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## Neurocognition as a Predictor of Response to Evidence-Based Psychosocial Interventions in Schizophrenia: What is the State of the Evidence?

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### Abstract

Impairment in functional status is a hallmark of schizophrenia that has been linked to deficits in aspects of neurocognition (e.g., attention, memory, and problem-solving). A growing number of evidence-based behavioral interventions have been developed to address impairment in functional status, yet the relationships between these interventions and neurocognitive impairment are not well-understood. We conducted a synthetic, critical literature review of studies of performance on neurocognitive tests as a predictor of response to evidence-based behavioral treatment in schizophrenia. Behavioral treatments were selected based on the Patient Outcomes Research Team (PORT; Dixon et al., 2010) recommendations for practice and areas of emerging interest. Comprehensive searches of PsychINFO and MEDLINE/PUBMED databases identified 20 relevant studies. Results revealed that: (1) attention and memory measured at study entry were most frequently linked to proximal measures of progress in social skill training programs, (2) composite measures of neurocognitive function, as well attention, memory and problem-solving, were linked to progress in work therapy and supported employment programs, and comprehensive, integrated programs of psychosocial rehabilitation, while (3) baseline impairment on neurocognitive tests was not shown to limit progress in treatment studies of cognitive-behavioral therapy. The relevance of these findings for clinical practice and future research is discussed.

### Introduction

Deficits in functional outcome are one of the hallmarks of schizophrenia, a component of DSM-IV (APA, 1994) diagnosis and encompass abilities for achieving meaningful social relationships, maintaining employment, and fulfilling personal needs through self-care activities and appropriate interactions with the environment (e.g., Bellack, Morrison, Wixted, & Mueser, 1990). Indeed, these deficits are evident in individuals at-risk for developing schizophrenia (Davidson, Reichenberg, Rabinowitz, Weiser, & Kaplan, 1999; Hans, Auerbach, Asarnow, Styr, & Marcus, 2000), are refractory to pharmacologic intervention (e.g., Bellack, Morrison, Wixted, & Mueser, 1990), and impoverished functional outcome negatively impacts subjective quality-of-life (Penn, Corrigan, Bentall, Racenstein, & Newman, 1997). In light of these findings, there has been rapidly growing

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interest in the development and implementation of psychosocial interventions devised to address these pervasive and persistent deficits in functional outcome in schizophrenia.

The Patient Outcomes Research Team (PORT) program, initiated by the U.S. Department of Health and Human Services, has investigated the empirical support for a variety of psychosocial treatments for schizophrenia (Lehman & Steinwachs, 1998; Lehman et al., 2004; Dixon et al., 2010). Most recent PORT analyses showed that a variety of psychosocial interventions, including cognitive-behavioral psychological interventions, supported employment, and skills training that includes behaviorally-based instruction, modeling and corrective feedback, all have strong levels of evidence that support their implementation in psychosocial rehabilitation (PSR) programs for individuals diagnosed with schizophrenia. Other treatments, including cognitive remediation for cognitive deficits in schizophrenia, did not merit a treatment recommendation but were considered areas of emerging interest in schizophrenia treatment.

Synthetic literature reviews and meta-analyses of published studies over the past 20 years have revealed relationships between performance on standardized neurocognitive tests, including measures of attention, memory, language, and problem-solving, as well as composite measures of neurocognition, and a variety of measures of functional outcome measured cross-sectionally or longitudinally (Green, 1996; Green, Kern, Braff & Mintz, 2000; Green, Kern & Heaton, 2004). Outcome measures in these reviews have been grouped into categories of laboratory-based measures of instrumental and social-skill, community outcome based on clinician rating and client self-report, and progress in rehabilitation programs. Measures of cognition have been found to explain a substantial proportion of the variance in outcome (20–60%, see Green, Kern, Braff & Mintz, 2000) with differences attributable to heterogeneity in samples and the study measures selected.

While links between neurocognitive tests and functional outcome are well-documented, the nature of the more specific relationship between neurocognitive tests and response to evidence-based behavioral treatment remains unclear. Two features of recent reviews and meta-analyses on cognition-outcome links in schizophrenia have limited the ability to make conclusions regarding the impact of neurocognitive function on behavioral treatment response in schizophrenia. First, reviews to date have studied the impact of cognition on behavioral treatment as a small component of more global reviews of cognition and functional outcome (e.g., Green, 1996; Green, Kern, Braff & Mintz, 2000). For example the Green, Kern, Braff & Mintz (2000) review of cognition and outcome included just 8 studies (out of a total of 41 data sets) focused on cognition as a predictor of response to behavioral treatment. No reviews, to our knowledge, have focused exclusively on cognition as a predictor of response to behavioral treatment. This is important, as it would seem likely that neurocognition would have a much different influence on progress in focused psychosocial rehabilitation interventions than on measures of community function measured in the absence of such interventions. Second, reviews that have included studies evaluating cognition as a predictor of response to behavioral treatment in schizophrenia have typically grouped very different behavioral treatments together (e.g., work therapy and social skills training; see Green, Kern, Braff & Mintz, 2000). It is possible that neurocognition could influence response to different behavioral treatments, consisting of very different methods for rehabilitation, in different ways.

The current review, then, was designed to investigate the impact of neurocognition on response to behavioral treatment in schizophrenia. More specifically, we sought to determine: (1) whether links described between cognition and functional outcome more generally, were also evident in studies of cognition and response to specific behavioral interventions, and whether cognition was more closely tied to progress in rehabilitation

programs than symptoms, (2) whether elementary neurocognition would impact different rehabilitation interventions (e.g., social skills training versus cognitive remediation) differently, (3) the mechanism by which deficits in cognition could impact the effects of structured behavioral interventions. To address this third aim we organized outcome measures in the reviewed studies into three domains: (a) proximal measures of outcome that assess acquisition of elementary skills in psychosocial rehabilitation programs, (b) measures of generalization of acquired skills to performance-based, mediational measures of functional capacity, that measure what a client is capable of doing in a standardized clinic-setting, (c) distal measures of community function, and, lastly (d) process variables of attendance and participation in rehabilitation groups that provide insights into motivation for treatment. We decided against the use of meta-analytic review techniques in light of both the small number of studies conducted in this research area to date, and the high diversity of outcome measures selected in different studies.

