ABSTRACT

Defining features of schizophrenia include abnormal perceptions (hallucinations) or thoughts (delusions), disordered thinking, disorganized or catatonic behavior, and “negative” symptoms, such as emotional blunting, decreased initiative, and impoverished speech. In addition, there is growing evidence that cognitive deficits precede, accompany, and outlast the more dramatic positive symptoms of schizophrenia and its treatment. Functions that appear to be most affected include verbal learning, memory, psychomotor speed, and vigilance. This article offers a review of the prevalence of cognitive impairment in schizophrenia, in addition to the nature and severity of the deficits and their functional significance. Recent studies have found that 75% to 85% of patients experience at least some degree of cognitive impairment. Moreover, even those who appear cognitively intact actually show mildly depressed functioning on sensitive measures of information processing. Cognitive impairment has been shown to negatively affect daily functioning, work outcomes, level of required residential care, and treatment adherence. Also included in the article is a discussion of the development process for a standardized cognitive battery designed to serve as an outcome measure for clinical trials of cognition-enhancing drugs and cognitive rehabilitation programs. (Adv Stud Med. 2007;7(3):72-78)

THE NATURE AND SIGNIFICANCE OF COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

David J. Schretlen, PhD, ABPP*

Increasingly recognized as a heterogeneous disorder with more than one etiology, schizophrenia burdens its patients with signs and symptoms in multiple domains. Defining features include abnormal perceptions (hallucinations) or thoughts (delusions), formal thought disorder (illogical speech), grossly disorganized or catatonic behavior, and “negative” symptoms, such as emotional blunting, decreased initiative, and impoverished speech. Patients experience varied admixtures of these abnormalities. One might be plagued by the whispered comments of unseen critics. Another believes that he is burdened with God-like power to control world events. Some patients are convinced that external forces or even an implanted device controls their thoughts and behavior. Many patients spend most of their time alone, doing little more than sitting or watching television. They speak with a monotone voice and make oddly idiosyncratic remarks when engaged in conversation. In addition, virtually all affected individuals show impaired functioning in the areas of work, social interaction, or self-care.

PREVALENCE OF COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

The standard diagnostic nomenclature for schizophrenia includes an extensive list of symptoms. Conspicuously absent from the diagnostic criteria is any reference to cognitive impairment.1 However, several lines of evidence suggest that neuropsychological compromise is a core feature of schizophrenia. Children who later develop the illness have been observed to display intellectual deficits long before the emergence of psychotic symptoms.2 Moreover, unaffected relatives of patients with schizophrenia exhibit qualitatively similar cognitive deficits, with severity corresponding to the degree of genetic susceptibility.3
Cognitive deficits do not result from hallucinations, delusions, apathy, or other primary disease symptoms; they also do not result from medications used to treat schizophrenia. Cognitive impairment also has been found to remain relatively stable over time, with the nature and severity of neuropsychological deficits seen in drug-naïve, first-episode patients resembling those of chronic patients. In short, there is growing evidence that cognitive deficits precede, accompany, and outlast the more dramatic positive symptoms of schizophrenia.

The recognition of cognitive impairment as a core feature of the illness raises the question of whether it is present in all cases. Although observed rates are lower, the exact proportion of individuals with schizophrenia who suffer from cognitive deficits remains unclear. Some early studies suggested that fewer than 50% of persons with schizophrenia may be afflicted. However, more recent studies have found that 75% to 85% of patients experience at least some degree of cognitive impairment. Those patients who show no signs of neuropsychological dysfunction also raise the question of whether it is possible to have schizophrenia without cognitive impairment. Although it is logically impossible to answer this question definitively, many patients who appear cognitively intact actually show mildly depressed functioning on selected, highly sensitive measures of information processing. For example, Kremen et al found that the 23% of patients with schizophrenia who produced “normal” neurocognitive profiles also showed higher estimated premorbid IQs than healthy control subjects. Furthermore, when each cognitively “normal” patient was matched in overall cognitive functioning with a healthy control subject, the patients performed significantly worse than control subjects on tests of executive functioning and psychomotor speed, yet they performed better than control subjects on tests of general verbal ability. When patients in another study were matched individually to within 3 IQ points with healthy adults, patients with above average to superior intelligence (IQs ≥110 points) still performed significantly worse than healthy adults on tests of immediate memory. These results suggest that most patients with schizophrenia, including those who appear cognitively intact or show above average intelligence, have at least mild selective deficits, relative to their own premorbid level of functioning.

