span, RAVLT, DSDT, WCST Symptom Psychotic and negative from BPRS	Social Cue Recognition Test	Immediate verbal memory, secondary verbal memory, early visual processing, negative symptoms correlated with social cue recognition summary score; vigilance, card sorting, psychotic symptoms did not.
Ikebuchi et al. 1996	20 S inpatients and outpatients (0.25)	Neurocognitive WAIS–R Symptom BPRS	Structured role-play	Performance IQ was significantly correlated with receiving and processing skills and global score on role-play test.

Table 1. Neurocognition and functional outcome in schizophrenia—Continued

Study	Sample[1] (Power[2])	Predictor/correlative measures	Outcome measures	Major findings
Klapow et al. 1997	55 S older outpatients (0.62)	Neurocognitive MMSE Symptom BPRS, SANS, SAPS	DAFS – simulated daily activities	MMSE was only significant predictor, even after controlling for symptom assessments and demographics.
Mueser et al. 1995	Male = 20 (0.25) Female = 18 (0.23) S or SA	WMS–R, visual-spatial, WAIS–R, FAS, language	Standardized role-play	WMS–R (mainly visual) with omnibus test related to outcome for females, but not for males.
Mueser et al. 1996	28 S or SA inpatients (0.35)	Emotion and face recognition	Unstructured role-play (Conversation Probe)	Facial emotion identification was associated with nonverbal performance on the Conversation Probe.
Penn et al. 1993	31 Dutch S inpatients (0.38)	COGLAB[4]	Means-Ends Problem-Solving Test, alternative solution generation test	Generally negative results
Penn et al. 1995	38 S and SA inpatients (0.46)	COGLAB[4]	Role-playing	Vigilance, RT correlated with role-playing.
Penn et al. 1996	Male = 21 (0.27) Female = 17 (0.22) S or SA chronic inpatients	COGLAB[4]	Unstructured role-play	RT, vigilance, masking, card sorting related to outcome for females, not males. Results held after controlling for positive symptoms.
Velligan et al. 1997	Study 1: 112 (0.92) Study 2: 41 (0.49) chronic inpatients	Neurocognitive Study 1: Mental status exam from Negative Symptoms Assessment Study 2: global from neuropsych battery Symptom BPRS	Functional Needs Assessment	Cognitive factor was the only one to enter the regression analysis. In path analysis, symptoms were not needed. Same for study 2.

C. Studies of psychosocial rehabilitation and skill acquisition

Study	Sample[1] (Power[2])	Predictor/correlative measures	Outcome measures	Major findings
Bowen et al. 1994	30 S inpatients (0.37)	CPT, Span, DSDT	Single session skill acquisition	Vigilance, early visual processing, and immediate verbal memory correlated with total skill acquisition.
Corrigan et al. 1994	30 S inpatients (0.37)	Neurocognitive CPT, Span, RAVLT, DSDT, WCST Symptom Psychotic and negative from BPRS	Single session skill acquisition	Immediate and secondary verbal memory, vigilance correlated with overall skill acquisition; card sorting, early visual processing, symptoms did not.
Kern et al. 1992	16 psychotic inpatients, mainly S (0.21)	CPT, Span, RAVLT, WCST, PPVT, Rey-O, Pin Test, Backward Masking	Pre- and posttests, on-task behaviors during training	Secondary verbal memory correlated with pretest; immediate and secondary verbal memory correlated with on-task behaviors; vigilance correlated with change score.
Lysaker et al. 1995	53 S and SA inpatients and outpatients (0.60)	Neurocognitive WCST, proverbs Symptom Psychotic and negative from the PANSS	Work-related social skills, WPP	Card sorting, proverb interpretation predicted improvement in social skills; symptoms did not.
McKee et al. 1997	19 S or SA inpatients (0.24)	Neurocognitive Symbol Digit Modalities Test, RAVLT, WISC–III mazes, FAS, Category Instance Generation Test, Stroop Color-Word Test Symptom SAPS, SANS	Program attendance and overall level of participation in Community Re-Entry Program	Executive function (Stroop) was positively associated with level of participation; Symbol Digit Modalities Test, WISC–III mazes, and negative symptoms were negatively correlated with program attendance.
Mueser et al. 1991	30 S and SA inpatients and outpatients (0.37)	Neurocognitive WMS Symptom Psychotic and negative from BPRS	Change scores from skills training program	Immediate verbal, secondary verbal, and visual memory predicted skills acquisition; symptoms did not.

