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Measuring Changes in Functional Status Among Patients With Schizophrenia: The Link With Cognitive Impairment

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Cognitive impairment associated with schizophrenia (CIAS) includes neuropsychological deficits in attention, working memory, verbal learning, and problem solving. These deficits have been shown to be linked to impairment in functional status (eg, social behavior, work performance, and activities of daily living) among patients with schizophrenia in cross-sectional studies. Less is known about the relationship between cognitive and functional change over time, such as potential functional implications of treatment-related improvement in CIAS. The purpose of this review is to summarize research on the association between change in CIAS and change in functional status, to discuss responsiveness of functional outcomes measures, and to provide recommendations for future research and measure development. Nine longitudinal studies were located on the link between CIAS and functional status, and 8 functional outcomes measures were used across these studies. The 9 studies offer initial support for a link between change in cognitive function and change in functional status. However, inconsistent findings across studies indicate that available research is preliminary, and substantial questions remain unanswered. Shortcomings of functional status measures are noted: most instruments were not developed for the target population, and none have demonstrated responsiveness to cognitive change among schizophrenic patients. It is recommended that new functional outcome measures be developed that are specifically designed to be responsive to change in cognition, with domains previously shown to be related to cognitive ability. When creating new functional outcomes measures for assessment of patients with schizophrenia, responsiveness to change in CIAS should be evaluated as part of the development and validation process.

Key words: schizophrenia/functional status/cognitive impairment/change/responsiveness

Introduction

A substantial body of research has shown that cognitive impairment is common among patients with schizophrenia, and these cognitive deficits appear to be distinct from positive and negative symptoms of the disorder.[1–8] The National Institute of Mental Health has established the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative, which has brought together representatives of academia, industry, and government in order to catalyze regulatory acceptance of cognitive impairment associated with schizophrenia (CIAS) as a target for drug registration and to promote development of novel treatments to enhance cognition in schizophrenia.[9–11] Based on literature review and expert input, participants at the first MATRICS consensus conference selected 7 key cognitive domains to be assessed among patients with schizophrenia: working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing, and social cognition.[10,12]

In recent years, CIAS has received increasing attention in the literature, likely for 2 reasons. First, CIAS has recently been identified as a potential target of pharmacological treatment based on data suggesting that second-generation antipsychotics may improve cognitive functioning among patients with schizophrenia.[13–23] Second, cognitive skills have been shown to be associated with functional status among patients with schizophrenia and may have a greater influence on functional outcomes than positive or negative symptoms.[24–26]

Functional status is a multidimensional construct that encompasses an individual's ability to perform activities of daily living (ADL) and participate in various life situations.[27] For example, functional domains associated with CIAS include social functioning, work functioning,

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health-related quality of life, and ADL.[20,24,25,28–31] These functional domains are important to assess in clinical trials of schizophrenia treatment because traditional efficacy measures do not reflect impairment in life functioning, which often persists after symptom improvement.[26]

Most studies on the association between functional status and cognition have been conducted at one point in time. Less is known about this relationship over time, including the possible functional implications of treatments targeting cognition in patients with schizophrenia. Two types of longitudinal studies have begun to examine these issues. The first type of study examines the link between a baseline cognitive assessment and later evaluation of functional status.[32] A recent article by Green and colleagues[9] reviewed 18 of these studies, each with a minimum 6-month follow-up period and an assessment of community outcome (eg, social, vocational, and independent living). Overall, results indicated that baseline cognitive assessment predicted subsequent functional outcome, which supports the development of treatments specifically targeting cognitive deficits in schizophrenia.

The current article reviews a second type of longitudinal study, which involves assessment of both cognition and functional status at multiple points in time. Although few of these studies have been conducted thus far, this line of research can provide unique insights into the functional implications of change in cognitive status resulting from either age-related declines or treatment-related improvements. Thus, the first goal of this review is to summarize research on the association between change in CIAS and change in functional status.

As more research begins to examine this longitudinal relationship, it will be important to assess functional outcomes with measures that are reliable, valid, and sensitive to treatment-related changes. A wide range of validated and partially validated measures has been used to assess the functional status of patients with schizophrenia. However, little is known about the measures' responsiveness to change in cognitive functioning. Consequently, the second goal of this article is to discuss responsiveness of functional outcomes measures and to provide recommendations for future research and measure development.

Relevant articles were located through a broad Medline search designed to identify studies of patients with schizophrenia that included both neuropsychological (eg, cognitive, memory, attention) and functional (eg, occupational, social, quality of life, and adaptive functioning) terms. Reference sections and review articles were examined to ensure that the search was comprehensive.

Studies of the Association Between Cognitive and Functional Change

Given the well-established link between cognitive and functional status at one point in time, it can be hypothesized that change in cognitive ability would be associated with a corresponding change in functional status. Six longitudinal treatment studies provide initial support for this hypothesis (table 1). Three of these studies involve pharmacological treatment. Buchanan et al[33] found that changes in memory over 1 year of open-label clozapine treatment were correlated with changes in quality of life. Similarly, Galletly and colleagues[34] found a statistically significant correlation between improvement in quality of life and performance on a digit symbol substitution task during open-label clozapine treatment. In this study, however, change in several other neuropsychological tests (eg, oral word association and category instance generation) was not significantly associated with change in quality of life. A third study, conducted by Velligan et al[35], did not directly examine the correlation between cognitive and functional status, but a possible connection may be inferred from treatment group differences. Quetiapine-treated patients demonstrated significantly greater improvement than patients treated with conventional antipsychotics in verbal fluency, verbal memory, and quality of life. The same pattern of results for cognitive and functional status in this study is consistent with a hypothesized link between the 2 domains. However, it should be noted that change in adaptive functioning was also assessed in this study, and no group differences were found.

