



Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS

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Abstract

It is generally accepted that cognitive deficits in schizophrenia are related to functional outcome. However, support for longitudinal relationships between cognition and functional outcome has not been as well documented. The current paper presents a review of 18 recently published longitudinal studies (minimum 6-month follow up) of the relationships between cognition and community outcome in schizophrenia. Results from these studies reveal considerable support for longitudinal associations between cognition and community outcome in schizophrenia. These studies demonstrate that cognitive assessment predict later functional outcome and provide a rationale for psychopharmacological interventions for cognitive deficits in schizophrenia. Although the relationships between cognition and community outcome are well-supported, it is clear that community functioning is also affected by a host of factors apart from cognition that are usually not considered in clinical trial studies (e.g., psychosocial rehabilitation and educational/vocational opportunities). In the second part of the paper, we consider intervening steps between cognitive performance measures and community outcome. These steps are apt to have important implications for clinical trials of cognition-enhancing agents in schizophrenia.

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As described in this issue ([Marder and Fenton, this issue](#)), the National Institute of Mental Health—Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH-MATRICES) ini-

tiative is dedicated to stimulating the development of cognition-enhancing drugs for schizophrenia. A key premise for MATRICS is that cognitive deficits as assessed with performance measures are related to the daily activities of patients with schizophrenia. This linkage to functional outcome is a large part of the reason why cognitive deficits are considered to be logical targets for psychopharmacological intervention. Because fundamental aspects of cognition appear

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to be necessary (together with important learning experiences) for effective everyday functioning (e.g., Heaton and Pendleton, 1981), improvements of disease-related cognitive deficits may provide essential building blocks for rehabilitation in this disorder. Although documenting the links between cognitive performance and functional outcome does not guarantee that a cognition-enhancing drug will directly improve functional outcome in schizophrenia, it is a logical first step in the process.

Two previous reviews of the literature have summarized the evidence for associations between cognition and functional outcome (Green, 1996; Green et al., 2000). These reviews considered a range of functional outcome measures, including measures of skill acquisition in psychosocial rehabilitation treatment, demonstration of ability to solve simulated interpersonal problems, and community (social and occupational) functioning. The reviews indicated consistent and highly significant relationships between a range of key cognitive constructs (e.g., episodic memory, immediate/working memory, vigilance, and executive functioning) and functional outcome in schizophrenia. The effect sizes of these relationships tended to be in the medium range ($r=0.30$ or $d=0.50$ are medium effect sizes), which means that the relationships are at a level that should be clinically noticeable (Cohen, 1977). If composite indices (e.g., summary scores) of cognitive measures are used instead of individual cognitive measures, the relationships can be quite large.

Based on the interviews of invited experts for MATRICS (Kern et al., *this issue*) it was obvious that almost all of the experts accepted the empirical support for cross-sectional linkages between cognitive deficits and functional outcome. However, there was less confidence among the experts about whether these relationships hold for prospective, as well as cross-sectional, relationships. This reduced confidence in prospective links between cognition and daily functioning reflects the fact that most studies in the previous reviews were cross-sectional and not capable of establishing predictive relationships.

Establishing the cross-sectional and longitudinal links between cognition and outcome provides a foundation for the broader question of how to demonstrate cognition-enhancing effects of medications. Specifically, it raises the question of how

improvements in cognition might, or might not, translate into improved community outcome. To address this question, it will be necessary to better understand the steps between cognitive improvement and functional changes, which is the focus of the second part of this paper.

Hence, this paper will consider two general questions. First, we will review recent longitudinal studies on the relationships between cognition and community outcome. Because the existence of longitudinal relationships between cognition and functional outcome is a key premise for MATRICS, it is important to assess the strength of the evidence for longitudinal relationships. Second, we will consider intervening steps between cognitive performance measures and community outcome. These steps are apt to have important implications for clinical trials of cognition-enhancing agents in schizophrenia.