Table 1. Neurocognition and functional outcome in schizophrenia—Continued

Study	Sample[1] (Power[2])	Predictor/correlative measures	Outcome measures	Major findings
Silverstein et al. 1998	26 chronic S inpatients (0.33)	Perceptual organization, RT, DS CPT, Sustained Attention Test, RAVLT, FAS, Theory of Mind, WCST	MMLT, observational ratings of 28 ward behaviors, hospital discharge	Verbal memory, verbal fluency, card sorting, and inferential reasoning were correlated with the MMLT; cognitive variables of RT and sustained attention were related to on-time behavior, and RT was related to keeping room clean; perceptual organization was related to hospital discharge.
Weaver and Brooks 1964	248 S inpatients and outpatients (0.99)	Psychomotor tests (including RT, dexterity, and motor learning)	Rehabilitation potential	Psychomotor speed predicted patients selected for rehabilitation programs.

Note.—AIPSS = Assessment of Problem Solving Skill; BD = block design; BPRS = Brief Psychiatric Rating Scale; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CPT = Continuous Performance Test; DAFS = Direct Assessment of Functional Status Scale; DS = digit span; DSDT = Digit Span Distractibility Test; DSym = Digit Symbol Substitution Test; FAS = a test of verbal fluency; GAS = Global Assessment Scale; GVO = good vocational outcome; MMLT = Micro Module Learning Test; MMSE = Mini Mental State Examination; NOSIE-30 = Nurse's Observation Scale for Inpatient Evaluation; PANSS = Positive and Negative Syndrome Scale; POV = poor vocational outcome; PPVT = Peabody Picture Vocabulary Test; RAVLT = Rey Auditory Verbal Learning Test; Rey-O = Rey-Osterrieth Complex Figure Test; RT = reaction time; S = schizophrenia; SA = schizoaffective disorder; SAFE = Social-Adaptive Functioning Evaluation; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; Span = Span of Apprehension; WAIS–R = Wechsler Adult Intelligence Scale–Revised; WCST = Wisconsin Card Sorting Test; WISC–III = Wechsler Intelligence Scale for Children III; WMS = Wechsler Memory Scale; WMS–R = Wechsler Memory Scale–Revised; WPP = Work Personality Profile.

[1]Sample size of the analyses relevant to the current review.

[2]Statistical power for a medium effect size of $r = 0.30$ with an alpha value of 0.05, two-tailed.

[3]Consists of word list learning and delayed recall, praxic drawings, modified Boston Naming Test, and category fluency.

[4]A computer-based battery of cognitive tests, including vigilance, card sorting, masking, and RT.

twice, once in each outcome domain. The remaining studies considered only one area of functional outcome. Hence, the table includes a total of 41 findings for the 37 separate studies.

Types of Neurocognitive Constructs

When starting to review this literature, one immediately confronts the variety of both predictor and outcome measures. There is considerable diversity in the selection of neurocognitive measures. However, most of the measures can be clustered into a smaller number of key neurocognitive constructs.

Secondary Memory. There are many ways to subtype memory and a large variety of assessment methods. Two types of memory are especially relevant to the current topic, namely, immediate memory and secondary memory. Secondary memory refers to the ability to acquire and store information over a longer period of time (usually lasting for several minutes and longer). This type of memory is usually assessed by asking individuals to attempt to learn a list of words or recall passages of text (e.g., Delis et al. 1987). The amount of information to be remembered exceeds the immediate memory span, meaning that it contains too much information to be held "on-line" at any one time. This is distinct from remote memory because assessments of secondary memory typically use delay periods of less than 1 hour, whereas remote memory typically refers to retention over days or years.

Immediate Memory. Immediate memory refers to the ability to hold a limited amount of information "on-line" for a brief period of time (usually a few seconds). Repeating a telephone number is an example of immediate memory. Immediate memory (also called the phonological loop) is considered to be a component of "working" memory (Baddeley 1986). We use the term "immediate memory" as opposed to working memory in this article because almost all of the studies in this review used measures requiring only brief storage of information, not the ability to manipulate the information, which is common in tests of working memory.