Three studies examined the link between cognitive and functional outcomes of psychosocial treatment for schizophrenia. Spaulding et al[36] reported mixed results regarding the association of cognitive and functional improvement over 6 months of psychosocial rehabilitation. Although significant correlations were found between change in social functioning and change in 2 executive functioning tasks (ie, COGLAB card sorting random errors and Halstead Reitan Trail-Making—Test B), 11 other cognitive tests were administered that were not related to social functioning over time. A second study, conducted by Hogarty et al.,[37] examined both neuropsychological improvement and functional change as indicated by a social adjustment composite score across a 2-year trial comparing cognitive enhancement therapy (CET) and enriched supportive therapy (EST).[37] Although the association between neuropsychological and functional change was not statistically evaluated, results for neuropsychological and social adjustment composite scores followed similar patterns, which is consistent with the hypothesis that there may be a link between improvements in the 2 domains. Specifically, the CET group demonstrated greater improvement than the EST group in neurocognition, processing speed, and social adjustment at 12 and 24 months.

In a third psychosocial treatment study, Wykes and colleagues[38] conducted a 3-month randomized trial of a schizophrenia treatment program involving individualized daily sessions targeting executive functioning and memory deficits. The treatment group did not

Table 1. Studies Suggesting a Link Between Cognitive and Functional Change Among Patients With Schizophrenia: Treatment Studies

Citation	Sample	Duration/Treatment	Cognitive Assessment	Functional Status Measures	Key Results
Buchanan et al[33]	33 patients with schizophrenia	1 year: open-label clozapine	Neuropsychological tests (executive functioning and visuospatial memory)	QLS	• Changes in memory over 1 year were correlated with changes in quality of life, whereas improvements in neuropsychological performance were unrelated to symptom changes.
Galletly et al[34]	19 outpatients with schizophrenia	Open-label clozapine treatment (mean duration = 6½ months)	Neuropsychological tests (eg, oral word association, category instance generation, WAIS-R block design, and similarities)	QLS	• Correlations between QLS change and neuropsychological change are presented. The only statistically significant correlation was between the QLS and digit symbol substitution ($r = 0.56$; $P < .01$). • Correlations between the QLS and other neuropsychological tests: similarities (0.25), verbal list delayed recall (0.34), oral word association (0.39), and block design (−0.15).
Hogarty et al[37]	121 stabilized patients with schizophrenia or schizoaffective disorder	2-year trial of CET compared with EST	A neurocognition composite score integrated verbal memory, working memory, language, cognitive flexibility, executive functioning, and psychomotor speed/vigilance. A processing speed composite score was derived from several tests of reaction time.	A social adjustment composite score was derived from 2 measures: (1) clinician ratings (major role adjustment inventory) of employment, relationships, role performance, and overall functioning and (2) Social Security employability criteria (includes daily living activities, social functioning, and work readiness)	• Differences between the 2 treatment groups followed similar patterns for neuropsychological tests and social adjustment. • At 12 months, the CET group demonstrated significantly greater improvement than the EST group in processing speed ($P < .001$), neurocognition ($P = .003$), and social adjustment ($P = .046$). • At 24 months, the CET group demonstrated significantly greater improvement than the EST group in processing speed ($P < .001$), neurocognition ($P = .02$), and social adjustment ($P = .01$). • In sum, improvement in neuropsychological indices was accompanied by improvement in social adjustment. However, statistical analysis of the association between neuropsychological and functional change was not reported.

Table 1. Continued

Citation	Sample	Duration/Treatment	Cognitive Assessment	Functional Status Measures	Key Results
Spaulding et al[36]	110 stabilized inpatients with schizophrenia	6 months: enriched psychosocial treatment environment	13 neuropsychological tests	AIPSS (video vignette measure of social functioning)	• Analyses found significant correlations between change in social functioning and change in 2 cognitive tasks (COGLAB card sorting random errors, Halstead Reitan Trail-Making—Test B). • A total of 13 cognitive tasks were assessed. Change in 11 of the 13 tasks was not significantly related to change in social functioning.
Velligan et al[35]	40 outpatients with schizophrenia	6 months: quetiapine (n = 20) or conventional antipsychotics (n = 20)	Neuropsychological tests including verbal fluency, Wisconsin card sort	QLS and MCAS (adaptive functioning including ADL, social competence, and behavior problems)	• Although analyses did not specifically examine relationship between change in cognition and change in functional status, a relationship between cognition and quality of life can be tentatively inferred from treatment group differences. • Quetiapine-treated patients showed significantly better improvements than conventionals-treated patients in verbal fluency, verbal memory, and quality of life but not adaptive functioning. • The authors theorize that improvements in adaptive functioning may lag behind improvements in cognition.
Wykes et al[38]	33 patients with schizophrenia with evidence of cognitive difficulties	3 months: cognitive remediation program (remediation group, n = 17, and control group, n = 16)	Broad neuropsychological battery (cognitive flexibility, planning, and memory)	SBS	• If improvement in cognitive flexibility tasks reached a threshold, then there was some evidence that social functioning also improved. Consequently, the authors conclude that reduction in cognitive deficits may affect social outcome, at least in the short term.