1. Longitudinal studies of cognition and community outcome in schizophrenia

For this review of the literature, we were primarily interested in longitudinal studies that examined the cognitive predictors of some aspect of community functioning. With this fairly specific goal in mind, we did not consider the cognitive predictors and correlates of rehabilitation success or performance on simulated tasks of interpersonal communication, as we have done in our previous reviews (Green, 1996; Green et al., 2000). We specifically selected studies that were not part of the previous reviews, so the review starts with studies published in 1999. We selected studies for this review that met the following criteria:

- Minimum 6-month follow up period,
- Not included in previous review (Green et al., 2000),
- Assessed some aspect of community outcome (i.e., social, vocational, independent living).

We located 18 published studies that met these criteria, shown in Table 1. The outcome measures for these studies ranged from specific measures of work outcome (such as job performance and job tenure) to general measures of social adaptation and degree of

independent living. Most of the studies used reports of community functioning from subjects or caregivers, as opposed to direct observation of daily activities.

Considering the results in terms of box scores, the studies were highly encouraging: 14 had positive results, 2 had negative, and 2 were mixed. The 12 positive studies had effect sizes for the relationships in the medium to large range (Bell and Bryson, 2001; Bryson and Bell, 2003; Dickerson et al., 1999; Friedman et al., 2002; Fujii and Wylie, 2003; Fujii et al., 2004; Gold et al., 2002; Jaeger et al., 2003; Keshavan et al., 2003; Robinson et al., 2004; Smith et al., 2002; Stirling et al., 2003; Velligan et al., 2000; Woonings et al., 2002). In two situations, the studies came from the same research group and may have had overlapping samples (Bell and Bryson, 2001; Bryson and Bell, 2003; Fujii and Wylie, 2003; Fujii et al., 2004).

Two studies had negative results that did not support links between baseline cognition and community outcome (Addington and Addington, 2000; Norman et al., 1999). One of these studies (Addington and Addington, 2000) found that cognition predicted social problem solving; however the results were not significant for social functioning, which is outcome more relevant to this review. Two of the studies were neither clearly positive nor clearly negative. One study had positive results for one out of two samples (Kasckow et al., 2001), and one had positive results for one out of two types of community outcome (Malla et al., 2002).

In addition to the studies in the table, we will briefly mention three unpublished studies from collaborative projects at UCLA and University of Southern California. All of these studies are positive with large effect sizes. One study (Nuechterlein et al., 1999) examined the predictors of returning to work or school after 1 year for 70 recent-onset schizophrenia or schizoaffective patients. Among the cognitive factors, an attentional/perceptual factor predicted work/school resumption, even after controlling for clinical symptoms. In a later study with a separate sample, Nuechterlein et al. (2003) examined the predictors of work resumption after 9 months in 35 recent-onset schizophrenia or schizoaffective patients. Cognitive factors at baseline accounted for 52% of the variance in outcome. Lastly, Brekke et al. (2003) found that cognitive variables at baseline were

significant predictors of change in global community outcome after 1 year in 139 schizophrenia or schizoaffective patients. Subjects with better cognition showed greater change in outcome over time. All of the participants in these three studies were participating in comprehensive psychosocial rehabilitation programs, which may have contributed to the positive results by providing greater opportunity for patients with relatively preserved cognitive skills to achieve better community outcomes.

The studies that comprise this review had several methodological advantages compared with earlier studies in this area. First, the sample sizes of the studies were reasonably large (see Table 1) and, as a result, the studies had greater statistical power than those included in previous reviews. Second, several of the studies examined fairly specific outcome measures, such as job tenure (Gold et al., 2002), success on a job rehabilitation placement (Bryson and Bell, 2003), or social success following a rehabilitation program (Woonings et al., 2002). Third, the follow up periods were reasonably long, with time periods ranging from 6 months up to 20 years (for a retrospective study) with 8 studies having a follow up of 2 years or more. Fourth, several of the studies examined correlations with *changes* in functional outcome, as opposed to static measures of outcome (Brekke et al., 2003; Friedman et al., 2002; Smith et al., 2002; Woonings et al., 2002). These findings of baseline cognition predicting change in outcome are particularly informative because they indicate cognition has added value for predicting how much people will benefit from an intervention, above and beyond associations with current functional status. Only two of the studies considered change in cognitive functioning (Friedman et al., 2002; Stirling et al., 2003), and these examined cognitive decline, not improvement. Change in cognition will become more relevant as a predictor of outcome in the coming years as more effective cognition-enhancing agents become part of clinical trials.