Vigilance. Also sometimes called "sustained attention," vigilance refers to the ability to maintain a readiness to respond to signal (i.e., target stimuli) and not respond to noise (i.e., nontargets) over a period of time. In other words, it involves an ability, called "sensitivity," to distinguish signal from noise. Vigilance is typically measured with a Continuous Performance Test in which subjects are presented with a series of briefly presented stimuli on a computer screen and instructed to respond only to selected target stimuli and ignore all others (Davies and Parasuraman 1982).

Executive Functioning/Card Sorting. The broader term "executive functioning" refers to volition, planning, purposive action, and self-monitoring of behavior. In this group of studies, card sorting tests were the most common way to assess executive functioning. Card sorting measures, such as the Wisconsin Card Sorting Test (WCST), were used in which the subject matches a stimulus card to one of four key cards according to certain matching principles (Heaton 1981). These tests assess the subject's ability to attain, maintain, and shift cognitive set.

Verbal Fluency. These tests measure one's ability to generate words. Subjects may be asked to produce words that begin with a certain letter, or to produce words from a certain semantic category (e.g., animals). The term "fluency" is slightly misleading because it refers to the number of correct items generated, not whether the subject speaks fluently (Benton and Hamsher 1978).

Early Visual Processing. Measures of early visual processing evaluate the basic stages of visual processing, such as the visual scanning of a display of stimuli and the early detection and identification of visual stimuli. Assessments of these processes involve very brief, tachistoscopic presentation of visual stimuli on a monitor, either alone (e.g., backward masking) or in the presence of competing stimuli (Asarnow et al. 1991).

Psychomotor Skills. Assessments of psychomotor abilities are usually speeded tests and can be separated into two types of skills: speed and dexterity. Motor speed is measured with rapid, repetitive finger movements. Dexterity is assessed with tasks that involve fine manual manipulation (e.g., with pegs or pins). We have also included in this category assessments of reaction time in which the subject responds as quickly as possible to a stimulus by pressing a button (Lezak 1995).

Types of Functional Outcome

The outcome measures fit, more or less naturally, into three general categories: (1) success in psychosocial rehabilitation programs, (2) studies of laboratory assessment of social problem solving ability or analog measures of instrumental skills, and (3) studies that have considered broader aspects of behavior in community outcome and activities of daily living. These three outcome domains are similar, but not identical, to the outcome domains used in our previous review of the literature (Green 1996). The boundaries are not absolute. The first two areas are highly

interconnected because performance of skills obviously depends on acquiring those skills in the first place. We also believe that the community outcome and activities of daily living are heavily dependent on skill acquisition. The intention was to distinguish the intermediate category, which includes acquisition and performance of isolated skills, from measures that involve integration of multiple skill areas. The categories also differ because the intermediate cluster includes laboratory analogs of social and work functioning, whereas the outcome in the community-based category is actual, not simulated. A brief description of key outcome categories follows.

Success in Psychosocial Skill Acquisition. Psychosocial skills training is a widely used method of psychosocial treatment for patients with schizophrenia. Psychosocial rehabilitation programs teach patients basic life skills (e.g., basic conversation skills, symptom and medication management, and leisure skills) and are designed to provide patients with greater functional independence. These training programs tend to be highly structured, and progress is closely monitored. It is possible to measure the amount of success in a skills training program, for example, by the degree of skill acquisition (e.g., Mueser et al. 1991; Bowen et al. 1994).

Laboratory Assessments of Instrumental Skills and Social Problem-Solving Ability. Studies in this category examine performance of skills, mainly with laboratory analog measures of social competence or social problem solving. In a typical assessment, subjects may watch videotaped vignettes that present an interpersonal problem. Subjects may be asked to identify the problem, suggest solutions to the problem, and demonstrate how they would act out the solution through role-play (e.g., Bellack et al. 1994).

Community Outcome/Daily Activities. This is the most varied category of functional outcome and includes such outcomes as occupational functioning, social attainment, and degree of independent living. This outcome area is based more on self-report than on demonstration but can also be rated from hospital charts or caregivers' reports. Assessments may include the activities of daily living, amount or level of work or school, and type and quality of social support networks (e.g., Brekke et al. 1997).

Table 1 includes two types of studies, and it will be helpful to identify them up front. Some of the studies used *global* measures of neurocognition, or composite measures in which performance across a battery is integrated into a single summary measure. In contrast, most of the studies examined *specific* associations between particular neurocognitive constructs (e.g., immediate memory or vigilance) and functional outcome. These two types of studies serve different functions. The first group provides information about the overall magnitude of the relationships across measures, whereas the other group suggests specific neurocognitive-functional connections.