Note: AIPSS, Assessment of Interpersonal Problem Solving Skills; MCAS, Multnomah Community Ability Scale; QLS, Quality of Life Scale; SBS, Social Behavior Schedule; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

Table 2. Studies Suggesting a Link Between Cognitive and Functional Change Among Patients With Schizophrenia: Nontreatment Studies

Citation	Sample	Duration/ Treatment	Cognitive Assessment	Functional Status Measures	Key Results
Friedman et al[39]	124 geriatric institutionalized patients with schizophrenia	4 years	Composite cognitive functioning score based on a neuropsychological battery including word list learning and delayed recall, praxic drawing, and Boston naming	ADL subscale of the ADAS-L	• Functional status and cognitive functioning both significantly worsened during the follow-up period. • Compared with negative symptoms and health status, change in cognitive function had the largest effect on change in ADL.
Harvey et al[40]	57 geriatric patients with schizophrenia	2½ years	MMSE	SAFE	• Cognitive and adaptive functioning both declined, but there was no change in schizophrenic symptoms. • Changes in cognition accounted for 25% of the variance in adaptive decline, whereas baseline cognition and symptoms were uncorrelated with adaptive decline.
Harvey et al[41]	424 elderly patients with schizophrenia	6 years	CDR and ADAS-L	CDR and ADAS-L	• Functional changes were significantly correlated with cognitive changes. • Cognitive changes were the best predictor of changes in functional status over time.

Note: ADAS-L, Alzhelmer's Disease Assessment Scale—Late Version (assesses cognition, functioning, and psychiatric impairment); CDR, Clinical Dementia Rating (contains items assessing both cognitive and functional status); MMSE, Mini-Mental State Examination; and SAFE, Social Adaptive Functioning Evaluation.

demonstrate greater improvement than a control group in symptoms or social functioning. However, if cognitive flexibility improved over a certain level, then social functioning also improved. This finding suggests a possible ''threshold'' relationship between cognitive and functional status. Improvement in cognitive function may have to reach a threshold before a meaningful change in functional status occurs.

Three longitudinal studies have examined the link between cognitive and functional status outside of a treatment context (table 2), and results were more consistent than findings of treatment studies. These studies focused on geriatric patients with schizophrenia over longer periods of time, ranging from 2½ to 6 years.[39–41] In all 3 samples, cognitive declines were associated with corresponding decreases in functional domains, which included ADL as well as social and adaptive functioning. Furthermore, compared to symptom change, cognitive change was more strongly related to functional status change in all 3 studies.

Taken together, findings from the 6 treatment and 3 nontreatment longitudinal studies provide initial support for the hypothesis that change in neurocognitive ability is associated with change in functional status

Table 3. Functional Outcome Measures Used in Studies Linking Cognitive and Functional Change Among Patients With Schizophrenia

Instrument	Key Validation Articles	Domains Assessed by Instrument	Intended Population	Studies On Association Of CIAS And Functional Status Measures
ADAS-L	• Weyer et al[44]	• Cognitive impairment (ie, registration, memory, and orientation) • Functional impairment (ie, toileting, feeding, and dressing) • Psychiatric impairment	• Alzheimer's disease	• Friedman et al[39]* • Harvey et al[41]*
AIPSS	• Donahoe et al[42]	• Receiving social skills • Sending social skills • Processing social skills	• Schizophrenia	• Addington and Addington[71]† • Addington and Addington[72]‡ • Spaulding et al[36]* • Addington et al[73]†
CDR	• Morris et al[74] • Morris[46] • Morris et al[76] • Hughes et al[45]	• Memory • Orientation • Judgment and problem solving • Community affairs • Home and hobbies • Personal care • Total score	• Alzheimer's disease • Dementia	• Harvey et al[41]* • Friedman et al[75]§
MCAS	• Dickerson et al[47] • O'Malia et al[48]	• ADL • Social competence • Behavioral problems • Total score	• Patients with severe mental illness	• Velligan et al[35]*
QLS	• Heinrichs et al[50] • Cramer et al[58]	• Quality of interpersonal relations • Instrumental role (eg, occupational functioning) • Intrapsychic foundations (eg, sense of purpose) • Use of common objects and performance of common activities • Total score	• Schizophrenia	• Addington and Addington[72]‡ • Buchanan et al[33]* • Galletly et al[34]* • Velligan et al[35]*
SAFE	• Israel and Roderick[77] • Harvey et al[49]	• Social-interpersonal functioning • Instrumental functioning • Life skills functioning • Total score	• Geriatric chronic psychiatric patients	• Harvey et al[40]* • McGurk et al[81]

Table 3. Continued

Instrument	Key Validation Articles	Domains Assessed by Instrument	Intended Population	Studies On Association Of CIAS And Functional Status Measures
Social Adjustment Composite Score (derived from clinician ratings and Social Security employability criteria)	• Hogarty et al[37]	• Clinician ratings (major role adjustment inventory): employment, relationships outside of home, role performance, overall functioning, and global assessment scale • Social Security employability criteria: mental ability, daily living activities, social functioning, instrumental task performance, and global work readiness	• Not specified	• Hogarty et al[37]¶
SBS	• Wykes et al[78] • Wykes et al[79] • Sturt and Wykes[80] • Wykes and Sturt[43]	• Social behavioral disturbance • Total score	• Psychiatric patients	• Wykes et al[38]*

*Examined association between cognitive change and functional change.
†Examined association between cognition at baseline and subsequent change in functional status.
‡Examined association between cognition and functional status at one point in time.
§Only used CDR total score which combines cognitive and functional status elements. Therefore, data do not provide an indication of the link between the 2.
¶Examined association of cognition and functional status at multiple points in time, but did not examine link between change in the 2 constructs.
ADAS-L, Alzheimer's Disease Assessment Scale–Late Version; AIPSS, Assessment of Interpersonal Problem Solving Skills; CDR, Clinical Dementia Rating; MCAS, Multnomah Community Ability Scale; QLS, Quality of Life Scale; SAFE, Social Adaptive Functioning Evaluation; SBS, Social Behavior Schedule.

among patients with schizophrenia. Findings from these studies suggest that change in functional outcomes may be associated with change in performance on neuropsychological tests of memory,[33] digit symbol substitution,[34] and executive functioning.[36] In addition, several studies suggest that change in overall neuropsychological performance may be associated with a corresponding change in functional status.[37,39–41] Further research is needed to examine the strength, nature, and consistency of this relationship.

