Assessing Cognitive Impairment in Patients With Schizophrenia

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Schizophrenia has existed as a distinct disorder for nearly a century, and, ever since this disorder was first described and studied, cognitive impairment has been recognized as a prominent feature. However, the positive symptoms of schizophrenia moved to the forefront of clinical and research attention in the latter half of the twentieth century. With the new movement toward functional recovery in schizophrenia, cognitive dysfunction has become an important treatment target. This shift in focus has been prompted by our evolving knowledge of brain changes associated with schizophrenia and by the mounting body of evidence indicating that cognition is closely related to functional outcome. Cognitive assessments can enhance the evaluation and treatment of all patients with schizophrenia, and clinicians may select from a variety of valid and reliable scales and assessment measures.

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In the broadest sense, cognition refers to all activities of the mind. As a disorder of the mind, schizophrenia seemingly would be inseparable from cognition, but the cognitive aspects of the disorder have not always been the focus of research and treatment. In recent years, however, our improved understanding of the causes and manifestations of cognitive impairments in schizophrenia and our growing realization that cognition is central to outcomes have redirected attention at this important aspect of the disorder. This renewed focus on cognition is leading to the development and implementation of treatments that are more likely to help individuals with schizophrenia lead fuller, more independent lives.

PUTTING COGNITIVE IMPAIRMENT IN PERSPECTIVE

Historical Perspective

Our concept of schizophrenia as a distinct disorder goes back about a century to the work of Emil Kraepelin, although he called this disorder dementia praecox. He noted the fundamental role of cognitive impairment in this disorder, as intellectual decline is inherent in the name "dementia."[1] Over time, the work of Eugen Bleuler led to the disorder being known as schizophrenia. He did not describe it as a disorder that is progressively neurodegenerative like dementia, although cognitive impairment was still a defining feature.[1,2] However, in the latter half of the 20th century, emphasis shifted to the positive symptoms of schizophrenia such as delusions and hallucinations. As medications became available midcentury to treat the positive symptoms of schizophrenia, outcomes were improved and outpatient treatment was possible.[3] However, despite their therapeutic benefits, antipsychotic medications have not often led to complete recovery, which has been attributed in part to their lack of effects on cognitive and negative symptoms.[3,4]

Current Perspective

As our understanding of the neuropsychological and structural abnormalities associated with schizophrenia has increased, the pendulum has swung away from a focus primarily on positive symptoms to cognitive and negative symptoms as treatment targets.[5] Many investigators, going back to Kraepelin and Bleuler, have suspected frontal lobe dysfunction to be involved in the disorder, because the frontal lobes are thought to be linked to cognitive and negative symptoms.[6] As neuroimaging techniques have improved, investigators have been able to gather evidence to support this theory. In the 1980s, Weinberger and colleagues[6] studied regional cerebral blood flow (rCBF) to the dorsolateral prefrontal cortex (DLPFC) in 20 medication-free individuals with chronic schizophrenia and 25 control subjects. The participants were assessed both at rest and while completing the Wisconsin Card Sort (WCS) test. Performance on the WCS is known to be correlated with activity in the DLPFC. The participants without schizophrenia had increased blood flow to the DLPFC when completing the WCS. The participants with schizophrenia did not experience this increased blood flow, thus providing evidence that cognitive impairment may be related to dysfunction in the prefrontal cortex.[6]

Cognitive deficits have been recognized as being fundamentally intertwined with functional outcomes.[7] In a 1996 review[8] of studies examining correlations between neurocognitive deficits and functional outcomes, Green revealed that several neurocognitive deficits were strongly associated with specific functional outcomes in schizophrenia (Table 1).[8] The strongest evidence showed that verbal memory was associated with all measures of functional outcome, but other correlations were found

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Clinical Points

- Remember that neuropsychological tests cannot diagnose schizophrenia but may be helpful for understanding cognitive deficits and treatment planning.
- Administer cognitive assessments to all patients with schizophrenia at baseline and throughout treatment using a validated and reliable instrument.
- Be alert for cognitive impairments in at-risk patients because they may be the first signs of schizophrenia.
- Consider how the results of cognitive assessments may relate to a patient's functional outcomes and tailor treatment accordingly.

between vigilance and both social problem solving and skill acquisition, and between card sorting and community functioning. Negative symptoms were also associated with social problem solving. Another notable finding was the lack of a significant association between psychotic symptoms and any of the measures of functional outcomes studied.