Studies That Have Used Global/Composite Measures of Neurocognition

As mentioned, some studies have used global or composite measures of neurocognition. The advantage of these measures is that they can provide an estimate of the total amount of variance in functional outcome that can be explained by neurocognition in general. The results of these studies suggest that somewhere between 20 and 60 percent of the variance in outcome can be explained by neurocognition. Consider these examples:

1. Using a sophisticated path analysis, Velligan and colleagues (1997) tested the pathways between positive symptoms, negative symptoms, cognition, and activities of daily living in two separate samples. A global measure of cognition accounted for 48 percent and 42 percent of the variance in the activities of daily living for the first and second samples, respectively. It is important to note that this study found that when the pathway from cognitive impairment to functional outcome was in the model, direct pathways from psychotic and negative symptoms to functional outcome were not needed. Their results provide rather strong support for the theory that cognitive impairment, rather than symptoms, influences functional outcome.

2. Another study by Harvey et al. (1998) considered three separate groups of elderly schizophrenia patients that differed substantially in level of adaptive functioning. One group from a nursing home had low levels of adaptive functioning, an acute group had relatively high levels, and a chronic group was intermediate. However, absolute levels of adaptive functioning did not affect the pattern of correlations, which were the same for all groups. In each group a composite measure of cognition correlated most strongly with adaptive functioning, explaining about 40 to 50 percent of the variance. Slightly lower correlations were uncovered for negative symptoms, and positive symptoms were essentially uncorrelated.

Studies That Examined Specific Neurocognitive Constructs

Given the overall findings that global or composite indicators of neurocognition are related to functional outcome, the question shifts to whether we can identify specific

domains of neurocognition that account for the relationships. We can survey the literature three different ways: (1) by the number of replicated findings, (2) through box scores, and (3) through meta-analysis. Figure 1 depicts the replicated findings. In the figure, the neurocognitive constructs are placed on the left, and the three functional outcome domains on the right. Associations are shown by two types of arrows that represent the number of replications. A heavy arrow indicates that at least four separate studies found a significant relationship between the neurocognitive construct and the outcome domain. The smaller arrows indicate that two or three studies reported a significant relationship.

The figure reveals a large number of replicated findings that were reported in four or more studies. Secondary verbal memory was reliably related to every outcome domain, and immediate memory was related to psychosocial skill acquisition. Card sorting and verbal fluency were both associated with community outcomes, and vigilance was linked to skill performance.

Examining the replicated findings is partially, not fully, informative about the consistency of the findings. The number of replicated findings tells us how many times a significant association was found, but it does not tell us how many times an association was looked for. It is somewhat like knowing the number of hits that a baseball player has without knowing his batting average. The equivalent of the batting average for reviewing a literature is the box score.

Figure 1. Neurocognitive prediction of functional outcome

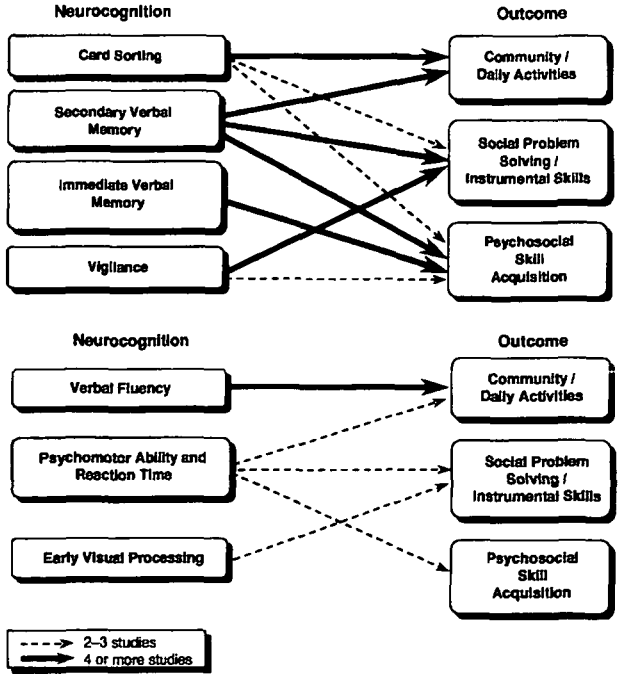


Table 2. Box scores

Domain	Positive	Null	Total
Secondary verbal memory	13	5	18
Immediate verbal memory	5	2	7
Card sorting	11	11	22
Vigilance	9	8	17