Functional Outcome Measures Used in Studies of Cognitive and Functional Change

One possible reason for the inconsistent findings regarding the link between cognitive and functional change is that measurement of functional status was not ideal or consistent across studies. In the 9 studies summarized above (tables 1 and 2), a total of 8 instruments were used to assess functional domains including social behavior, occupational role, adaptive skills, quality of life, and ADL. All 8 instruments, along with subdomains and relevant citations, are summarized in table 3.

Two of the instruments focus primarily on social functioning: the Assessment of Interpersonal Problem-Solving Skills (AIPSS)[42] and the Social Behavior Schedule (SBS).[43] Several of the other instruments assess social functioning subscales along with domains that fall within the broad overlapping constructs of "adaptive functioning" and ADL. Instruments with adaptive functioning/ADL scales include the Alzheimer's Disease Assessment Scale—Late Version (ADAS-L),[44] the Clinical and Dementia Rating (CDR),[45,46] the Multnomah Community Ability Scale,[47,48] and the Social Adaptive Functioning Evaluation (SAFE) measure.[49] These instruments vary widely in terms of the specific skills that are assessed such as community affairs, hobbies, and personal care, as well as more basic skills such as toileting and feeding.

The remaining 2 instruments integrate a broader range of functional constructs, including occupational domains. Several studies used the Quality of Life Scale (QLS).[50] Similar to "functional status," "quality of life" is a multidimensional construct, which has been defined as an individual's subjective perception of the impact of health status on physical, psychological, and

social functioning.[51,52] The QLS total score is based on a semistructured interview that yields 4 subscales measuring interpersonal relations, instrumental role, intrapsychic foundations, and experience with common objects and activities. The study by Hogarty et al[37] used a composite social adjustment score derived from a similarly broad range of domains including employment, relationships, ADL, and mental ability.

There are several limitations of the functional outcomes measures used in these longitudinal studies. Only 2 of the 8 measures, the AIPSS and QLS, were designed specifically for use in patients with schizophrenia. The ADAS-L and CDR were designed for use among patients with dementia, while the others were developed for more general groups of psychiatric patients (ie, SAFE and SBS). Furthermore, the ADAS-L, CDR, and the SAFE were developed to assess the functioning of elderly patients. Schizophrenia typically has an onset in early adulthood, and consequently, these instruments may not assess skills relevant to a general sample of patients with schizophrenia that could include younger individuals. Instruments are more likely to be sensitive to change within a given population if they are developed and validated among the target patient population.[51] Therefore, most of the measures used in the reviewed studies are not likely to have optimum responsiveness among patients with schizophrenia.

Furthermore, most of the 8 measures do not assess the full range of functional status domains that are specifically relevant to schizophrenic patients. Cross-sectional studies suggest that cognitive deficits are associated with a range of functional deficits, including independent living ability, occupational limitations, and self-care difficulties.[26] However, most of the functional outcomes measures used in the longitudinal studies are relatively narrow in focus, such as the AIPSS and SBS which only assess social functioning. Therefore, these measures can only provide one part of a larger picture of the relationship between cognition and functional status among these patients.

Responsiveness and Minimally Important Difference

The responsiveness of an instrument is the extent to which the instrument accurately reflects the change in a patient's condition and discriminates between patients who change over time and those who do not.[51–54] None of the currently reviewed functional status instruments have been evaluated in terms of responsiveness to change in cognitive impairment among patients with schizophrenia. Responsiveness is considered to be a critical measurement property because an instrument without adequate responsiveness could fail to detect a clinically significant change in a patient's condition. Furthermore, an instrument with inadequate responsiveness would not be suitable for assessment of treatment effectiveness because the instrument could fail to identify meaningful between-group differences in change.

Responsiveness is an important step in the process of instrument development and psychometric validation, often following evaluation of reliability (eg, interrater, internal consistency, and test–retest) and validity (eg, content, criterion, and discriminant).[51,52,54] A related construct is the minimally important difference (MID), which is used to interpret treatment-related changes. The MID is defined as the smallest difference in a score that is clinically meaningful, usually based on patients' perceptions.[55] Evidence of an instrument's responsiveness and MID accumulates over multiple studies using both anchor-based and distribution-based methods.[56] The anchor-based methods examine the relationship between changes in the instrument being examined and changes in clinical or patient-reported outcomes. The distribution-based methods (eg, effect size, standard error of measurement, standardized response mean) provide an index of responsiveness based on the observed changes and an estimate of score dispersion.[54,56,57]

Ideally, multiple approaches are used, with both anchor- and distribution-based results contributing to the overall evaluation of responsiveness and identification of the MID. Responsiveness and MID are not static characteristics of functional outcome measurement. Instead, these properties may vary with the type of study and the characteristics of the patient population (eg, demographics, disease severity, and previous treatment).[54]

Although none of the reviewed functional outcomes instruments have been assessed in terms of responsiveness to cognitive change, responsiveness of the QLS has been evaluated relative to a clinical anchor.[58] During a 1-year study of treatment with either clozapine or haloperidol ($n = 423$ at baseline), change in overall clinical condition was categorized by clinicians using a 5-level global rating scale. The degree of improvement in QLS total scores was strongly associated with clinician-rated improvement, suggesting that the instrument is responsive to clinical change. Responsiveness of the QLS was also assessed with a distribution-based approach using the same sample.[59] Effect sizes were computed to assess sensitivity of the QLS to change over time and to treatment effect. Both effect sizes were in the moderate range (0.35 and 0.34, respectively), which provides support for the responsiveness of the QLS. It is hoped that future research will examine responsiveness of the QLS and other functional outcomes instruments, specifically in relation to improvement in cognitive indices.