### Search Strategy and Inclusion Criteria

Articles included in the review were identified through a computer-based PsychInfo (American Psychological Association, 2000) search conducted from 1980 to 2010. The search was conducted using the following key words: “schizophrenia” AND “outcome”, “psychosocial function”, “cognitive remediation”, “cognitive rehabilitation”, “cognitive-behavioral therapy”, “social skills training”, “family therapy”, “family psychoeducation”, “supported employment”, “work therapy”. A parallel search using the same key terms was completed with the MEDLINE (National Library of Medicine, 1994) database from 1980 to 2008. Nineteen-eighty was selected as a cut-off in light of the introduction of the DSM-III for more reliable diagnostic criteria for schizophrenia (APA, 1987). The reference sections of articles located from both searches were studied for relevant citations.

Articles were included if they met the following criteria: (a) longitudinal design, (b) the study included at least one standardized measure of neurocognition measured at baseline, (b) the study included at least one measure of functional outcome at follow-up, (c) the study described a psychosocial intervention that included at least one treatment recommended or cited as a treatment of emerging interest by the most recent PORT report on behavioral interventions (Dixon et al., 2010), (d) publication between 1980–2010, (e) a peer-reviewed English language journal, and (f) majority of clients had a diagnosis of schizophrenia. To increase the likelihood of stability of reported findings, only behavioral interventions for schizophrenia in which at least three studies including at least one cognitive measure as a predictor of treatment response were included. Effect sizes were obtained by evaluating correlation coefficients provided in each reviewed study between baseline cognitive test performance and response to the active psychosocial intervention in that study. Ranges for effect sizes were as follows: <.1 (minimal to small), .1–.3 (small to moderate), .3–.5 (moderate to large) and .5 and above (large; Lipsey & Wilson, 2001).

### Types of Behavioral Interventions

**Social Skills Training (SST):** While skills training programs vary widely in content, duration, and the setting where they are implemented, they share a common set of strategies for teaching new skills based on social learning theory (Bandura, 1969), including goal-setting, role-modeling, behavioral rehearsal, positive reinforcement, corrective feedback, and homework assignments to help promote generalization to the community. They typically include a structured curriculum focused on important rehabilitation domains (e.g., community re-entry after a hospitalization, medication management skills, illness management skills, etc.).

**Vocational Rehabilitation:** Studies of evidence-based vocational rehabilitation interventions can be classified into one of two categories: a) Work therapy usually consisting of part-time sheltered job placements typically on hospital grounds, consistent with clients expressed job interests, and usually coupled with an employment skills discussion group for coping successfully with work-related concerns (Bryson & Bell, 2001), or b) supported employment, which is defined as programs that use an individual placement and support model emphasizing integration of clinical and employment services, and rapid placement in competitive employment positions (McGurk, Mueser & Pascaris, 2005).

**Cognitive-Behavioral Therapy (CBT):** While there is considerable heterogeneity in the definition of elements of CBT for psychosis, most investigators/clinicians agree that CBT treatment is an individualized intervention involving collaboration between client and therapist, in which core thoughts and beliefs (cognitions) that are fundamental to clients distress are identified, the clinician play a role in helping the client consider a range of interpretations for their experience, and behaviors that may be reinforcing clients problems are identified and addressed (e.g., Morrison & Barratt, 2010).

**Cognitive Remediation:** Cognitive remediation is a novel treatment modality in schizophrenia, in which skills in attention, memory and problem-solving are targeted for improvement either through the development of strategies for bypassing persistent difficulties in cognition, or through specific, repeated practice on cognitive exercises designed to strengthen underfunctioning cognitive systems.

**Comprehensive Psychosocial Rehabilitation:** These are multi-modal intensive treatment programs that consist of a variety of behavioral interventions, often including vocational counseling, psychoeducation, skills training and other rehabilitation interventions.

### **Outcome Measures**

**Proximal Measures:** For the purposes of this review proximal measures were defined as those outcome measures that assessed acquisition of specific skills taught in each behavioral intervention. As different behavioral interventions teach different elementary skills, proximal measures were unique to each intervention. For SST interventions, proximal measures were categorized as assessments of content mastery of skills taught in SST as assessed through paper-and-pencil tests, as well as role-play social skill assessments based on skills taught directly in the skills training program. For vocational rehabilitation programs, proximal measures were defined as ratings of specific work skills trained in work therapy programs. For CBT proximal measures were measures of cognitive insight that indexed specific skills in questioning dysfunctional beliefs taught in CBT sessions. For cognitive remediation, proximal measures were defined as performance on neuropsychological tasks, whereas for integrated rehabilitation treatment proximal measures were determined by the specific elements of the rehabilitation program (SST, cognitive remediation, etc.).

**Mediational Measures:** For the current review, a mediational measure was defined as a capacity-based measure of social and everyday life skill (e.g., role-play tests) that was clinic administered and assessed what clients are capable of doing, rather than achieved community function, and that assessed skills that were not taught directly in the relevant behavioral treatment program. This latter feature of the definition is important, as a role-play test of social problem-solving, for example, would be considered a mediational measures only if social-problem solving was not trained in a social skills training program. If social-problem solving was trained the social skills program it would be classified as a proximal measure. The UCSD Performance Based Skills Assessment is an example of a commonly

used meditational measure of functional capacity (Patterson, Goldman, McKibbin, Hughs & Jeste, 2001).

**Distal Measures:** These measures were defined as client reported and/or clinician-rated community function, including number and quality of social relationships, and recreational engagement, as well as hours worked in competitive employment. The Independent Living Skills Survey (ILSS; Wallace, Liberman, Tauber & Wallace, 2000) would be a commonly used example of a distal measure of community functioning.

**Process Variables:** These were defined as variables that assess motivation for treatment and included attendance and engagement in rehabilitation treatment groups (often measured by eye-contact, appropriate verbalizations etc.).

### **Social-Skills Training**

As can be seen in Table 1, a total of eight studies have investigated the relationship of deficits on neurocognitive tests to response to social skills training. Seven of these studies have used proximal measures of outcome, while only one study selected a mediational measure of outcome (Bowen et al., 1994), and only one study (Granholm et al., 2008) selected a distal measure of outcome. Three studies have evaluated the impact of baseline neurocognitive test performance on process variables of attendance and session engagement (Granholm et al, 2008; McKee, Hull & Smith, 1994; Kern, Green & Satz, 1992).