Table 2 shows the box scores for some of the key neurocognitive constructs that were implicated in both the previous review and the current one. The table shows the number of positive findings compared with the number of null findings. A complete box score should also show "paradoxical" findings, that is, findings that are significant and in the opposite direction. However, we did not uncover any paradoxical relationships, an observation that is notable by itself because it reflects the rather consistent direction of relationships.

The box scores are consistent with the replicated findings. For example, 13 out of 18 studies reported a significant relationship between secondary verbal memory and functional outcome, and 5 out of 7 reported significant associations between immediate memory and functional outcome. The number of positive findings is impressive in light of the rather low statistical power of most of these studies (see table 1 for listing of power). While the box scores are more informative than number of replications alone, they have limitations. For one, in a box score tally, all studies get one vote. However, there is wide variation in the number of subjects across the studies, and it would be helpful if the studies could be weighted accordingly. Another limitation is that box scores do not provide a clear sense of the magnitude of the effect. Knowing that secondary verbal memory is significant in 13 out of 18 studies does not tell us if the effect size is small, medium, or large. For these kinds of questions, a meta-analysis is valuable.

Results were summarized across studies for four of the key neurocognitive constructs (secondary verbal memory, immediate memory, executive functioning/card sorting, and vigilance) using standard meta-analytic procedures for combining correlation coefficients (Hedges and Olkin 1985). In almost all cases, study results were presented originally in the form of correlation coefficients (Pearson r). In a very few, other statistics (e.g., t) were converted into the equivalent value of r for meta-analysis. When values were not presented, we presumed them to be nonsignificant and estimated them by a value halfway between 0.00 and the lowest possible significant correlation based on the particular sample size. Results in the different outcome domains were treated and analyzed separately, but when more than one correlation coefficient

Table 3. Meta-analyses

Domain	Total sample size	Pooled estimated r^1	Standard error	Effect size	p value[2]
Secondary verbal memory	727	0.29	0.039	medium	< 0.000001
Immediate verbal memory	188	0.40	0.077	medium–large	< 0.000001
Card sorting	1002	0.23	0.033	small–medium	< 0.000001
Vigilance	682	0.20	0.040	small–medium	< 0.000001

[1] Estimates weighted by sample size

[2] Ratio of pooled estimate of r divided by its standard error referred to a normal distribution

was reported within one outcome domain in a single study, the separate values of r were first transformed using Fisher's z and then averaged, yielding no more than one result for meta-analysis per domain per study. The meta-analytic procedures followed several steps. The homogeneity of the various results was tested with the Q statistic. In addition, the pooled estimate of r (or, equivalently, z) was obtained on the basis of weighted z values and tested for significance by reference to the normal curve. An a priori hypothesis (discussed in a later section) about subsets within one domain was tested by separating the studies into groups and testing the difference using weighted linear regression.

The results from four separate meta-analyses are displayed in table 3. At a glance, one can see that the analyses are adequately powered with sample sizes ranging from 188 to 1,002. All of the relationships between the constructs and the outcome domains are highly significant (all p values < 0.000001). The estimated pooled r's for the relationships range from 0.20 to 0.40, and the effect sizes range from small-medium to medium-large. The Q statistic revealed significant heterogeneity in only the group of studies on vigilance. The heterogeneity was largely due to two outliers: one study with a very high association (Bowen et al. 1994) and one study with a very low association (Bellack et al. 1999). Overall, the meta-analyses convincingly demonstrate what was suggested in the previous review (Green 1996), that each of these four neurocognitive constructs have significant relationships with functional outcome.

Are We Measuring the "Right Stuff"?

From this review of the literature, one can conclude that neurocognitive variables are indeed related to functional outcome and that the effect sizes (20%–60% for the composite measures) are not trivial. Obviously, functional outcome is determined by a host of factors. The current literature offers convincing support for the idea that neurocognitive abilities constitute one key determinant. From this literature, we have learned about *whether* neurocognition is related to functional outcome. However, we have learned very little about *how* neurocognition is related to functional outcome. Identifying mechanisms and mediators was not a goal for these studies. Instead, these studies were testing neurocognitive-functional relationships to see if they existed, or to better understand heterogeneity in functional outcome. Once relationships have been demonstrated, it is reasonable to make a more concerted effort to identify mechanisms.