Discussion and Recommendations for Future Research

Overall, the 6 treatment and 3 nontreatment longitudinal studies discussed in the current article offer initial support for a link between change in cognitive function and

change in functional status among schizophrenic patients. Each study found some similarities between patterns of cognitive and functional declines or improvements. However, inconsistencies across studies indicate that the research conducted so far should be considered a first step, and substantial questions remain unanswered. Although cognitive and functional changes were clearly associated in 3 longitudinal studies of age-related decline,[39–41] this link was not consistently demonstrated in studies of treatment-related improvement. For example, change in the majority of cognitive deficits (ie, 11 of 13 neuropsychological tests) analyzed by Spaulding and colleagues[36] was not significantly related to change in social functioning. In addition, patients with schizophrenia who were treated with second-generation antipsychotic medication in the study by Velligan et al[35] significantly improved in both cognitive functioning and quality of life but not in adaptive functioning.

These inconsistencies raise several questions for future research. First, both cognitive and functional statuses are multidimensional constructs, and inconsistent findings across studies may reflect the fact that the various studies did not examine the same aspects of these constructs. Research is needed to identify the functional outcome domains and measures that will be most sensitive to concurrent change in cognition. Cross-sectional research has demonstrated a clear association at one point in time between CIAS and impairment in independent living skills, occupational functioning, and social functioning.[25] However, sufficient longitudinal research has not yet determined whether each of these functional domains respond to cognitive change over time at the same rate. It is possible that change in some functional status domains may depend on several interrelated factors, such as the phase of treatment, phase of schizophrenia, or severity of psychotic symptoms.

Questions also remain regarding the nature of the link between cognitive and functional status over time. In the 9 reviewed studies, cognitive and functional change were more consistently related to each other when both were declining rather than improving. There are several possible reasons for the more robust association in the 3 studies with cognitive decline (Table 2). First, these 3 studies had longer durations than the improvement studies. It can be hypothesized that change in outcomes such as occupational or social functioning may lag behind cognitive change. If so, longer-term studies would be more likely to detect these delayed functional outcomes. Study durations of less than 1 year (eg, several of the studies listed in Table 1) may not be sufficient to detect all the functional implications of cognitive change. Furthermore, over a longer period of time, one could reasonably expect to find cognitive change of a greater magnitude than in shorter studies. This greater cognitive change would be more likely to have a measurable impact on functional status.

Alternatively, characteristics of the samples could account for differences in results. In all 3 studies showing cognitive decline (Table 2), the samples consisted of elderly patients with schizophrenia. Perhaps the decline seen in these older patients is qualitatively different from change that might be observed in younger patients. For example, it is possible that some elderly patients in these 3 studies dropped below a minimal level of cognitive ability required to perform many functional tasks. Further longitudinal research on age-related decline in treatment-related improvement among diverse samples is needed to better understand the relationship between cognition and functional status over time.

Another remaining question involves a possible threshold effect. While some studies revealed a direct correlation between cognitive and functional change,[33,41] one study found a significant association only when cognitive ability reached a certain threshold.[38] This threshold finding suggests the possibility that a minimal level of cognitive functioning is necessary for functional status to improve. This hypothesis is supported by another study which found that neuropsychological performance at baseline significantly predicted patients' subsequent response to a 6-month work rehabilitation program.[28] In this study, cognition was not assessed at end point, so results do not provide an indication of the association between cognitive and functional change. Nevertheless, findings suggest that there may be a minimal level of cognitive functioning that is required for functional status improvement to occur. If this threshold hypothesis is eventually supported by future research, it would suggest that the treatment of cognitive impairment is a critical first step toward helping schizophrenic patients improve in meaningful functional domains such as work and social functioning.

In order to gain a better understanding of the link between change in cognitive function and change in functional status, it will first be necessary to improve measurement of functional outcomes among patients with schizophrenia. Although many measures of social functioning, work performance, and quality of life are available, there is no consensus regarding which instruments are most sensitive to change in cognitive functioning. For example, despite the importance of researching functional outcomes of treatment of CIAS, the MATRICS group has not yet recommended specific measures of functional status that are most likely to be sensitive to cognitive change.[60]

Ideally, new functional outcome measures should be developed that are specifically designed to be responsive to change in cognition. The domains assessed by such instruments should be chosen based on theory and previous studies indicating which functional domains are most closely related to cognitive ability. For example, occupational functioning is known to be strongly associated with verbal memory and executive functioning.[28–30,35,61–65] Therefore,

it will be important for a functional status instrument to thoroughly assess occupational functioning. At the April 2004 FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia, ideal characteristics of a functional outcomes instrument were suggested.[60] These suggested guidelines indicated that instruments should have the following characteristics: good face validity for patient improvement; expectations that the instrument would change in close temporal proximity to change on cognitive performance measures; ability to yield results that are not heavily dependent on range of rehabilitation opportunities or levels of social support; practical for researchers; and tolerable for participants.