From this review of recent studies in this area, it is reasonable to conclude that cognitive performance at baseline tends to be related to community outcome months or years later. Further, some studies showed that changes in outcome over the follow up period were associated with baseline cognitive performance. This review does not allow any firm conclusions

Table 1
Longitudinal studies of neurocognition and functional outcome

Study	Sample size/power	Length of follow up	Neurocognitive predictors	Outcome measures	Major findings	Effect size—for main finding ^a
Addington and Addington, 2000	65 S	6 months	Verbal IQ, Rey complex figure, WMS-R logical memory and paired associates; WCST, verbal fluency, CPT, Span	SFS (Birchwood et al., 1990), QOL Scale (Heinrichs et al., 1984), social problem solving	Cognitive measures predicted social problem solving, but not social functioning and QOL	Not applicable
Bell and Bryson, 2001	33 S or SA	6 months	WCST, IQ, CPT, WMS-R, HVLIT, proverbs, emotion recognition	Work Behavior Inventory (Bryson et al., 1997)	Cognitive measures predicted rate of improvement in work performance; symptoms did not	Large
Bryson and Bell, 2003	96 S or SA	6 months	WCST, IQ, CPT, WMS-R, HVLIT, proverbs, emotion recognition PANSS	Work Behavior Inventory (Bryson et al., 1997)	Cognitive measures predicted improvement in work performance; symptoms did not. Vigilance was strongest for 1st 13 weeks, verbal memory was strongest for 2nd 13 weeks	Large
Dickerson et al., 1999	72 S	2 years	IQ subtests, WCST, WMS-R, Rey Complex Figure, Trail Making, Aphasia screening, Fluency PANSS	SFS (Birchwood et al., 1990), MCAS (Barker et al., 1994)	Cognitive measures predicted change in social and community outcome; Aphasia screening and negative symptoms predicted outcome status	Medium for change in outcome; large for outcome status
PANSS Friedman et al., 2002	124 S elderly patients	4 years (three assessments)	CERAD Neuropsychological Battery	ADLs from Alzheimer's Disease Assessment Scale	Baseline cognition predicted ADLs at 4 years. Change in cognition (2nd to 3rd assessment) related to change in ADLs (2nd to 3rd assessment)	Medium for baseline prediction. Large for change scores

Fujii and Wylie, 2003	26 S	20-year retrospective	IQ, Trail Making B, Halstead categories test, digit span, logical memory, finger tapping	Functional Level Scale (Leff et al., 1985).	Functional level was predicted by logical memory	Large
Fujii et al., 2004	30 chronic mental illness (mainly S or SA)	15-year retrospective	IQ, WMS, Halstead categories test, digit span, finger tapping	Quality of Life scale (Lehman, 1988)	Memory, executive functioning, motor speed, and working memory predicted objective indices of quality of life	Large
Gold et al., 2002	40 chronic mental illness (mainly S or SA)	2 years	Reading, IQ, Trail Making A and B, Stroop, CPT, WCST, verbal fluency, LNS, finger tapping, Purdue pegboard, WMS-III, RBANS	Total number of hours worked	Wide range cognitive measures predicted number of hours worked at 12 and 24 months	Large to medium
Jaeger et al., 2003	124 S or SA	1.5 years	IQ, WMS-R, LNS, Stroop, WCST, Trail Making A and B, verbal fluency, figural fluency, Grooved pegboard, tapping PANSS	Community outcome (work, school, independent living)	Attention, working memory, and verbal fluency factors predicted outcome after controlling for negative symptoms	Large
Kasckow et al., 2001	48 S inpatients; 37 outpatients	6 months	MMSE	Quality of Well Being (Kaplan and Anderson, 1990)	Strong prediction for inpatients; ns for outpatients	Large for inpatients; not applicable for outpatients
Keshavan et al., 2003	104 first episode psychotic patients (mainly S or SA)	1 and 2 years (68 patients for 2-year follow up)	WCST, Trail Making A and B, WMS-R visual learning, digit span, CVLT SANS, SAPS	Strauss Carpenter Outcome	Cognitive measures predicted outcome at year 2; predictions for year 1 were ns	Medium to large
Malla et al., 2002	66 1st episode psychotic disorders	1 year	IQ, WMS-III, PASAT, WCST, CPT, verbal fluency	Social relations, daily life activities (Becker et al., 1993)	Cognition predicted social relations, but not daily life activities	Medium for social, not applicable for daily life activities
Norman et al., 1999	50 S	1 year	WCST, RAVLT, WMS-R logical memory, BVRT, Rey complex figure, design fluency, verbal fluency	Community adaptation (Rosen et al., 1989)	Non significant cognitive prediction of outcome	Not applicable