The ways in which neurocognitive measures are selected has probably limited our ability to identify mechanisms. The neurocognitive assessments for these studies typically come from two sources. For the most part, they are selected from standard clinical neuropsychological measures that would be found in neuropsychological clinics. These measures, which are usually well standardized, were developed for distinguishing impaired (often from focal or diffuse cerebral injury) from normal performance. In addition, many laboratories add measures drawn from experimental psychology, such as the Continuous Performance Test for vigilance (Nuechterlein 1991). Measures such as the Continuous Performance Test have shown considerable promise as indicators of vulnerability to schizophrenia. In studying relationships with functional outcome, the tests are being used for different purposes than the ones for which they were developed.

While these neurocognitive tests perform reasonably well as predictors and correlates of functional outcome, we might expect other tests designed and selected for assessing related capacities to be more useful. To accomplish this greater degree of "fine-tuning," we first need to clarify

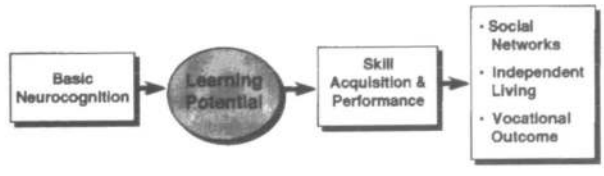
exactly what we hope to measure. We previously suggested that social cognition may be one promising mediator between basic neurocognition and social competence (Kee et al. 1998; Green and Nuechterlein 1999). Another key mediator would be the process(es) that underlie one's ability to acquire and perform instrumental life skills. As mentioned above, community functioning can be considered as the sum total of the acquisition and performance of key life skills. We can evaluate "success" in a rehabilitation program by using gross measures of acquisition, which presumes a capacity for learning. However, we may want to have a different measure, one that directly assesses *learning potential.* Learning potential involves a focus on latent capacity rather than on developed abilities (Grigorenko and Sternberg 1998). It is dependent on basic neurocognition and is related to psychosocial skill acquisition, but it is not identical to either.

The idea of "learning potential" requires a fundamental shift in assessment: from what the individual currently knows to what the individual is capable of learning. A possible role for learning potential as a mediator between basic neurocognition and skill acquisition is illustrated in figure 2. Assessments of learning potential fall under the general category of "dynamic assessment," which refers to systematically eliciting and determining intra-individual variability during the course of a test (Guthke et al. 1997). Before we discuss applications of these sorts of dynamic assessments to schizophrenia, we provide a brief discussion of the conceptual and psychometric origins of the concept of learning potential.

Origins of Learning Potential: Vigotsky and Zubin

Lev Vigotsky was a supremely gifted Soviet psychologist who was active in the years following the Russian revolution and civil war. He had profound influence on an impressive variety of content areas, and several volumes have been dedicated to his contributions (Kozulin 1990). Literacy became a major issue in the Soviet Union in the 1920s when Lenin mandated a massive drive to eliminate illiteracy (Sutton 1988). Vigotsky and his students dedicated themselves to addressing this practical problem of illiteracy, which was especially high among the national minorities of Central Asia (Wertsch 1985).

Figure 2. Learning potential as a mediator for functional outcome



Vigotsky and his students claimed that the tests available at that time were not useful for their purposes because the tests had been developed for other purposes. (We would argue that our review of the literature highlights the same problem.) There were no tests that could be meaningfully used with the national minorities, such as those in Uzbekistan. The existing tests, even when translated into local languages, almost always revealed a mental backwardness among the children of the national minorities. The flaw, according to Vigotsky, was not just in the specific test; instead, an entirely new approach was needed. He believed that new tests would have to assess a person's capacity for learning, not only what he or she had previously learned. Vigotsky outlined the key components of a theory of learning potential but was not able to formally test his theory because he died at an early age. Further, a Stalinist decree banned his work soon after his death. Hence, his insightful work was essentially unknown outside of the Soviet Union until several decades later.