### **Neurocognition as a Predictor of Proximal Skills Training Outcomes**

Evidence that deficits in neurocognition could impede the acquisition of elemental social skills through comprehension of information presented in social skills training programs was first demonstrated by Bowen et al. (1994). In that study, 30 individuals with schizophrenia and 15 healthy controls were evaluated with two measures of sustained visual vigilance, a working memory measure and a forced-choice test of early iconic memory. A single medication-management skills training session was administered and then comprehension of orally presented and videotaped information (proximal measures) using material derived from this session, was assessed along with a meditational measure of social-skill. Results revealed that sustained attention and verbal recall correlated with acquisition of elementary social skills (proximal measures) and explained over 50% of the variance in skill acquisition. Thus, these findings suggest that if neurocognitive operations impact acquisition of elementary social skills in a single session, it is likely they will impact acquisition of social skills across sustained programs of skills training.

Other studies have provide additional support for the idea that attention and verbal memory specifically, play an important role in the acquisition of elementary social skill as measured by proximal indices of skill acquisition. For example, Kern, Green & Satz (1992) in a sample of 16 middle-aged, hospitalized individuals with schizophrenia, showed that sustained visual vigilance, among a range of different neurocognitive skills measured at entry to a highly intensive, daily, 2-hr, 8-month skills training package consisting of medication and symptom management modules, predicted change scores on a proximal measure of skills-content mastery. Similarly, Silverstein, Schenkel, Valone and Nuernberger (1998), in a sample of chronically hospitalized clients, reported that sustained attention and verbal learning measures predicted nearly 50% of change in proximal measures of skill acquisition after a conversation skills training program.

Several studies have evaluated the relative predictive value of symptoms versus neurocognitive performance for improvement on proximal outcome measures (content mastery tests or social role-plays taught directly in the intervention). Mueser, Bellack,



Douglas and Wade (1991) in a sample of 55 individuals diagnosed with schizophrenia or schizoaffective disorder recently admitted to an inpatient unit for an exacerbation of psychiatric symptoms, investigated acquisition of elementary social-skills in: 1) expressing negative feelings, and 2) compromise and negotiation, each trained in three sessions over a week. Outcome was measured with a role-play test consisting of six role-plays focused on skills taught directly in the SST program. Assessments of overall assertiveness, along with components skills were rated. Results revealed that the SST program produced improvement in role-play skill measures. Results also revealed that the scores from memory measures, and particularly scores on concentration and verbal memory tests, were strong predictors of improvement in social skill, while no symptom subscales or demographic characteristics predicted improvement in role-play outcome measures. The authors concluded that acute symptoms were only weakly related to social-skills at study entry and did not predict response to treatment whereas memory skills, which were linked to social-skill at baseline, also impeded acquisition of elementary skills in assertiveness during the intervention for people with schizophrenia. Interestingly, clients with the most severely impaired memory still improved on measures of social skill, suggesting that clients most in need of improvements in social skill can still show some improvement with training. Similar findings were reported by Smith, Hull, Romanelli, Fertuck & Weiss (1999) who investigated the relationship of symptoms and measures of attention and executive-function and verbal list-learning, to progress in a 16-session skills training program focused on community re-entry for inpatients. Progress in skills training was measured with a proximal skills training content mastery assessment. Results revealed that verbal learning was linked most closely to improvement on measures of skill acquisition across the treatment trial, with no relationship between symptoms and skill change.

These findings have been extended by Ucock et al. (2006), who showed that measures of sustained attention, and problem-solving were linked to improvement on a proximal outcome measure of social problem-solving skills (the AIPSS) in 32 outpatients randomly assigned to a social-problem solving skills training intervention. Symptoms and demographic variables were not linked to improvement in this study. We also note that one recent study failed to show a specific relationship between any measures of neurocognition and content mastery of skills after a combined cognitive behavioral therapy and SST training program (Granholm et al., 2008).

**Neurocognition as Predictor of Mediation SST Training Outcomes**—Only the Bowen et al. (1994) study investigated predictors of response to SST as measured by a mediational measure of outcome, the AIPSS. Attention in this study was linked to mediational role-play measure suggesting this neurocognitive test may play a role in generalization of effects of SST.

**Neurocognition as Predictor of Distal SST Training Outcomes**—A recent study has investigated the specificity of relationships of neurocognitive skills to progress in a combined social-skills and cognitive-behavioral therapy (CBT) program for middle-aged and older patients with schizophrenia, relative to a treatment-as-usual (TAU) control condition using a direct measure of skills taught in combined CBT and SST, and the Independent Living Skills survey, a distal, self-report measure of basic and social functioning to assess generalization of treatment. Granholm et al. (2008) investigated the utility of a comprehensive battery of neurocognitive tests, grouped into domains of speed of processing, executive, verbal learning and memory, and attention and vigilance, for predicting response to their combined intervention. Data from sixty-five, older community-dwelling patients with schizophrenia who participated were presented. Composite measures of neurocognition, as well as attention and vigilance, and speed of processing scores were linked to poorer overall psychosocial status for the entire sample (experimental and

treatment-as-usual control [TAU] group) after treatment, while composite measures of neurocognitive function, executive control, attention and vigilance, and verbal learning and memory were related to skill acquisition as assessed through content mastery tests. Importantly, however, the group X condition interaction was not significant for either outcome measure, suggesting that levels of neurocognitive impairment had little impact on outcome in the CBT+SST training group relative to the TAU control group.