Because the field of psychiatry has moved toward the goals of remission and recovery rather than mere symptom improvement, treatment must better address cognitive and negative symptoms of schizophrenia in addition to resolving positive symptoms. This article describes assessment of cognitive symptoms.

RELEVANCE OF COGNITION TO SCHIZOPHRENIA

The Role of Cognitive Assessment in Populations With Schizophrenia

After more than a hundred years of investigation, we know that cognitive impairment is a core feature of schizophrenia. Individuals with schizophrenia have been found to exhibit low IQ and below-average cognitive performance years before the emergence of psychosis.[7] In fact, cognitive impairment may be an indicator of the prodromal phase of schizophrenia.[9] Furthermore, Wozniak et al[10] showed cognitive deficits to be unchanged over a 1-year follow-up study of adolescents with schizophrenia spectrum disorders, even though clinical symptoms improved. However, cognitive assessment is currently not very useful for diagnosing schizophrenia, because a clear profile on neuropsychological tests has not been defined. Tamminga and colleagues[11] administered a cognitive assessment to a group of individuals with schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis. They found that, because the results overlapped among the different disorders, they were unable to differentiate participants by diagnosis. Although the testing does not represent a clear diagnostic marker, it can offer an understanding of cognitive deficits and guide treatment targets and recommendations.

Cognitive Domains Most Relevant to Schizophrenia Outcomes

Although widespread agreement exists that cognitive deficits are a key feature of schizophrenia, different investigators have emphasized different areas of cognition when studying this disorder. When the National Institute of Mental Health (NIMH) undertook the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project, the investigators wanted to identify distinct, separable cognitive domains commonly affected in patients with schizophrenia.[12] To achieve this goal, Nuechterlein and colleagues[12] reviewed numerous studies of cognitive impairment in schizophrenia and identified 7 distinct domains that were replicated across studies and could be considered fundamental cognitive deficits in schizophrenia. Following are the identified domains they included in a consensus cognitive battery:

Processing speed. One measure of cognition is the speed with which an individual is able to perform perceptual or motor tasks. This domain includes verbal fluency.

Attention/vigilance. Attention and vigilance influence an individual's ability to complete tasks requiring sustained focus.

Working memory. The domain of working memory concerns the individual's ability to temporarily retain information for immediate recall and manipulation.

Verbal learning and memory. Tests of verbal learning and memory require encoding and recalling verbal information, such as word lists or short narratives.

Visual learning and memory. Tests of visual learning and memory assess an individual's immediate or delayed ability to recall visual information, such as faces or scenes, or the ability to reproduce simple images such as line drawings.

Reasoning and problem solving. The domain of reasoning and problem solving is often referred to as part of executive functioning. Reasoning and problem solving reflects an individual's ability to complete verbal and nonverbal tasks that require complex planning or decision-making skills.

Table 1. Strength of Associations Between Neurocognitive Measures and Functional Outcomes in Patients With Schizophrenia[a]

Neurocognitive Measure	Community Outcome	Social Problem Solving	Skill Acquisition
Secondary verbal memory	●	●	●
Vigilance	…	●	●
Card sorting/executive function	●	○	◐
Immediate verbal memory	…	◐	●
Negative symptoms	◐	●	○
Early visual processing	…	◐	◐
Complex reaction time	◐	…	…
Reaction time	…	◐	…
Visual memory	◐	…	…
Verbal fluency	◐	…	…
Proverb interpretation	…	…	◐
Psychomotor speed	…	…	◐
Psychotic symptoms	○	○	○

[a]Based on Green.[8]
Symbols: ● = probable association; ◐ = possible association; ○ = negative association; … = no data.