The mode of assessment for functional status evaluation should also be carefully considered. Self-report, proxy-report, and direct performance observation measures are available for patients with schizophrenia, and each approach has strengths and weaknesses.[66] Self-report measures have the advantage of capturing the patient's perspective, and some research suggests that patients with schizophrenia can reliably report their own condition.[67,68] However, self-report methodology should be used with caution among this population because patients are not likely to have accurate insights into their own condition and quality of life during acute phases of the disorder.[69] Proxy-reporters who know the patient well may be the best choice for assessment of the patient's actual functional status in multiple domains, but findings suggest that some proxies may underestimate the patient's physical and psychological quality of life.[70] Instruments involving direct observation of patients' performance, such as the University of California at San Diego performance-based skills assessment, can offer an unbiased evaluation of functional ability.[66] However, these instruments only assess the capacity to perform tasks in a testing context, rather than the patients' actual performance of these tasks in everyday situations. In treatment evaluation studies, it is likely that functional capacity may improve before actual performance outside the testing situation. The choice between these assessment approaches will depend on the research questions, resources, and design of each individual study.

When developing new functional status instruments, it is recommended that responsiveness and MID be evaluated as part of the development and validation process. One strategy would be to conduct anchor-based assessment using neuropsychological measures as the anchoring instruments. Correlational analyses comparing change in scores of the functional instrument in question with change in neuropsychological anchors would provide direct evaluation of an instrument's sensitivity to cognitive improvement. If it is not possible to create new measures, responsiveness of commonly used functional status instruments can be assessed by collecting new longitudinal data or by conducting a secondary analysis of pre-existing longitudinal data sets.[58]

Development of responsive instruments is likely to be a challenging task because of characteristics of the population in which they will be used. Many patients with schizophrenia may have external restrictions on functional change. For example, some patients who demonstrate cognitive improvement may be unable to change their living situation due to economic limitations. Such external restrictions will need to be identified so that they do not confound analyses involving the relationship between cognition and functional status over time. Another challenge stems from the heterogeneity of patients with schizophrenia, who are highly diverse in terms of disease trajectory, symptom severity, and living situation. It may not be possible to develop a single instrument that is appropriate for every patient.

Despite the inherent challenges, there is much to be gained from improved functional status measurement. Improved and psychometrically sound functional outcomes instruments will help standardize measurement across studies. With more consistent measurement, evidence can accumulate, and a clearer understanding of the link between changes in cognition and functional status will emerge. Clinical trials of second-generation antipsychotics are increasingly focusing on the cognitive effects of these medications. A greater understanding of the link between cognitive and functional change will guide research on treatment outcome by providing an indication of which cognitive deficits are most likely to have a lasting impact on patients' lives. These cognitive deficits can then become a priority for clinical trials of existing treatments as well as for treatment of patients with schizophrenia in clinical practice.

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References

1. Banaschewski T, Schulz E, Martin M, Remschmidt H. Cognitive functions and psychopathological symptoms in early-onset schizophrenia. *Eur Child Adolesc Psychiatry.* 2000; 9:11–20.
2. Elvevag B, Goldberg TE. Cognitive impairment in schizophrenia is the core of the disorder. *Crit Rev Neurobiol.* 2000;14:1–21.
3. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology.* 1998;12:426–445.
4. Kuperberg G, Heckers S. Schizophrenia and cognitive function. *Curr Opin Neurobiol.* 2000;10:205–210.