The concept of learning potential presents a substantial practical challenge regarding measurement. Even if we agree that learning potential is a valuable idea, how do we turn that into a method for dynamic assessment? One of the key psychometric influences for modern approaches to dynamic assessment comes from Joseph Zubin. His interests in this area appear to have been entirely independent of the work of Vigotsky. In 1950, Zubin proposed four axioms about applying statistical methods to pathological conditions (Zubin 1950). Instead of the more typical emphases on group means, his interest was on repeated testing and within-subject variability. Zubin wrote that the variability within a person is "characteristic of the individual and varies as much or more from person to person as does the level around which this variability occurs." To examine this within-subject variability, repeated assessments are required. With repeated assessments, one can study the influences on performance, such as training and intervention.

Zubin had anticipated the focus of dynamic assessment. As opposed to static assessment at one point in time, dynamic assessment requires repeated assessments, often with feedback between the examiner and the test taker. The focus is not how much someone knows to start with but how much someone can learn with intervention. This capacity for learning should be dependent on (but not identical to) certain basic neurocognitive processes, and it should be closely related to certain external outcome variables relevant to schizophrenia, such as psychosocial rehabilitation.

Applications of Dynamic Assessments to Schizophrenia

Surprisingly few of the laboratories that have developed dynamic assessment methods have applied them to the study of schizophrenia. One exception is work from Wiedl and colleagues at the University of Osnabruck (Wiedl and Schottke 1995). Their applications of dynamic assessment have involved a categorical approach in which they divide patients into subgroups based on performance before and after a training intervention. The categorical approach was an attempt to address basic problems in analyzing data from dynamic assessment methods. Eventually, dynamic assessment methods may benefit from dynamical, nonlinear models that have been used with other types of tasks (Paulus et al. 1996).

The measure of choice for Wiedl's work was the WCST, which has been the focus of numerous attempts at remediation with schizophrenic patients (Goldberg et al. 1987; Kern et al. 1996). There is considerable between-subject variability in the response to training on this measure. In our initial publication on this topic (Green et al. 1990), we suggested that training on the WCST appeared to reveal two groups of patients: learners and nonlearners. The idea of heterogeneity on WCST performance was reinforced by our studies of the neuropsychology of schizophrenia (Braff et al. 1991). The idea of learning subtypes has been thoughtfully developed within the context of dynamic assessment by Wiedl and colleagues.

Based on performance on the WCST both before and after training, three groups are identified (Schottke et al. 1993). Learners start out with poor performance and improve a requisite amount following instructions. Nonlearners start out poorly and do not improve with instruction. High scorers start out performing well and continue to perform well after instruction. Group membership cannot be determined by performance at the first test (learners look like nonlearners) nor by change scores (high scorers look like nonlearners). It should be emphasized that the nonlearner status is not general—it is specific to this particular task and this particular training method. Different types of instruction, such as more detailed, errorless learning techniques (Kern et al. 1996), would be well suited for patients who are nonlearners on the briefer instructional method.

Validity of learner status for schizophrenia patients is starting to be demonstrated (Wiedl and Weinhobst 1999). The groups have been shown to differ in length of hospitalization and in the level of demand of their current rehabilitation program (i.e., nonlearners were placed in less demanding types of rehabilitation programs than learners and high scorers). In terms of predictive validity, learner status at baseline was related to degree of success on a brief psychosocial rehabilitation program. Recent data indicate that the groups also differ significantly in vigilance as measured by performance on the Continuous Performance Test (Wiedl et al., submitted).

Returning to the review of the literature, the neurocognitive measures were largely static (based on single assessment) as opposed to dynamic (based on within-subject change across assessments). However, some measures of secondary memory were similar to dynamic assessment measures. Secondary memory measures were of two types: (1) memory for lists of words and (2) memory for passages and prose. The list learning measures are somewhat similar in format to dynamic assessment measures because the former involve memory for a repeated list of words and they assess within-session learning. The tests of passages and prose are also excellent measures of secondary memory, but they do not have a dynamic assessment component. If learning potential is truly relevant to functional outcome in schizophrenia as we propose, then the list learning tests should be especially good predictors and correlates, even compared with the other tests of secondary memory. We conducted two additional meta-analyses in which we divided the 18 studies of secondary verbal memory and functional outcome into two categories: (1) studies that used list learning tests, and (2) studies that used tests of passages and prose. The relationships with functional outcome were significant in both groups of studies; however, the strengths of the associations were significantly different. The estimated r for the list learning studies was 0.42; for the other studies, it was 0.24. Hence, the only test in our review that had properties of dynamic assessment seemed to be particularly related to functional outcome, even compared with other memory measures that did not have those properties.