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Table 1 (continued)

Study	Sample size/power	Length of follow up	Neurocognitive predictors	Outcome measures	Major findings	Effect size—for main finding ^a
Robinson et al., 2004	94 S/SA	3–8 years (median of 4 years)	Multiple tests of language, memory, attention, executive functioning, motor function, visual spatial function	Social Adjustment Scale II (Schooler et al., 1979)	All cognitive domains predicted outcome	Medium
Smith et al., 2002	46 S/SA	1 year (3 month intervals)	Digit span distractibility test, CVLT SANS, SAPS	Social Behavior Scale (Wykes and Sturt, 1986).	Working memory associated with increase in social behavior over 1 year; Disorganized and negative symptoms also predicted	Large
Stirling et al., 2003	37 S/SA (24 retested at follow up)	10 years	IQ subtests, memory for designs, WCST, fluency, SANS, SAPS	Work and social outcome	Changes in IQ, memory for designs, and fluency correlated with outcome	Medium and large
Velligan et al., 2000	40 S	1.5 years	CPT-IP, digit span, HVLTL, RT, WCST, Rey complex figure	GAF, ADLs, work, independent living (Barker et al., 1994)	Consistent relationships with verbal memory and executive functioning; selected relationships with vigilance and visual memory	Medium and Large
Woonings et al., 2002	44 S	8 months	RAVLT, CPT, WCST, Tower of Hanoi, immediate memory	Social functioning (Baker and Hall, 1988)	Vigilance and card sorting predicted baseline social functioning and change in social functioning following rehab	Medium

Abbreviations: ADLs—Activities of Daily Living; BVRT—Benton Visual Retention Test; CERAD—Consortium to Establish a Registry for Alzheimer's Disease; CPT—Continuous Performance Test; CPT-IP—Continuous performance Test, Identical Pairs; CVLT—California Verbal Learning Test; GAF—Global Assessment of Functioning; HVLTL—Hopkins Verbal Learning Test; LNS—Letter Number Sequencing; MCAS—Multnomah Community Ability Scale; MMSE—Mini Mental State Examination; PANSS—Positive and Negative Syndrome Scale; PASAT—Paced Auditory Serial Addition Test; QOL—Quality of Life; RAVLT—Rey Auditory Verbal Learning Test; RBANS—Repeatable Brief Assessment of Neuropsychological Status; RT—Reaction time; S—Schizophrenia; SA—Schizoaffective Disorder; SANS—Schedule for the Assessment of Negative Symptoms; SAPS—Schedule for the Assessment of Positive Symptoms; SFS—Social Functioning Scale; Span—Span of Apprehension; WCST—Wisconsin Card Sorting Test; WMS-R—Wechsler Memory Test, Revised.

^a For correlations (*r*), small, medium, and large effect sizes are 0.1, 0.3 and 0.5, respectively. For group differences (*d*), small, medium, and large effect sizes are 0.2, 0.5, 0.8, respectively (Cohen, 1977).

about which cognitive constructs (e.g., attention, verbal memory, executive functions, etc.) are especially related to community outcome more than others. In summary, the evidence for longitudinal relationships between cognition and community outcome in schizophrenia is impressive.