5. Mohamed S, Paulsen JS, O'Leary D, Arndt S, Andreasen N. Generalized cognitive deficits in schizophrenia: a study of first-episode patients. *Arch Gen Psychiatry.* 1999;56:749–754.
6. Palmer BW, Heaton RK, Paulsen JS, et al. Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology.* 1997;11:437–446.
7. Townsend LA, Malla AK, Norman RM. Cognitive functioning in stabilized first-episode psychosis patients. *Psychiatry Res.* 2001;104:119–131.
8. Walder DJ, Walker EF, Lewine RJ. Cognitive functioning, cortisol release, and symptom severity in patients with schizophrenia. *Biol Psychiatry.* 2000;48:1121–1132.
9. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res.* 2004;72:41–51.
10. Green MF, Nuechterlein KH, Gold JM, et al. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. *Biol Psychiatry.* 2004;56: 301–307.
11. Marder SR, Fenton W. Measurement and Treatment Research to Improve Cognition in Schizophrenia: NIMH MATRICS initiative to support the development of agents for improving cognition in schizophrenia. *Schizophr Res.* 2004;72:5–9.
12. Nuechterlein KH, Robbins TW, Einat H. Distinguishing separable domains of cognition in human and animal studies: what separations are optimal for targeting interventions? A summary of recommendations from breakout group 2 at the measurement and treatment research to improve cognition in schizophrenia new approaches conference. *Schizophr Bull.* 2005;31:870–874.
13. Collaborative Working Group on Clinical Trial Evaluations. Measuring outcome in schizophrenia: differences among the atypical antipsychotics. *J Clin Psychiatry.* 1998;12:3–9.
14. Meltzer HY, Park S, Kessler R. Cognition, schizophrenia, and the atypical antipsychotic drugs. *Proc Natl Acad Sci U S A.* 1999;96:13591–13593.
15. Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull.* 1999;25:233–255.
16. Purdon SE, Jones BD, Stip E, et al. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. *Arch Gen Psychiatry.* 2000;57:249–258.
17. Purdon SE, Malla A, Labelle A, Lit W. Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. *J Psychiatry Neurosci.* 2001;26: 137–149.
18. Sharma T. Atypical antipsychotics and cognition in schizophrenia. *Arch Gen Psychiatry.* 2002;59:571–572.
19. Sharma T. Impact on cognition of the use of antipsychotics. *Curr Med Res Opin.* 2002;18:s13–s17.
20. Sharma T, Antonova L. Cognitive function in schizophrenia. Deficits, functional consequences, and future treatment. *Psychiatr Clin North Am.* 2003;26:25–40.
21. Sharma T, Mockler D. The cognitive efficacy of atypical antipsychotics in schizophrenia. *J Clin Psychopharmacol.* 1998;18(suppl 1, pt 2):12S–19S.
22. Velligan DI, Miller AL. Cognitive dysfunction in schizophrenia and its importance to outcome: the place of atypical antipsychotics in treatment. *J Clin Psychiatry.* 1999;23:25–28.
23. Woodward ND, Purdon SE, Meltzer HY, Zald DH. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *Int J Neuropharmacology.* 2005;8(3):457–472.
24. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry.* 1996;153: 321–330.
25. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull.* 2000;26:119–136.
26. Harvey PD, Green MF, Keefe RS, Velligan DI. Cognitive functioning in schizophrenia: a consensus statement on its role in the definition and evaluation of effective treatments for the illness. *J Clin Psychiatry.* 2004;65:361–372.
27. Clauser SB, Bierman AS. Significance of functional status data for payment and quality. *Health Care Finance Rev.* 2003;24(3):1–12.
28. Bell MD, Bryson G. Work rehabilitation in schizophrenia: does cognitive impairment limit improvement? *Schizophr Bull.* 2001;27:269–279.
29. Bryson G, Bell MD. Initial and final work performance in schizophrenia: cognitive and symptom predictors. *J Nerv Ment Dis.* 2003;191:87–92.
30. McGurk SR, Mueser KT, Harvey PD, LaPuglia R, Marder J. Cognitive and symptom predictors of work outcomes for clients with schizophrenia in supported employment. *Psychiatr Serv.* 2003;54:1129–1135.
31. Palmer BW, Heaton RK, Gladsjo JA, et al. Heterogeneity in functional status among older outpatients with schizophrenia: employment history, living situation, and driving. *Schizophr Res.* 2002;55:205–215.
32. Sota TL, Heinrichs RW. Demographic, clinical, and neurocognitive predictors of quality of life in schizophrenia patients receiving conventional neuroleptics. *Compr Psychiatry.* 2004;45:415–421.
33. Buchanan RW, Holstein C, Breier A. The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance. *Biol Psychiatry.* 1994;36: 717–725.
34. Galletly CA, Clark CR, McFarlane AC, Weber DL. Relationships between changes in symptom ratings, neurophysiological test performance and quality of life in schizophrenic patients treated with clozapine. *Psychiatry Res.* 1997;72: 161–166.
35. Velligan DI, Prihoda TJ, Sui D, Ritch JL, Maples N, Miller AL. The effectiveness of quetiapine versus conventional antipsychotics in improving cognitive and functional outcomes in standard treatment settings. *J Clin Psychiatry.* 2003;64: 524–531.
36. Spaulding WD, Fleming SK, Reed D, Sullivan M, Storzbach D, Lam M. Cognitive functioning in schizophrenia: implications for psychiatric rehabilitation. *Schizophr Bull.* 1999;25: 275–289.
37. Hogarty GE, Flesher S, Ulrich R, et al. Cognitive enhancement therapy for schizophrenia: effects of a 2-year randomized trial on cognition and behavior. *Arch Gen Psychiatry.* 2004;61:866–876.
38. Wykes T, Reeder C, Corner J, Williams C, Everitt B. The effects of neurocognitive remediation on executive processing in patients with schizophrenia. *Schizophr Bull.* 1999;25: 291–307.
39. Friedman JI, Adler DN, Howanitz E, et al. A double blind placebo controlled trial of donepezil adjunctive treatment to

risperidone for the cognitive impairment of schizophrenia. *Biol Psychiatry.* 2002;51:349–357.