Nature and Severity of the Deficits

Any group of individuals with schizophrenia will perform worse than demographically similar healthy adults on virtually any reliable and valid measure of neurocognitive functioning. The very consistency of this observation complicates identification of a neuropsychological “signature” of schizophrenia. Whether investigators examined a very discrete aspect of information processing or broad cognitive domains, hundreds of studies have shown that schizophrenia confers cognitive impairment, with some deficits being less prominent than others. In fact, accumulating literature suggests a neurodevelopmental basis for this illness, because affected children manifest intellectual deficits years prior to developing psychotic symptoms and adults with schizophrenia even show impairment on tests designed to assess “premorbid” ability. Keefe et al found that patients in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study scored well below expectations on a word reading test used to estimate premorbid ability. In another study, 91 adults with schizophrenia performed worse than their first-degree relatives, patients with affective psychoses, their relatives, and healthy control subjects on another word reading task (the National Adult Reading Test or NART) designed to assess premorbid IQ.

Attempts to identify a neuropsychological profile of schizophrenia must begin with the recognition that this disease affects virtually all cognitive domains. In examining the literature, studies that assess a broad spectrum of abilities can shed light on differential impairment across domains, whereas meta-analyses (quantitatively combined findings from narrower studies) can offer insight into particular types of cognitive deficits. The latter analysis involves computing the magnitude of difference between 2 groups (ie, healthy adults vs patients with schizophrenia) on a common dependent variable (ie, IQ) that is reported by several different investigators. Between-group differences in IQ are expressed in terms of the variance shown by each group (usually the pooled SD), which also is used to estimate the size of the effect. These effect size estimates can then be averaged across studies to quantify the magnitude of the group difference on each cognitive measure reported in the existing literature.

The most widely cited meta-analysis of cognitive functioning in schizophrenia was conducted by
Heinrichs and Zakzanis, which computed 509 effect sizes for the comparisons that were reported in 204 studies based on 7420 patients and 5865 healthy control subjects. As one would assume, the studies that provided data for their meta-analysis used a multitude of different cognitive tests. The authors assigned effect sizes to 1 of 22 variables, which were based on a single test or combined measures from different instruments. The 22 variables were then grouped into 8 cognitive domains: memory, motor skills, attention, general intelligence, spatial ability, executive functioning, language, and tactile-transfer. Although their assignment of individual measures to 22 variables and the grouping of variables into cognitive domains could be questioned, the task was daunting and the resulting effect sizes make intuitive sense in most respects. The effect sizes ranged from 0.5 to 1.4 (mean of 0.9), indicating that patients performed nearly 1 SD below healthy control subjects across all measures of cognitive function. However, a counterintuitive finding was that one of the largest effects was for Wechsler Adult Intelligence Scale-Revised (WAIS-R) Performance IQ scores, whereas one of the smallest effects emerged for a WAIS-R subtest (Block Design) that is used to compute Performance IQ. In any case, the effect size for Full Scale IQ scores was 1.1, suggesting that patients with schizophrenia scored slightly more than 16 IQ points below that of healthy control subjects.

The statistical method of factor analysis is another way of defining cognitive domains. This method can elucidate a few “latent” abilities that account for most of the observed variation in performance on many different tests. However, one limiting factor is the dependence of the latent factor structure on specific measures included in the analysis. Different factor solutions can come from 2 patient samples administered the same test, as well as from a single sample, depending on which measures are included in the analysis. Also, the possibility that schizophrenia alters the underlying organization of cognitive domains cannot be excluded. For example, a factor analysis of test scores included in the CATIE study baseline assessment revealed that a single factor best described the data, even though the measures were selected with the goal of representing 5 cognitive domains. Such findings complicate conceptualization of cognitive domains based on factor analysis.

Despite limitations that are inherent to various approaches used to identify schizophrenia-associated cognitive domains, converging evidence suggests that verbal learning, memory, psychomotor speed, and vigilance are among the affected functions. Visual learning/memory, problem solving, verbal fluency, and executive functioning also are impaired, but perhaps not disproportionately. Functions that are probably least affected by schizophrenia include attention span, perceptual discrimination, and basic linguistic abilities, such as naming and receptive vocabulary.

Some investigators have argued that schizophrenia is characterized by a unique pattern of cognitive deficits. However, recent studies suggest that the cognitive deficits shown by patients with bipolar disorder are, albeit milder, qualitatively similar to those seen in schizophrenia. In one analysis, 9 cognitive measures (each assigned to 1 of 6 cognitive domains) were administered to 106 outpatients with schizophrenia, 66 outpatients with bipolar disorder, and 316 reasonably healthy control subjects. Test scores were adjusted for age, sex, race, and years of education, and estimated premorbid IQ, and effect sizes for differences between healthy control subjects and each patient group were computed (Figure). Both patient groups performed significantly worse than healthy