Table 2. Comparison of Tests for Measuring Cognition in Schizophrenia

Test	Cognitive Domain						Other Domains Assessed	Time to Administer, min
	Processing Speed	Attention/ Vigilance	Working Memory	Verbal Learning/ Memory	Visual Learning/ Memory	Reasoning/ Problem Solving		
WAIS-III Short Form[17]	✓		✓			✓	Acquired knowledge	15
RBANS[20]		✓	✓	✓	✓			30
MCCB[23]	✓	✓	✓	✓	✓	✓	Social cognition	60–90
BACS[25]	✓	✓	✓	✓		✓		30
BCA[27]	✓	✓		✓		✓		15
SCoRS[28]		✓	✓	✓		✓	Motor skills	30

Abbreviations: BACS = Brief Assessment of Cognition in Schizophrenia, BCA = Brief Cognitive Assessment, MCCB = Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, SCoRS = Schizophrenia Cognition Rating Scale, WAIS-III = Wechsler Adult Intelligence Scale-Third Edition.

Social cognition. The subtest used in the battery focuses on the emotional management aspect of social cognition. However, theory of mind (the ability to infer intentions or mental states of others) and social and emotional perception are also considered part of this domain and have been linked to deficits in schizophrenia.[12,13]

This list does not include every aspect of cognition affected by schizophrenia. Verbal comprehension is also a fundamental area of deficit in schizophrenia, but researchers decided it would not be useful to include in the cognitive battery due to resistance to change.

COGNITIVE ASSESSMENT

When evaluating a patient with schizophrenia, clinicians must begin with a general assessment to establish the patient's average cognitive functioning. Clinicians should find out how well the patient performs at school or work and solves problems in his or her daily life. The classic mental status examination is crucial.[14] Unusual thought content and deficits in executive function can also be revealed by using such methods as proverb interpretation.[15] Clinicians should also establish the patient's IQ and document any developmental delays or changes in overall functioning. For example, sometimes patients report that they have become unable to read more than 1 page of a book at a time. Depending on the general cognitive assessment findings, neuropsychological and functional assessments can be performed for more specific documentation of deficits.

Tests for Measuring Cognition

A number of established tests are available to assist clinicians in evaluating the cognitive and neuropsychological status of individuals with schizophrenia.[16] These tests vary in length, ease of use, and specific domains assessed. Useful instruments for clinical practice are described here (Table 2).

Wechsler Adult Intelligence Scale and Wechsler Memory Scale. The Wechsler Adult Intelligence Scale[17] (WAIS) and the Wechsler Memory Scale[18] (WMS) were developed for use in healthy populations and are the most frequently used tools for assessing intelligence and memory in healthy individuals. The length of the original scales may be fatiguing for individuals with schizophrenia, but shortened versions have been found to be almost as effective for assessing intelligence and memory as the full versions. Velthorst and colleagues[19] shortened the WAIS by creating a version that included only select items from 3 subtests. This version can be administered in 15 minutes. In a study of individuals with schizophrenia, they found their shortened version to provide a reliable estimate of intelligence as measured by the full WAIS and to effectively differentiate between individuals with schizophrenia and healthy controls.[19]

Repeatable Battery for the Assessment of Neuropsychological Status. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was initially developed to provide a sensitive, yet brief, instrument for the early detection of dementia.[20] The battery can be completed in under 30 minutes and assesses impairment in 5 cognitive domains commonly affected by dementing illnesses. Randolph and colleagues[20] found the RBANS to be sensitive enough to detect and differentiate different types of dementia even in patients that were only mildly impaired. Although this instrument was designed to be used in patients with dementia, the 5 cognitive domains assessed are also often affected in patients with schizophrenia.[21] Wilk and colleagues[21] used the RBANS to assess cognition in 181 patients with schizophrenia and schizoaffective disorder. They found that the RBANS was reliable and sensitive enough to differentiate between patients and healthy controls and was well suited for repeated administration and ongoing assessment.