40. Harvey PD, Parrella M, White L, Mohs RC, Davidson M, Davis KL. Convergence of cognitive and adaptive decline in late-life schizophrenia. *Schizophr Res.* 1999;35:77–84.
41. Harvey PD, Bertisch H, Friedman JI, et al. The course of functional decline in geriatric patients with schizophrenia: cognitive-functional and clinical symptoms as determinants of change. *Am J Geriatr Psychiatry.* 2003;11:610–619.
42. Donahoe CP, Carter MJ, Bloem WD, Hirsch GL, Laasi N, Wallace CJ. Assessment of interpersonal problem-solving skills. *Psychiatry.* 1990;53:329–339.
43. Wykes T, Sturt E. The measurement of social behaviour in psychiatric patients: an assessment of the reliability and validity of the SBS schedule. *Br J Psychiatry.* 1986;148:1–11.
44. Weyer G, Erzigkeit H, Kanowski S, Ihl R, Hadler D. Alzheimer's Disease Assessment Scale: reliability and validity in a multicenter clinical trial. *Int Psychogeriatr.* 1997;9: 123–138.
45. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry.* 1982;140:566–572.
46. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology.* 1993;43:2412–2414.
47. Dickerson FB, Origoni AE, Pater A, Friedman BK, Kordonski WM. An expanded version of the Multnomah Community Ability Scale: anchors and interview probes for the assessment of adults with serious mental illness. *Community Ment Health J.* 2003;39:131–137.
48. O'Malia L, McFarland BH, Barker S, Barron NM. A level-of-functioning self-report measure for consumers with severe mental illness. *Psychiatr Serv.* 2002;53:326–331.
49. Harvey PD, Davidson M, Mueser KT, Parrella M, White L, Powchik P. Social-Adaptive Functioning Evaluation (SAFE): a rating scale for geriatric psychiatric patients. *Schizophr Bull.* 1997;23:131–145.
50. Heinrichs DW, Hanlon TE, Carpenter WT Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull.* 1984;10:388–398.
51. Leidy NK, Revicki DA, Geneste B. Recommendations for evaluating the validity of quality of life claims for labeling and promotion. *Value Health.* 1999;2:113–127.
52. Revicki DA, Osoba D, Fairclough D, et al. Recommendations on health-related quality of life research to support labeling and promotional claims in the United States. *Qual Life Res.* 2000;9:887–900.
53. Deyo RA, Centor RM. Assessing the responsiveness of functional scales to clinical change: an analogy to diagnostic test performance. *J Chronic Dis.* 1986;39:897–906.
54. Hays RD, Revicki DA. Reliability and validity (including responsiveness). In: Fayers P, Hays RD, eds. *Assessing Quality of Life in Clinical Trials: Methods and Practice* 2nd ed. Oxford: Oxford University Press. 2005;25–39.
55. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials.* 1989;10:407–415.
56. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc.* 2002;77:371–383.
57. Sprangers MA, Moinpour CM, Moynihan TJ, Patrick DL, Revicki DA. Assessing meaningful change in quality of life over time: a users' guide for clinicians. *Mayo Clin Proc.* 2002;77:561–571.
58. Cramer J, Rosenheck R, Xu W, Henderson W, Thomas J, Charney D. Detecting improvement in quality of life and symptomatology in schizophrenia. *Schizophr Bull.* 2001;27: 227–234.
59. Cramer JA, Rosenheck R, Xu W, Thomas J, Henderson W, Charney DS. Quality of life in schizophrenia: a comparison of instruments. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. *Schizophr Bull.* 2000;26:659–666.
60. Buchanan RW, Davis M, Goff D, et al. A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schizophr Bull.* 2005;31:5–19.
61. Bryson G, Bell MD, Kaplan E, Greig T. The functional consequences of memory impairments on initial work performance in people with schizophrenia. *J Nerv Ment Dis.* 1998; 186:610–615.
62. Kern RS, Green MF, Mintz J, Liberman RP. Does 'errorless learning' compensate for neurocognitive impairments in the work rehabilitation of persons with schizophrenia? *Psychol Med.* 2003;33:433–442.
63. Lysaker PH, Bell MD, Zito WS, Bioty SM. Social skills at work: deficits and predictors of improvement in schizophrenia. *J Nerv Ment Dis.* 1995;183:688–692.
64. Martinez-Aran A, Penades R, Vieta E, et al. Executive function in patients with remitted bipolar disorder and schizophrenia and its relationship with functional outcome. *Psychother Psychosom.* 2002;71:39–46.
65. Velligan DI, Bow-Thomas CC, Mahurin RK, Miller AL, Halgunseth LC. Do specific neurocognitive deficits predict specific domains of community function in schizophrenia? *J Nerv Ment Dis.* 2000;188(8):518–524.
66. Patterson TL, Goldman S, McKibbin CL, Hughs T, Jeste DV. UCSD Performance-Based Skills Assessment: development of a new measure of everyday functioning for severely mentally ill adults. *Schizophr Bull.* 2001;27:235–245.
67. Goldberg RW, Seybolt DC, Lehman A. Reliable self-report of health service use by individuals with serious mental illness. *Psychiatr Serv.* 2002;53:879–881.
68. Liraud F, Droulout T, Parrot M, Verdoux H. Agreement between self-rated and clinically assessed symptoms in subjects with psychosis. *J Nerv Ment Dis.* 2004;192:352–356.
69. Doyle M, Flanagan S, Browne S, et al. Subjective and external assessments of quality of life in schizophrenia: relationship to insight. *Acta Psychiatr Scand.* 1999;99:466–472.
70. Becchi A, Rucci P, Placentino A, Neri G, de Girolamo G. Quality of life in patients with schizophrenia—comparison of self-report and proxy assessments. *Soc Psychiatry Psychiatr Epidemiol.* 2004;39:397–401.
71. Addington J, Addington D. Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. *Schizophr Res.* 2000;44:47–56.
72. Addington J, Addington D. Neurocognitive and social functioning in schizophrenia. *Schizophr Bull.* 1999;25:173–182.
73. Addington J, McCleary L, Munroe-Blum H. Relationship between cognitive and social dysfunction in schizophrenia. *Schizophr Res.* 1998;34:59–66.
74. Morris JC, Ernesto C, Schafer K, et al. Clinical dementia rating training and reliability in multicenter studies: the Alzheimer's Disease Cooperative Study experience. *Neurology.* 1997;48:1508–1510.
75. Friedman JI, Harvey PD, Coleman T, et al. Six-year follow-up study of cognitive and functional status across the lifespan

in schizophrenia: a comparison with Alzheimer's disease and normal aging. *Am J Psychiatry.* 2001;158:1441–1448.

76. Morris JC, McKeel DW, Jr., Fulling K, Torack RM, Berg L. Validation of clinical diagnostic criteria for Alzheimer's disease. *Ann Neurol.* 1988;24(1):17–22.
77. Israel AC, Roderick HA. A measure of the stability of family activities: an initial examination. *Assessment.* 2001;8(4):417–424.
78. Wykes T, Sturt E. In: Salek S, ed. *Compendium of Quality of Life Instruments.* Vol 3. Chichester, West Sussex: Wiley; 1998.
79. Wykes T, Sturt E. In: Wade DT, ed. *Measurement in neurological rehabilitation.* New York: Oxford University Press; 1992:283–284.
80. Sturt E, Wykes T. Assessment schedules for chronic psychiatric patients. *Psychol Med.* 1987;17(2):485–493.
81. McGurk SR, Moriarty PJ, Harvey PD, Parrella M, White L, Davis KL. The longitudinal relationship of clinical symptoms, cognitive functioning, and adaptive life in geriatric schizophrenia. *Schizophr Res.* 2000;42(1):47–55.