**Figure. Cognitive Profiles of Patients with SZ and BD**

Mean effect sizes for 6 cognitive domains based on demographically adjusted T-scores produced by patients with SZ and BD, compared to healthy adults. Repeated measures analysis of variance planned contrasts confirmed that each patient group differed significantly from healthy controls on every cognitive domain (P < 0.05). Bonferroni-corrected post hoc comparisons showed the SZ and BD groups differed significantly (P < 0.05) on all domains except attention. BD = bipolar disorder; SZ = schizophrenia. Reprinted with permission from Schretlen et al. Biol Psychiatry. 2006;[Epub ahead of print].
control subjects in every domain, and patients with schizophrenia performed significantly worse than those with bipolar disorder in all but 1 domain (attention). But despite clear differences in the severity of cognitive deficits between patients with schizophrenia and those with bipolar disorder, the cognitive profiles produced by these groups were qualitatively similar. These observations suggest that any treatment that improves cognition in schizophrenia may have broader application.

**Functional Significance of Cognitive Impairment**

Cognitive functioning has attracted increasing attention because it appears to play a central role in many aspects of functional outcome in schizophrenia. For example, Velligan et al found that measures of global cognitive functioning accounted for more than 40% of the variance in activities of daily living in 2 separate patient samples. Most importantly, after researchers accounted for cognitive function, they found that severity of psychosis and negative symptoms did not improve the prediction of everyday functioning in either sample. Cognitive impairment has also been found to correlate with the required level of residential care. Patients with more severe deficits are more likely to require long-term hospitalization or nursing home placement. Difficulties in performing specific everyday tasks, such as planning activities and paying bills, also have been shown to correlate with the severity of cognitive deficits.

Schizophrenia is one of the most common causes of work disability. Although estimates of the proportion of patients with schizophrenia who do not work vary, a recent large-scale US survey found that 22.5% of patients are employed, with 12% having full-time status. In the CATIE study, only 15% of patients were working (7% full-time and 8% part-time) at baseline. Several studies reveal that cognitive test performance correlates with or predicts work outcomes, such as employment status, work duration, and earned income. Although it is also important to consider the well-documented impact of other symptoms (ie, positive and negative) on work outcomes, cognitive impairment appears to disrupt work ability independently from other symptoms and in proportion to the degree of deficit.

In addition to limiting the ability to live independently, manage activities of daily living, and work competitively, cognitive deficits in schizophrenia are associated with poor treatment adherence, medical comorbidities, and increased treatment costs. Patients may lose medications, forget to take doses or refill prescriptions, fail to establish routines for medication use, and misunderstand dosing directions. Comorbidities are likely to further complicate treatment compliance, because patients who poorly adhere to schizophrenia medication are expected to have similar issues with treatment for other conditions. Deficits in attention and memory may also impede the ability of some patients to make healthy lifestyle choices, such as not smoking. In a recent prospective study of 85 patients with schizophrenia, poor cognitive test performance at baseline predicted increased costs for medical, psychiatric, and community care, even after symptom severity and social withdrawal were taken into account. Increasing evidence also indicates that cognitive difficulties contribute to decreased quality of life (QOL) in patients with schizophrenia. Several studies have shown that patients with more severe cognitive deficits are less accurate in rating their social functioning than patients with less severe deficits.

Contradictory findings have been reported for all the aforementioned research. Some studies failed to find significant associations between cognitive functioning and other aspects of illness outcome or morbidity, whereas others found that, compared with cognitive functioning, symptom severity, or social support account for more variance in work, QOL, and other outcomes. Still, there is a reasonable and growing consensus that cognitive impairment is not only a core feature of schizophrenia, it is also an aspect of the illness with broad implications.

Unfortunately, despite the critical role of cognitive impairment in schizophrenia, antipsychotic drugs have, at best, modest impact on cognition. Even patients receiving adequate antipsychotic treatment continue to experience significant cognitive and functional impairment. These considerations led the National Institute of Mental Health (NIMH) to establish an initiative called Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). In 2004, MATRICS investigators, officials from the NIMH and the US Food and Drug Administration, and experts from academia and the pharmaceutical industry held a meeting to develop guidelines for clinical trials of cognition-enhancing drugs for schizophrenia. Initial priorities included identifying specific cognitive deficits that characterize schizophrenia and developing instruments to measure them.
STANDARDIZED TESTING OF COGNITIVE FUNCTIONING

Numerous reliable cognitive tests have been validated for the assessment of schizophrenia. Some assessments, such as the Wechsler scales of intelligence, are lengthy and include several subtests. Others, like the Trail Making Test, are less time consuming and sensitive, but involve nonspecific tasks that require many cognitive processes for successful performance. Still other tests assess discrete cognitive functions, like reaction time. Most tests are administered individually using pencil and paper or other stimuli, but a few are administered using computer or audio cassette. In practice, neuropsychologists usually administer a battery of tests to assess functioning across multiple cognitive domains.