2. Mapping changes in cognitive performance measures onto changes in functional outcome

At the MATRICS meeting in April 2003 (see summary in Green et al., 2004), a key discussion point was whether changes in cognitive performance alone should be sufficient for a drug to receive approval from the U.S. Food and Drug Administration (FDA). On the one hand, improvement on a cognitive performance measure appears to be the most reliable and sensitive way to establish that a drug improves cognition. On the other hand, changes on cognitive performance measures alone may not be sufficient evidence of patient improvement (i.e., may not have sufficient face validity of clinical change) for the FDA to grant approval to a drug. Depending on the final decision of the FDA, it may be necessary to show that a drug brings about improvement on some type of functional outcome measure, as well as cognitive performance gains, to receive approval. This requirement for improvement on two types of measures (i.e., co-primary outcome measures) would be similar to the requirements for anti-dementia drugs.

One might initially think that community functioning could serve as a co-primary outcome measure for drug approval, in addition to cognitive performance. However, requiring changes in community status, such as work and social outcome, introduces a host of conceptual and psychometric challenges. First, there is increasing evidence that intervening variables (e.g., social cognition) may act between measures of neurocognition and functional outcome (Brekke et al., 2003; Green and Nuechterlein, 1999). The presence of these intervening variables will obscure the translation of cognition-enhancing effects into changes in functional status. Partly for these reasons, it is expected that improvements in cognition will take a long time to translate into functional improvements (Brekke et al., 1997). Second, there is a measurement problem in schizophrenia: self-report measures of

functional status tend to be less reliable than objective cognitive performance measures. Lastly, the changes in daily functioning are far removed from the biological systems that would be altered by cognition-enhancing drugs, and they rely on social/environmental opportunities. They would heavily depend on factors that are typically beyond the control of clinical trial studies, including availability of psychosocial rehabilitation, social support networks, local employment rates and educational opportunities. If the changes in later functional outcome are ultimately required for drug approval, it may be necessary to include systematic rehabilitation treatment in addition to pharmacological intervention in clinical trials. Thus patients who evidence pharmacologically enhanced cognition might have notably better functional outcome when provided with psychosocial or cognitive rehabilitation, but possibly not in the absence of such non-pharmacological treatment.

Fig. 1 illustrates some of the key steps that operate between cognitive performance measures and community outcome. The *x*-axis represents a dimension that runs from proximal, within-subject factors to distal, interpersonal factors. This dimension also reflects differences in sensitivity to the cognition-enhancing effects of drugs with the measures toward the left being more directly sensitive to medication effects. The *y*-axis represents locations of assessments ranging from the cognitive performance laboratory to the community. Arrows on the figure show well-supported linkages between cognitive performance measures and the other types of assessments. One implication of this model is that, if it becomes necessary to select a co-primary measure, it is better to select one that is located closer to the left of the diagram (i.e., one that is more sensitive to the effects of drugs and more immediately tied to cognitive change).

Community outcome is the most distal of the constructs on the figure, and might not be an appropriate co-primary measure for the reasons listed above. A requirement for changes in functional status as a co-primary outcome variable may be setting a bar too high and could lead to the failure of applications to the FDA, even for drugs that do improve cognitive performance measures. An alternative co-primary measure might involve an interview-based assessment of cognition in which patients rate their own cognitive