MATRICS Consensus Cognitive Battery. The MATRICS Consensus Cognitive Battery (MCCB) initiative was begun by the NIMH to assist in the development of new drugs for schizophrenia that would improve cognition.[22] Thus, unlike the Wechsler scales or the RBANS, the MCCB was designed specifically for populations with schizophrenia. The MCCB can be administered in 1 to 1.5 hours and consists of 10 tests assessing 7 cognitive domains.[23] Using the MCCB, Kern and colleagues[23] found that individuals with schizophrenia were considerably impaired in all 7 cognitive domains when compared with healthy controls. The greatest impairments were found in the domains of processing speed and working memory. Although the MCCB was developed to measure cognition in trials of pharmacologic agents, it can also be used to assess cognition in a clinical setting and the outcomes of cognitive remediation.[24]

Brief Assessment of Cognition in Schizophrenia. Keefe and colleagues[25] created the Brief Assessment of Cognition in Schizophrenia (BACS) to provide an assessment instrument that was as brief as the RBANS but covered more cognitive domains, with particular focus on the domains most related to functional outcomes. The BACS was designed for both academic and clinical use and can be administered in 30 minutes. Keefe et al[25] determined the BACS to be as sensitive and reliable an assessment of cognitive functioning as lengthier batteries commonly used to evaluate cognition. In a later study, Keefe and colleagues[26] found that BACS scores were significantly correlated with measures of functional capacity ($P < .001$), making this instrument particularly useful for evaluating facets of cognition that are related to real-world functioning.

Brief Cognitive Assessment. Velligan and colleagues[27] created the Brief Cognitive Assessment (BCA) in an attempt to provide clinicians with a tool that would make cognitive testing more feasible in clinical practice. Their goal was to develop an assessment that was brief and easy to administer without sacrificing validity or reliability. The BCA is intended to be used repeatedly to track changes in cognitive function over time so that clinicians can detect changes in symptomatology and determine the efficacy of treatments. Taking only 15 minutes to administer, the BCA is extremely time-efficient. The investigators determined that although the results of the BCA were not as thorough as those provided by longer assessments, the BCA was able to provide valid and reliable assessments of general cognitive functioning and was an easy and practical tool to use in treatment settings.

Schizophrenia Cognition Rating Scale. The Schizophrenia Cognition Rating Scale (SCoRS) was developed by Keefe and colleagues[28] to enable clinicians to reliably assess improvement in neurocognitive deficits as observed by patients and their families or caregivers. The SCoRS is an interview-based assessment consisting of 18 items related to cognitive deficits and their effects on functioning. The full assessment requires interviews with the patient and with an informant, each lasting about 12 minutes. The interviewer then derives a global score that incorporates his or her own observations of the patient. After administering the scale to 60 patients with schizophrenia, Keefe and colleagues[28] found that SCoRS ratings were strongly correlated with composite measures of cognitive performance and real-world functioning.

Test for Functional Outcomes

The strong tie between cognition and functional outcomes lends support for completing specific functional testing to better understand patient outcomes. This was recognized by the NIMH-MATRICS Neurocognition Committee, and several measures were considered as possible coprimary measures.[29] Although the committee did not recommend any particular measure, the University of California San Diego Performance-Based Skills Assessment was noted to have the advantage of strong correlation to cognitive performance.[29]

University of California San Diego Performance-Based Skills Assessment. The University of California San Diego Performance-Based Skills Assessment (UPSA) evolved from the idea that clinicians and investigators needed a way to measure functional outcomes related to an individual's actual ability to function independently in daily life.[30] The UPSA measures skills in the areas of household chores, finance, transportation, communication, and the planning of recreational activities. A trained interviewer presents the patient with several role-playing scenarios commonly encountered by community-dwelling individuals, such as using a recipe to make a grocery list and go shopping, making a telephone call, or writing a check to pay a bill. Using the UPSA, Patterson and colleagues[30] found that individuals with schizophrenia displayed significantly greater functional impairment in each area compared with healthy controls. The UPSA scores were strongly correlated with the severity of negative symptoms and of cognitive impairment but not with that of positive symptoms. Recently, versions of the UPSA have been developed for computer and tablet administration,[31,32] which will make this assessment easier to use clinically.