From one perspective, the availability of varied instruments is useful because it allows for the elucidation of which cognitive functions are more or less compromised by schizophrenia. If every study used the same tests, it would be impossible to disentangle the impairment of underlying cognitive abilities from the method variance associated with each test. Test limitations would also hinder the discovery of new cognitive abnormalities and their relationship with other disease markers. Conversely, the diversity of instruments complicates a comparison of findings across studies. One compromise is to identify a brief set of tests that assess a core group of cognitive domains and augment these with others as needed. In order to develop such a test battery, a MATRICS committee consulted experts in the field and identified criteria for test selection. The latter included test-retest reliability, appropriateness as a repeated measure, relationship to functional outcomes, potential sensitivity to medications, and tolerability and practicality. In identifying “separable cognitive factors,” the committee reviewed 13 factor analytic studies of patients with schizophrenia versus healthy control subjects and found 6 replicated cognitive factors to adequately represent the major cognitive deficits seen in schizophrenia and later added a seventh factor (social cognition). The final set of factors represents an abstraction of previous reports in the sense that no single study actually found these 6 factors. Following a series of additional steps and β testing, the NIMH-MATRICS Consensus Cognitive Battery (MCCB) was finalized and published by Matrics Assessment Inc. The 7 factors and tests used to assess them are shown in the Table.

### Table. MATRICS Consensus Cognitive Battery

<table>
<thead>
<tr>
<th>Domain</th>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of processing</td>
<td>Brief Assessment of Cognition in Schizophrenia: Symbol-Coding</td>
<td>Timed test in which respondent uses a key to write digits that correspond to symbols</td>
</tr>
<tr>
<td></td>
<td>Category Fluency: Animal Naming</td>
<td>Oral test of speeded animal naming in 1 min</td>
</tr>
<tr>
<td></td>
<td>Trail Making Test: Part A</td>
<td>Timed test of scanning and sequencing numbered circles</td>
</tr>
<tr>
<td>Attention-vigilance</td>
<td>Continuous Performance Test-Identical Pairs</td>
<td>Computer-administered test of ability to press buttons when matching numbers are presented consecutively</td>
</tr>
<tr>
<td>Working memory</td>
<td>Wechsler Memory Scale-3rd Edition: Spatial Span</td>
<td>Test of ability to tap sequence of irregularly spaced cubes in same (or reverse) sequence as examiner</td>
</tr>
<tr>
<td></td>
<td>Letter-Number Span</td>
<td>Oral test of ability to re-order strings of letters and numbers</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>Hopkins Verbal Learning Test-Revised</td>
<td>Test of ability to remember as many words as possible after each of 3 oral presentations of 12-word list</td>
</tr>
<tr>
<td>Visual learning</td>
<td>Brief Visuospatial Memory Test-Revised</td>
<td>Test of ability to remember as many figures as possible after each of 3 presentations of 6 geometric figures</td>
</tr>
<tr>
<td>Reasoning &amp; problem solving</td>
<td>Neuropsychological Assessment Battery Mazes</td>
<td>Seven timed pencil-and-paper mazes of increasing difficulty that measure look-ahead planning</td>
</tr>
<tr>
<td>Social cognition</td>
<td>Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions</td>
<td>Pencil-and-paper multiple-choice test that assesses how people manage their emotions</td>
</tr>
</tbody>
</table>

MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia.

The MCCB was designed to serve as an outcome measure for clinical trials of cognition-enhancing drugs and cognitive rehabilitation programs. Two tests (Hopkins Verbal Learning Test-Revised and Brief Visuospatial Memory Test-Revised) have 6 alternate forms and 1 test (Neuropsychological Assessment Battery Mazes) has 2 forms. This structure provides the MCCB with some suitability for repeated assessments. Several tests in the battery are published separately with their own normative samples. Performances on all of the tests can be expressed in a uniform metric (T-scores), and they are adjusted for age and sex. The MCCB measures were co-normed on a sample of healthy adults aged 20 to 59 years and, for validation purposes, a β version was administered to 176 adult outpatients with schizophrenia and then re-administered 4 weeks later. Results of these studies have not yet been published in peer-reviewed journals. The MATRICS initiative will ensure adoption of the MCCB in clinical trials. However, many other reliable and valid tests of cognitive abilities warrant consideration, not only for clinical assessment, but for use in neuropsychological investigations and in clinical trials as well.

CONCLUSIONS

Cognitive impairment is increasingly recognized as a critical aspect of schizophrenia, with a direct impact on functional outcomes. Studies continue to uncover varying degrees of impairment throughout the entire course of the illness, including the prodrome period. Even patients who appear cognitively intact usually have subtle deficits on close examination. In order to optimize available therapeutic modalities and, more importantly, to develop viable cognition-enhancing treatments, it is important to standardize assessment of cognitive function and focus on schizophrenia-associated cognitive factors.

REFERENCES