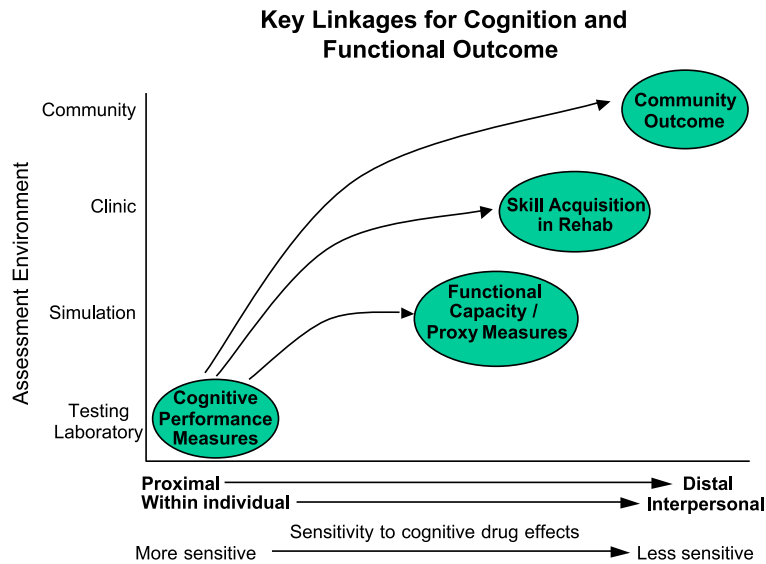


Fig. 1. Key linkages for cognition and functional outcome.

abilities, or caregivers give their impressions of a subject's cognitive level. Such measures have not yet been validated for use in schizophrenia, although efforts are underway to do so. Another possible alternative for a co-primary measure may be standardized tests of functional capacity. Functional capacity refers to an individual's capacity for performing key tasks of daily living. Assessments of functional capacity may use props and role playing to assess instrumental skills such as whether a person can maintain a social conversation, prepare a meal, take public transportation, or manage their medications. Assessments of functional capacity are simulated activities conducted in the clinic and do not rely on observing the individual in the community (Bellack et al., 1994; Patterson et al., 2001). If a patient performs well on a measure of functional capacity (also called "proxy" measures), that does not guarantee that he or she will perform the tasks in the community. It does mean, however, that the person probably could perform the task in the community if they had a chance and wanted to do so. Such proxy measures of functional capacity indicate what a participant can do as a result of cognitive enhancement, as opposed to what he or she actually does (which will be affected by a variety of uncontrolled environmental, motivational, and experiential factors). Changes in functional capacity are likely to occur

more closely in time with changes in underlying cognitive performance.

In support of the utility of functional capacity measures, several studies have found significant cross-sectional associations between cognitive performance and proxy measures of social problem solving and daily activities (Addington and Addington, 1999; Bellack et al., 1994; Heaton et al., 2004; Heaton et al., 1996; Klapow et al., 1997). The data linking proxy measures to community functioning are lacking in schizophrenia at this point, although such links have been established with other diseases (Heaton et al., 2004). Nonetheless, proxy measures of functional capacity do have substantial face validity and might be appropriate for clinical trials of cognition-enhancing agents in schizophrenia, if co-primary measures are required.

3. Summary

In summary, we have documented rather consistent relationships between baseline assessments in schizophrenia and community functioning at a minimum of 6 months later. The cross-sectional relationships between cognition and functional outcome have been well established in previous reviews (Green, 1996; Green et al., 2000), and the demonstration of these

longitudinal relationships in the current review indicates that cognitive performance at one point in time predicts community functioning at a later point.

Although the relationships between cognition and community outcome are well-supported, it is clear that community functioning also is affected by a host of factors that are usually beyond the control of clinical trial studies, such as motivation, social support, and educational/vocational opportunities. A requirement that cognition-enhancing drugs would also need to show short-term change in community outcome may be an overly strict requirement for FDA approval. If a co-primary outcome variable is needed for drug approval, “proxy” measures of functional capacity may be a reasonable alternative; it appears that cognitive performance measures are linked to proxy measures, and the proxy measures are clear analogues for daily activities (i.e., have more face validity). However, the validity of these proxy measures (especially in terms of their relationships to community outcome) still needs to be established.

Documenting longitudinal relationships between cognition and functional outcome is a logical initial step for the goals of MATRICS. The MATRICS initiative seeks to stimulate the development of cognition-enhancing agents and thereby, to provide meaningful improvements in patients’ community functioning. Establishing predictive relationships between cognitive performance and community functioning adds encouraging support for this endeavor.

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