### Neurocognition as a Predictor of Process Variables Influencing Skills Training Outcome

Three studies to date (Granholtm et al., 2008; Kern, Green & Satz, 1991; McKee, Hull & Smith, 1997) have investigated how cognitive skills may influence attendance and participation in skills training groups. Kern, Green & Satz (1991) investigated on-task behavior in social skills training groups, as measured by behaviors such as appropriate eye-contact, and appropriate questions using a trained observer during skills training sessions. They showed that intrusions on a verbal learning test negatively correlated with on-task behavior, while measures of selective attention positively correlated with on-task behavior. Similarly, McKee, Hull & Smith (1997) in a sample of 19 chronic inpatients investigated the relative role of symptoms and neurocognitive measures of processing speed, verbal list learning, attention, verbal fluency, and verbal inhibition on attendance and level of participation in a 16-session, 5-day-per-week program of community re-entry skills (consisting of medication management skills, symptom identification and collaborative treatment planning). Results revealed that measures of verbal inhibition predicted participation, whereas negative symptoms and attention predicted attendance. Positive symptoms did not relate to either measure of outcome in this study. Granholtm et al., (2008), found that degree of neurocognitive impairment related to measures of group engagement, but not attendance.

### Summary

Seven of eight studies of SST have shown links between neurocognitive function measured at study entry and treatment outcome. More specifically, findings that attention and verbal memory predict proximal measures of skills–training outcomes in schizophrenia regardless of whether skills interventions are brief (1 session) or longer duration (6-months) have been replicated. No studies have shown links between positive and/or negative symptoms and response to SST whether clients are in an inpatient or outpatient setting, but the number of studies examining symptoms along with neurocognition remain small (3 studies). Surprisingly, only one study has investigated the impact of neurocognitive test performance on improvement or more distal measures of SST. This study failed to find a specific relationship between cognition and a distal measure of community function in a skills training condition, relative to a treatment-as-usual control condition. Attention, verbal memory, verbal inhibition and negative symptoms have been linked to process variables of attendance and session engagement in SST. A strength of these studies is that they nearly all measured change in functioning over time, rather than a static index of outcome at the termination of treatment.

**Vocational Rehabilitation**—Three studies to date have focused on cognitive predictors of response to either: (1) supported employment, or (2) supervised work-therapy programs (see Table 2).

**Work Therapy:** Lysaker, Bell, Zito, and Bioty (1995) investigated the utility of performance on a measure of problem-solving, the WCST, for predicting improvement over a 10-week work therapy program for fifty-three individuals with schizophrenia classified as impaired on a measure of work related social skills. Individuals were chronically-ill and middle-aged and the majority were outpatients. Work therapy consisted of 10–20 hr

sheltered job placements typically on VA hospital grounds, consistent with clients expressed job interests, and coupled with a weekly employment skills group for coping successfully with work-related concerns. The results revealed that for clients with impaired social-skill, performance on a measure of problem-solving uniquely predicted acquisition of social-skills related to work while symptoms and demographic variables did not predict improvement in work-related social-skills. In a related study, Bell and Bryson (2001) studied 33 middle-aged, chronic outpatients who completed at least 22 weeks of a work rehabilitation program at a variety of supervised job sites on hospital grounds. Performance in these work sites was then evaluated biweekly using a standardized scale of work behaviors over the trial. Four of the five work behavior domains showed improvement over the work rehabilitation trial and were linked to crystallized verbal IQ, attention, verbal memory, executive function and processing speed. Symptom ratings did not predict change in work function ratings with the exception of negative symptoms, which predicted cooperativeness on the job across the trial.

### Supported Employment Programs

McGurk, Mueser, Harvey, LaPuglia, and Marder (2003), in a two-year longitudinal study of 30 clients with schizophrenia in a supported employment program, investigated the degree to which demographic variables, positive and negative symptoms, and performance on neurocognitive tests, including measures of executive function, attention, psychomotor speed and verbal learning, could be linked to achievement in competitive employment settings (distal outcome measure) and utilization of employment support services. For the current review we focused on results related to competitive employment only. Better executive functioning and lower levels of negative symptoms were associated with more hours worked and more wages earned, whereas better verbal learning was associated with more hours worked. Patients with higher levels of negative symptoms achieved less in terms of competitive work. Four year follow-up data indicated that from years 2 to 4 baseline cognitive functioning was even more predictive of work after supported employment services relative to the two-year follow-up period (McGurk & Mueser, 2006).

**Cognitive-Behavioral Therapy**—Three studies to date have evaluated the relationships of baseline impairment on neurocognitive tests to progress in programs of CBT or CBT +SST (see Table 3). Results revealed that there was no indication that baseline neurocognitive impairment moderated the effects of CBT in two of three studies. In one study (Geraty et al. 1997), poorer executive function (Cognitive Estimation Test) paradoxically predicted a *stronger* response to CBT as measured by an index of symptoms.

**Cognitive Remediation**—Three studies have investigated the relationship of baseline neurocognitive test performance to response to cognitive remediation interventions (see Table 4). Fiszdon, Cardenas, Bryson, and Bell (2005), studied 58 patients with schizophrenia and evaluated the relationship of demographic, symptom, process and neurocognitive variables to the probability of showing normalized performance (improvement to within 1 SD of healthy control performance) after training on a memory task that served as an element of a comprehensive, computer-assisted, drill-and-practice remediation program (proximal measure of outcome). Results revealed that sustained visual vigilance, along with immediate verbal memory, time between termination of intervention and follow-up assessment, and measures of hostility accounted for 70% of the variance in chances of normalization on the selected memory task in this cognitive remediation protocol.

Medalia and Richardson (2005) have reported that sustained attention, but not processing speed, working memory and immediate story recall, was related to improvement across three mixed samples of psychiatric in and outpatients. Improvement in the study was



measured by standardized neurocognitive measures distinct from the Neuropsychological and Educational Approach to Remediation (NEAR) treatment program employed in the study. Patients were classified as “improved” if they improved on any proximal measure of neurocognitive function to a degree that could have occurred by chance only 5 times or less out of 100.

Kurtz, Seltzer, Fujimoto, Shagan and Wexler (2009), in a recent study investigated the relationship between four measures of neurocognitive function, crystallized verbal ability, auditory sustained attention and working memory, verbal learning and memory, and problem-solving, two measures of symptoms, total positive and negative symptoms, and the process variables of treatment intensity and duration, to change on a performance-based measure of everyday life-skills after a year of computer-assisted cognitive remediation offered as part of intensive outpatient rehabilitation treatment. Thirty-six patients with schizophrenia or schizoaffective disorder were studied. Results of a linear regression model revealed that auditory attention and working memory predicted a significant amount of the variance in change in performance-based measures of everyday life skills after cognitive remediation, even when variance for all other neurocognitive variables in the model was controlled.