Implications for Rehabilitation

Can knowledge of a patient's neurocognitive strengths and weaknesses guide delivery of psychosocial rehabilitation? One approach might involve maintaining the same type of intervention but changing its intensity, based on the patient's neurocognitive abilities. For example, assessment of neurocognitive abilities might be used to place patients in different rehabilitation tracks. If patients have deficits in verbal memory, the instructor may decide to use more repetition of the instructional material or, alternatively, present the material at a slower pace. Note that this type of tailoring the instruction to the neurocognitive needs of the patients does not require substantial modification of the content of the training program.

Another approach would be to use a neurocognitive assessment to assign patients to a separate training method altogether. For example, subjects who are con-

sidered nonlearners based on the dynamic assessment mentioned above are still likely to be good candidates for alternative types of instruction, such as those based on errorless learning principles. Errorless learning is a method of training that minimizes errors during skill acquisition. Training begins at the simplest, most basic skill level in which there is a high probability for success and progresses stepwise through a series of increasingly complex training stages. It has been used effectively with the developmentally disabled and more recently in studies with schizophrenia patients (Kern et al. 1996). Errorless learning and similar teaching approaches deemphasize the acquisition of skill through didactic instruction and instead emphasize procedural aspects of learning, an area that is putatively more intact in persons with schizophrenia. Alternative rehabilitation instructional modes, while promising, are largely experimental and have not yet been developed for use on a large scale.

Conclusions

In our review of the literature, we uncovered significant associations between neurocognition and functional outcomes though a survey of replicated findings, box scores, and meta-analyses. The meta-analyses revealed associations between specific neurocognitive constructs and functional outcome. The relationships are larger when we consider global or composite measures of neurocognition. We propose that a concept like learning potential can be viewed as a mediator—one mechanism through which basic neurocognitive processes are related to skill acquisition and functional outcome in schizophrenia (see figure 2). It is not the only one—we previously suggested that social cognition was another promising mediator (Kee et al. 1998; Green and Nuechterlein 1999). The search for mediators between neurocognition and functional outcome is important for several reasons. First, this literature has been largely atheoretical, and identifying mediating variables will help to provide a theoretical framework for understanding the relationships between neurocognition and outcome. Second, the mediators themselves might reasonably become the target of interventions. For example, interventions to improve perception of emotion are being developed. Even learning potential may be a characteristic of a person who is available for intervention. Third, assessments of potential mediators such as learning potential and social cognition might reasonably be added to existing batteries in an effort to assess the "right stuff" for adaptive functioning in schizophrenia.

Future studies will explore the mechanisms and mediators underlying relationships between neurocognition and functional outcome. It should be noted that these neurocognitive-functional relationships are by no means unique to schizophrenia. The impact of neurocognitive deficits in other disorders such as multiple sclerosis (Rao et al. 1991) and AIDS (Heaton et al. 1994) are well documented. Indeed, even in a nonclinical elderly sample, cognitive deficits assessed by a mental status examination predicted activities of daily living (Moritz et al. 1995). Hence, we should not be surprised that neurocognition is related to functional outcome in schizophrenia. On the contrary, if the findings did not show such a relationship, we would be confronted with a much more puzzling mystery to explain.

In conclusion, we can state with considerable confidence, based on the updated review of the rapidly expanding literature, that certain aspects of neurocognition (e.g., secondary verbal memory, immediate memory, vigilance, and executive functioning/card sorting) are related to functional outcome in schizophrenia. These relationships are highly significant with medium to large effect sizes. In addition, when studies examine the effects of composite neurocognitive measures, the percentage of variance explained in functional outcome is not small (generally 20%–60%). The major limitation of this line of investigation is that we still know rather little about the underlying mechanisms through which these effects operate. One possibility, admittedly speculative at this time, is that the neurocognitive effects on functional outcome operate through the construct of learning potential.

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Acknowledgments

The authors thank Mary Jane Robertson, M.S., for her help in the preparation of the manuscript and figures. Kimmy S. Kee, Ph.D., and Mark J. Sergi, Ph.D., contributed to the literature review.

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