CONCLUSION

The renewed attention on cognitive impairment in schizophrenia is a promising development in our understanding of and ability to successfully treat schizophrenia. We now understand the important correlation between cognitive impairment and functional outcomes, and an array of tools is available to briefly and effectively assess cognition in patients at the outset and throughout treatment. In clinical settings, these cognitive measurements can guide clinicians in selecting and modifying pharmacologic and behavioral treatments. In academic settings, cognitive assessment tools can help researchers develop treatments that are more effective than current antipsychotic agents for improving cognition. These developments are enabling clinicians to provide better care to patients with schizophrenia so that they can achieve optimal functional outcomes and experience an improved quality of life.

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REFERENCES

1. McGlashan TH. *Schizophr Bull*. 2011;37(6):1101–1103.
2. Green MF, Harvey PD. *Schizophr Res Cogn*. 2014;1(1):e1–e9.
3. Insel TR. *Nature*. 2010;468(7321):187–193.
4. Correll CU. *J Clin Psychiatry*. 2013;74(2):e04.
5. Dunlop J, Brandon NJ. *J Psychopharmacol*. 2015;29(2):230–238.
6. Weinberger DR, et al. *Arch Gen Psychiatry*. 1986;43(2):114–124.
7. Kahn RS, Keefe RS. *JAMA Psychiatry*. 2013;70(10):1107–1112.
8. Green MF. *Am J Psychiatry*. 1996;153(3):321–330.
9. Fusar-Poli P, et al. *Arch Gen Psychiatry*. 2012;69(6):562–571.
10. Wozniak JR, et al. *Early Interv Psychiatry*. 2008;2(3):169–177.
11. Tamminga CA, et al. *Schizophr Bull*. 2014;40(suppl 2):S131–S137.
12. Nuechterlein KH, et al. *Schizophr Res*. 2004;72(1):29–39.
13. Keefe RS, Harvey PD. Cognitive Impairment in Schizophrenia. In: Geyer MA, Gross G, eds. *Novel Antischizophrenia Treatments*. New York, NY:

Springer; 2012:11–37.
14. Martin DC. The mental status examination. In: Walker HK, Hall WD, Hurst JW, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. Boston, MA: Butterworths; 1990.
15. Thoma P, et al. *Psychiatry Res*. 2009;170(2-3):132–139.
16. Kraus MS, Keefe RS. *Br J Psychiatry suppl*. 2007;50(50):s46–s51.
17. Wechsler D. *Wechsler Adult Intelligence Scale*. 4th ed. San Antonio, TX: Pearson; 2008.
18. Wechsler D. *Wechsler Memory Scales*. 4th ed. San Antonio, TX: Pearson; 2009.
19. Velthorst E, et al. *Cogn Neuropsychiatry*. 2013;18(6):574–593.
20. Randolph C, et al. *J Clin Exp Neuropsychol*. 1998;20(3):310–319.
21. Wilk CM, et al. *Am J Psychiatry*. 2002;159(5):838–844.
22. Marder SR, Fenton W. *Schizophr Res*. 2004;72(1):5–9.
23. Kern RS, et al. *Schizophr Res*. 2011;126(1–3):124–131.
24. Keefe RS, et al. *J Clin Psychiatry*. 2012;73(7):1016–1022.
25. Keefe RS, et al. *Schizophr Res*. 2004;68(2–3):283–297.
26. Keefe RSE, et al. *J Clin Exp Neuropsychol*. 2006;28(2):260–269.
27. Velligan DI, et al. *Schizophr Res*. 2004;71(2-3):273–283.
28. Keefe RSE, et al. *Am J Psychiatry*. 2006;163(3):426–432.
29. Green MF, et al. *Am J Psychiatry*. 2008;165(2):221–228.
30. Patterson TL, et al. *Schizophr Bull*. 2001;27(2):235–245.
31. Moore RC, et al. *Schizophr Res*. 2013;144(1–3):87–92.
32. Moore RC, et al. *Schizophr Res*. 2015;164(1-3):187–192.