**Comprehensive Outpatient Rehabilitation**—Four studies to date have investigated the role of neurocognitive measures for prediction of response to integrated programs of rehabilitation consisting of a range of evidence-based behavioral interventions (see Table 5). Woonings, Appelo, Kluiters, Sloof, and Van Den Bosch (2002) in a sample of 44 middle-aged, hospitalized clients with schizophrenia investigated the relationship of measures of immediate memory, verbal list learning, vigilance, and problem-solving, along with a measure learning how to learn, on change in functioning after a comprehensive rehabilitation program using the Rehabilitation and Evaluation Scale, designed to assess institutionalized patients deviant and more general behaviors. The intervention was an 8-month rehabilitation program consisting of psychoeducation, cognitive remediation training, training in planning everyday activities, and social and vocational skills training. Results revealed that vigilance and problem-solving but not verbal memory were linked to change in psychosocial status across the trial. Prouteau et al. (2005) also found that vigilance was linked to a subjective measure of quality-of-life at the termination of a course of Integrated Psychological Therapy (IPT) including cognitive remediation, and social-skills training components along with other behavioral interventions. Non-verbal memory was linked to outcome in this study as well.

Kurtz, Wexler, Fujimoto, Shagan and Seltzer (2008) investigated the relationship between five measures of neurocognitive function, crystallized verbal ability, visual sustained vigilance, verbal learning, problem-solving, and processing speed, and two measures of symptoms, total positive and negative symptoms, and change on a performance-based measure of everyday life-skills (UPSA; mediational measure) after a year of outpatient rehabilitation. For the majority of clients rehabilitation consisted of a three-day per week program including structured group therapy, life-skills training, and exercise, vocational counseling and computer training. Forty-six patients with schizophrenia or schizoaffective disorder were studied. Results of a linear regression model revealed that verbal learning predicted a significant amount of the variance in change in performance-based measures of everyday life skills after outpatient rehabilitation, even when variance for all other variables in the model was accounted for. Measures of crystallized verbal ability, sustained visual vigilance, problem-solving, processing speed and symptoms were not linked to functional status change. These findings emphasized the importance of verbal learning for benefiting from psychosocial and cognitive rehabilitation interventions.

In the largest sample study to date, Brekke, Hoe, Long and Green (2007) studied a composite measure of cognition, including indices of attention, fluency, verbal learning and memory, problem-solving, along with social cognitive and service intensity measures, as a predictor of change in a distal, clinician-rated index of community function, (the Role Functioning Scale), during a 12-month interval of community psychosocial rehabilitation. One-hundred and two, chronically-ill clients with schizophrenia were enrolled in intensive outpatient treatment at one of four study sites, all consisting of social and vocational rehabilitation services, housing supports, crisis hotline and substance abuse and health services. Results revealed that the composite measure of cognition at study entry, along with service intensity during treatment, predicted the most substantial amount of change in the outcome measure across the 12-month follow-up interval.

## Discussion

### Conclusions

This review revealed several important findings with respect of the motivating aims of this article. First, measures of composite cognitive function, attention and working memory, verbal and non-verbal memory, and problem-solving were linked to progress in a variety of evidence-based behavioral treatments: social skills training, work therapy and supported employment, cognitive remediation and integrated psychosocial rehabilitation, with the majority of effect-sizes in the moderate-large range. These findings suggest that links established between elementary neurocognitive functions and outcome in literature reviews focused primarily, or exclusively, on outcome in clients with schizophrenia in the absence of focused behavioral treatments (see Green, 1996; Green, Kern, Braff & Mintz, 2000; Green, Kern & Heaton, 2004) are similar in type and magnitude to those evident in studies of prediction of response to evidence-based behavioral treatments. We note that cognitive impairment, however, was not linked to progress in studies of CBT in clients with schizophrenia in this review. Among symptom measures, only negative symptoms measured at baseline were linked to treatment outcome in response to behavioral treatment, influencing distal measures of employment function in studies of supported employment, and process measures of attendance in studies of social-skills training. Second, with respect to specificity of effects, there was some evidence that attention, verbal memory and problem-solving showed closest links to skills training outcomes, attention and working memory showed links with cognitive remediation interventions, attention, verbal learning and problem-solving showed closest links to outcomes in vocational rehabilitation programs, and composite neurocognitive function, and verbal and non-verbal memory predicted changes in outcome as a function of integrated programs of rehabilitation. Two of three studies of CBT in psychosis failed to show any effect of baseline neurocognitive test performance on treatment response. This finding may not be surprising in light of the focus of CBT on positive symptom reduction, rather than improvement in functioning characteristic of other psychosocial treatments in this review. Measures of positive symptoms are not well-linked with performance in neurocognitive tests. We note that findings regarding CBT, cognitive rehabilitation, vocational rehabilitation and integrated programs of rehabilitation are presented with a high degree of caution given the small number (3, 3, 3 and 4, respectively) of prediction studies conducted to date on these interventions. Third, with respect to mechanism of effects, evidence to date suggests that neurocognition influences the acquisition of proximal, elementary social skills, mediational, capacity-based measures of social-skill not taught directly in skills training programs, as well as process measures of attendance and group engagement. These latter finding might suggest that performance on cognitive tests are serving, at least to some degree, as a proxy for levels of client motivation. As patterns of relationships between different aspects of cognition and acquisition of elementary social skills are not isomorphic with patterns of

relationships between neurocognition and process variables, this finding suggests that neurocognitive batteries are most likely assessing something more than motivation alone, however. At this time, there is no evidence that performance on neurocognitive tests predicts effects of SST on more distal measures of community function. Links between neurocognitive test performance and proximal outcome measures of cognitive remediation and vocational rehabilitation have been supported, and there is evidence that neurocognition influences distal outcomes of competitive employment after vocational rehabilitation training, and community function after integrated programs of rehabilitation.

## Limitations

The results of our review revealed many limitations of the extant literature on neurocognitive predictors of behavioral treatment response in schizophrenia. First, while there was some evidence of specificity in the relationship of cognitive skills to outcome on proximal measures of skills training outcome, differences between significant and non-significant correlation coefficients were small and in no studies were tested for conventional levels of statistical significance. Differences in psychometric properties of tests, including task difficulty and reliability, could have influenced observed specificity of effects as well. Furthermore, in light of work suggesting impairment on a variety of individual neurocognitive tests in schizophrenia often reflects a common impairment across multiple neurocognitive domains (e.g., Dickinson, Ragland, Gold & Gur, 2008) evidence of specificity in this research domain must be viewed with caution at this time. Second, there are a very small number of studies of neurocognition as a predictor of response to nearly all of the behavioral interventions studied in this paper including work rehabilitation (3 studies), CBT (3 studies), cognitive remediation (3 studies) and comprehensive programs of rehabilitation (4 studies). Thus, conclusions regarding each of these treatment domains are highly tentative. Third, The absence of a range of proximal, mediational, distal and process measures in each study (nearly 40% of studies reviewed in this paper included only one proximal measure of outcome) precluded meaningful conclusions regarding the degree to which neurocognitive test results influenced acquisition of elementary skills in rehabilitation, versus generalization of elementary skills to more distal measures of outcome, and whether neurocognitive test performance may be serving as a proxy for motivation in these studies, as evidenced by links to attendance and engagement in groups. Fourth, only one out of eight studies (Ucok et al., 2006) of social-skills training assessed the effects of symptoms in stabilized outpatients on progress in skills training programs, thus the relative role of persistent, chronic symptoms on progress in rehabilitation programs (rather than acute symptoms associated with a hospital admission), relative to elementary measures of neurocognition, remains largely unknown. This is of particular concern as the vast majority of clients with the diagnosis at any one time are receiving treatment as stabilized outpatients (Brier, 1995). Fifth, it is of concern that two studies that assessed the specificity of effects of neurocognition on response to behavioral treatment strategies (Granholm et al, 2008; Leclerc, Lesage, Ricard, Lecomte & Cyr, 2000) relative to a treatment-as-usual control group, failed to find that cognition moderated the effects of behavioral treatment on outcome. All other studies in the review reported findings for the relationship of baseline neurocognitive performance and functioning in response to an active behavioral intervention, without comparisons to relationships between baseline neurocognitive impairment and functioning in a control condition. Thus, it remains unknown whether the results of many of the studies included in this review reflect cognition, treatment outcome links, evident regardless of whether clients received structured, evidence-based behavioral interventions or not.

## Areas for Future Research

Based on this analysis of study limitations, several directions for future research can be formulated. First, studies including a range of outcome measures that vary in terms of their proximity to the site of the behavioral intervention will be crucial in understanding the mechanisms of effects of baseline neurocognitive functioning on response to evidence-based behavioral treatments. Second, only two studies to date have assessed the predictive value of neurocognition at different follow-up periods after an intervention (Mueser, Bellack, Douglas & Wade, 1991; McGurk & Mueser, 2006). Both of these studies suggests that the predictive value of neurocognition at an immediate follow-up after an intervention may be different from their effects at a follow-up after additional time has elapsed after intervention termination. Thus, studies should assess the effects of neurocognition on outcome of behavioral treatments at a variety of follow-up intervals. Third, future studies should move from exploratory studies of prediction of response to behavioral treatments, to hypothesis-driven studies in which specific neurocognitive functions are predicted to be linked to response to specific interventions (e.g., verbal memory and the acquisition and retention of elementary social-skills in skills training programs). Fourth, these studies provide support to the idea that improving cognitive function *may* improve response to behavioral treatments given the observed link between neurocognition and SST, vocational rehabilitation and integrated programs of psychosocial rehabilitation (we note that longitudinal association does not imply causation). However, with the exception of one study of supported employment (see McGurk, Mueser & Pascaris, 2005), no studies, to our knowledge have formally investigated the use of cognitive rehabilitation as an adjunctive treatment in a randomized, controlled format to enhance benefit from other evidence-based rehabilitation strategies.

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**Table 1**  
Longitudinal studies of neurocognition as a predictor of response to social skills interventions (n=8).

Study	Sample	Intervention	Intervention Duration	Neurocognitive Measures	Outcome Measures	Finding	Effect Sizes
Bowen et al., 1994	30 chronic inpatients MA=36 % male=80 Edu=12.9 Dur ill=? AO=? Hosp=?	Medication management skills	1-day	CPT, DSDT, Forced-Choice Span of Apprehension	Proximal Measure: Comprehension of oral and videotaped information in training, information presented on videotape. Mediational Measure: AIPSS	Sustained attention and verbal memory was linked to proximal measures of skills taught in the training program, whereas sustained attention was linked to social role-plays not taught directly in the skills training program.	For comprehension total scores: 100% in the large range. For social-role play total scores: 100% in moderate to large range.
Granholm et al., 2008	65 outpatients MA=53.3 % male=74 Edu=12.4 Dur ill=? AO=? Hosp=?	CBT and SST	6-months	Processing speed, executive-function, attention and vigilance (factors)	Proximal Measure: Content mastery tests. Distal Measure: ILSS Process Measures: Participation and attendance	There was no evidence that severity of neuropsychological impairment predicted the magnitude of improvement as a function of the intervention.	Group participation, large range. NR for other measures.
Kern, Green & Satz, 1992	16 chronic inpatients MA=34.1 % male=44 Edu=11.8 Dur ill=? AO=? Hosp=?	Medication and symptom management modules	8-months	Backward masking, CPT, DSDT, WCST, RAVLT, RCFT, PPVT, Pin Test	Proximal Measure: Content mastery test, Process Measure: Measure of on-task behavior	Vigilance, susceptibility to distraction and verbal learning linked to proximal outcome measures.	For on-task behavior, 14% large range, 21% moderate to large, 29% small-to-moderate, 36% minimal effect.
McKee, Hull & Smith, 1997	19 chronic inpatients MA=30 % male=47 Edu=13 Dur ill=? AO=? Hosp=?	Medication management, symptom identification and collaborative treatment planning.	3-weeks	SDMT, RAVLT, WISC-III Mazes, FAS, Category Instance Test, Stroop Color- Word Test	Process Measures: Level of participation in groups, attendance	Executive-function, but not symptoms, contributed unique variance to the level of participation of participation variable, whereas attention and negative symptoms predicted attendance.	NR
Mueser, Douglas, Bellack & Wade, 1991	45 acute inpatients MA=33.2 % male=56 Edu=11.5 Dur ill=? AO=? Hosp=5.4	Expressing negative feelings and compromise and negotiation.	2-weeks	WMS	Proximal Measures: Role-play tests and ratings of assertiveness	Pre-intervention memory scores, but not symptoms, related to improvement in social-skills across the treatment trial.	For role-play assessments and overall memory quotient scores: Small-to-moderate effect at immediate

Study	Sample	Intervention	Intervention Duration	Neurocognitive Measures	Outcome Measures	Finding	Effect Sizes
Silverstein, Schenkel, Valone, & Nuernberger, 1998	NR	Conversation skills	NR	IQ, attention, verbal list learning, problem-solving	Proximal Measure: Content-mastery tests	Attention and verbal memory linked to skill acquisition.	test, large effect at follow-up. NR
Smith, Hull Romanelli, Fertuck & Weiss 1999	32 acute inpatients MA=34.6 % male=56 Edu=? Dur ill=? AO=18.2 Hosp=7.6	Community re-entry module	3 weeks	TMT, CVLT	Proximal Measure: Community reintegration content mastery test	Skill acquisition predicted by group membership and verbal memory, but not symptoms.	Post-treatment content mastery score: 75% of effects in the large range, 25% in the moderate-large range.
Ucook et al., 2006	32 outpatients MA=28.3 % male=? Edu= 11.7 Dur ill=7.1 AO=? Hosp=?	Social problem solving training	6-weeks	WCST, CPT, Digit Span	Proximal Measure: AIPSS	Skill acquisition predicted by sustained attention and executive function.	Total AIPSS scores; 25% of effects in the large range, 25% in moderate-large range, 50% in small-to-moderate range.

Note. AO=Age-of-onset; AIPSS: Assessment of Interpersonal Problem Solving; CBT=cognitive-behavioral therapy; CPT=Continuous Performance Test; CVLT=California Verbal Learning Test; DSDT-Digit Span Distractibility Test; Dur ill=duration of illness; Edu=Education; FAS=Controlled Oral Word Association Test; Hosp: Hospitalization; ILSS=Independent Living Skills Survey; MA=Mean age; NR: Not reported; PPVT=Peabody Picture Vocabulary Test; RAVLT=Rey Auditory Verbal Learning Test; RCFT=Rey Complex Figure Test; SDMT=Symbol Digit Modalities Test; SST=social-skills training; TMT=Trailmaking Test; WCST=Wisconsin Card Sorting Test; WISC-III=Wechsler Intelligence Scale for Children; WMS =Wechsler Memory Scale.

**Table 2**

Neurocognition as a predictor of response to vocational interventions (n=3).

Study	Sample	Intervention	Intervention Duration	Neurocognitive Measures	Outcome Measures	Finding	Effect Sizes
Bell & Bryson, 2001	30 outpatients MA=45.1 %male=97 Edu=12.67 Dur ill=? AO=27.5 Hosp=10.61	Work therapy	6-months	WCST, IQ, CPT, WMS-R, HVLT, proverbs, emotion recognition	Proximal Measure: Work Behavior Inventory	Cognitive measures, but not symptoms, linked to improvement in work skills in supervised work settings.	For statistically significant relationships between cognition and WBI, all effects in the moderate-to-large range.
Lysaker, Bell, Zito & Bioty, 1995	53 (majority outpatient) MA=42.8 %male=98 Edu=12.6 Dur ill=? AO=22.8 # Hosp=8.3	Work therapy	10-weeks	WCST, Gorham's Proverbs	Proximal Measure: Work-Related Personality Profile	Executive-function and thought disorder, but not negative symptoms, linked to improvement in work-related social skills after training.	For WPP scores effect-size in the large range.
McGurk, Mueser, Harvey, LaPiglia & Marder, 2003; McGurk & Mueser, 2006	30 outpatient MA=39.7 %male=77 Edu=12.2 Dur ill=15.7 AO=22.3 # Hosp=?	Supported employment	2-years	WCST, TMT, Digit span, CVLT	Distal Measure: Hours worked, wages earned, service use	Executive-function and negative symptoms linked to hours worked and wages earned.	For wages earned 15% of effects in the moderate-to-large range, 75% of effects in the small-to-moderate range. Hours worked: 50% of effects in the moderate-to-large range. 25% in the small-to-moderate range.

Note: AO=Age-of-onset; CPT=Continuous Performance Test; CVLT=California Verbal Learning Test; Dur ill=duration of illness; Edu=Education; FAS=Controlled Oral Word Association Test; Hosp: Hospitalization; MA=Mean age; NR: Not reported; HVLT=Hopkins Verbal Learning Test; TMT=Trailmaking Test; WCST=Wisconsin Card Sorting Test; WMS =Wechsler Memory Scale.

Table 3

Neurocognition as a predictor of response to cognitive-behavioral therapy (n=3).

Study	Sample	Intervention	Intervention Duration	Neurocognitive Measures	Outcome Measures	Finding	Effect Sizes
Geraty et al., 1997	60 outpatients MA=40 % male=63 Edu=? Dur:ill=14 AO=? Hosp=4.8	CBT	9-months	Cognitive Estimates Test, Verbal Fluency test, Test of probabilistic reasoning	Distal: BPRS	Cognitive Estimates Test inversely correlated with improvement in the treatment, but not control group.	NR
Graholm et al., 2008	65 outpatients MA=53.3 % male=74 Edu=12.4 Dur:ill=? AO=? Hosp=?	CBT+SST	6-months	Processing speed, executive-function, attention and vigilance (factors)	Proximal Measure: Skills- training, content mastery tests. Distal Measure: ILSS	There was no evidence that severity of neuropsychological impairment predicted the magnitude of improvement as a function of the intervention.	Group participation, large range. NR for other measures.
Leclerc, Lesage, Ricard, Lecomte, & Cyr, 2000	99 outpatients and inpatients. % male=58 Edu=10.2 MA=40.6 Dur:ill= AO=24.2 Hosp=4	Coping Skills CBT Module	3-months	Short- and long-term memory functioning, attention.	Distal Measures: ILSS, RES, PANSS	Cognitive measures did not moderate effects of treatment between the intervention and control groups	NR

Note: AO: Age-of-onset; BPRS: Brief Psychiatric Rating Scale; CBT: Cognitive-behavioral therapy; Dur:ill=Duration of illness; Edu=Education; ILSS: Independent Living Skills Survey; MA: Mean age; NR: Not reported; PANSS: Positive and negative syndrome scale; RES: Rosenberg Self-esteem Scale; SST: Social-skills training.



Table 4

Neurocognition as a predictor of response to cognitive rehabilitation (n=3).

Study	Sample	Intervention	Intervention Duration	Neurocognitive Measures	Outcome Measures	Finding	Effect Sizes
Fiszdon, Cardenas, Bryson & Bell, 2005	58 outpatients MA=41.4 % male=76 Edu=13.2 Dur ill=? AO=? Hosp=?	Comprehensive, computer-assisted drill- and-practice approach to cognitive remediation.	6-months	Digit span, CPT, TMT B, WCST, HVLT, Full-scale IQ	Proximal Measure: Digits sequenced recall test	Vigilance, immediate verbal memory, latency between last training and testing, and hostility combined to account for 70% of improvement in remediation trial.	NR
Kurtz, Wexler, Fujimoto, Shagan & Seltzer, 2008	36 outpatient MA=32.4 % male=69 Edu=13.4 Dur ill=8.7 AO=24.2 Hosp=3.9	Comprehensive, computer-assisted drill- and-practice approach to cognitive remediation.	12-months	Vocabulary, Digit Span, CVLT, PCET	Mediational Measure: UPSA	Sustained auditory attention explained variance in improved everyday life skills beyond that predicted by demographic, symptom and process variables.	For total UPSA scores: 50% moderate-to-large, 25% small-to-moderate, 25% minimal to none.
Medalia & Richardson, 2005	Three samples: 55, 36 and 26 MA=36, 35, 36 % 'male'=62, 67, 62 Edu=11, 10, ? Dur ill=? AO=? Hosp=?	NEAR	10-26 sessions	RBANS, WAIS, Minnesota Clerical Test, CVLT	Proximal Measures: RBANS, WAIS, Minnesota Clerical Test, CVLT	Minnesota Clerical Test at baseline predicted a stronger response to cognitive remediation. Other baseline measures did not predict response to the cognitive remediation intervention.	NR

Note: AO=Age-of-onset; CPT=Continuous Performance Test; CVLT=California Verbal Learning Test; Dur ill=Duration of illness; Edu=Education; HVLT=Hopkins Verbal Learning Test; MA=Mean Age; NEAR=Neuropsychological Education to Rehabilitation NR: Not reported; PCET=Penn Conditional Exclusion Test; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; TMT-B=Trailmaking Test B; WAIS=Wechsler Adult Intelligence Scale; WCST=Wisconsin Card Sorting Test.

**Table 5**  
Neurocognition as a predictor of response to comprehensive outpatient rehabilitation (n=4).

Study	Sample	Intervention	Intervention Duration	Intervention	Neurocognitive Measures	Outcome Measures	Finding	Effect Sizes
Brekke, Hoe, Long & Green, 2007	102 outpatients MA=38.22 % male=68.6 Edu=12.06 Dur:ill=13.73 AO=? #hosp=?	Mental health treatment, housing services, social and vocational rehabilitation, substance abuse treatment, and 24-hr crises response	12-months	Mental health treatment, housing services, social and vocational rehabilitation, substance abuse treatment, and 24-hr crises response	Composite cognition score	Distal Measure: RFS	Stronger neurocognition at baseline predicted stronger functional improvement.	Change in RFS in the small-to-moderate range.
Kurtz, Seltzer, Fujimoto, Shagan & Westler, 2009	46 outpatients MA=34.6 % male=72 Edu=13.4 Dur:ill=9.6 AO=25.6	Group daily goal setting, exercise, computer training, vocational counseling, life-skill training	12-months	Group daily goal setting, exercise, computer training, vocational counseling, life-skill training	Vocabulary, CPT, CVLT, PCET, PSI	Mediational Measure: UPSA	Verbal learning was linked to improvement in everyday life skills, after controlling for demographic symptom and process variables.	Total UPSA: 25% in the small-to-moderate range, 75% in the minimal range.
Prouteau et al., 2005	55 outpatients (?) MA=34.3 % male=65.5 Edu=11.6 Dur:ill=7.4 AO=? Hosp=?	IPT	12-months	IPT	Motor screening, paired-associates learning, reaction time, rapid visual information processing, Stocking of Cambridge	Distal Measure: MCAS, CASIG (subjective QOL subtest)	Poor attention predicted stronger Subjective quality-of-life, and stronger associate visual memory predicted better community autonomy in activities-of-daily living, and less physical and psychiatric symptoms that impair functioning.	NR
Woonings et al., 2002	44 inpatients MA=30.7 % male=86 Edu=? Dur:ill=8.7 AO=22.1	Psychoeducation, cognitive remediation training, planning and structuring everyday activities, social	8-months	Psychoeducation, cognitive remediation training, planning and structuring everyday activities, social	RAVLT, CPT, WCST, Tower of Hanoi, VMT	Distal Measure: Social functioning	Attention and executive function, but not learning, were correlated with improved	Change in social functioning: 8% moderate-to-large, 58% small-to-moderate,

Study	Sample	Intervention	Intervention Duration	Intervention	Neurocognitive Measures	Outcome Measures	Finding	Effect Sizes
	Hosp=3,7	and vocational skills training.		and vocational skills training.			rehabilitation outcome.	33% minimal.

Note: AO=Age-of-onset; CASIG=Client Assessment of Skills; CPT=Continuous Performance Test; CVLT=California Verbal Learning Test; Dur ill= duration of illness; Edu=Education; FAS=Controlled Oral Word Association Test; Hosp: Number of hospitalizations; HVLT=Hopkins Verbal Learning Test; MA=Mean Age; MCAS=Multnomah Community Ability Scale; NR=Not reported; PCET=Penn Conditional Exclusion Test; PSI=Processing Speed Index; RAVLT=Rey Auditory Verbal Learning Test; RFS=Role Functioning Scale; UPSA=UCSD Performance-based Skills Assessment; VMT=Varied Mapping Test; WCST=Wisconsin Card Sorting Test.