

Beyond Psychosis: Emerging Priorities in Schizophrenia Targeting **Cognitive Impairment** to Improve Functional Outcomes

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Cognitive Impairment: Rediscovering a Core Element of Schizophrenia

Henry A. Nasrallah, M.D.; Peter J. Weiden, M.D.

Introduction

The breadth of presenting problems in individuals with schizophrenia represents a true clinical challenge. In day-to-day practice, many dramatic symptoms, such as positive symptoms or hostility, may be associated with a current or potential crisis and thus command the clinician's attention. Such symptoms may distract from other debilitating features of the disorder that deserve prominent consideration, such as cognitive impairment, which is both pervasive and disabling.

In fact, although functional disability is easily recognized in schizophrenia, the role that cognition plays in this disability may be underappreciated, despite common examples: the recent-onset patient who can't return to college even after her psychotic symptoms are controlled because she finds herself unable to follow lectures, study, and learn textbook material, or develop an organized approach to homework. The more chronically ill but stable patient who can't navigate changing bus routes to make it to clinic on time or struggles to plan and remember his grocery shopping needs. The patient who cannot recall the details of TV shows she spends all day watching, or the patient who is so unable to handle social situations with family or others that he avoids them altogether. Such issues present significant challenges for patients, caregivers, and the clinicians attempting to support them and have shaped the negative perception of this disabling brain disorder.

FACULTY



Henry A. Nasrallah, M.D.

Sidney W. Souers Professor
& Chairman
Department of Neurology
and Psychiatry
St. Louis University School
of Medicine
Chief of Psychiatry and Neurology
University Hospital -
St. Louis University
St. Louis, MO



Peter J. Weiden, M.D.

Professor
Department of Psychiatry
University of Illinois at Chicago
Chicago, IL

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Cognitive impairment is a core component of schizophrenia

Cognition is a multifaceted and complex set of mental processes that enable one to “know” the world and the surrounding environment and interact accordingly.¹ In the context of health and illness, cognition can be operationally defined as the processes an individual uses to organize information, utilize that information to guide behavior,² and match responses to changing environmental demands.³ A wide range of cognitive abilities are impaired in schizophrenia, including memory, attention, speed of processing, verbal learning, executive functioning,^{3,4} and social cognition, ie, the mental operations underlying social interactions (such as the ability to correctly perceive and interpret the reactions of others).³ While some patients may be aware of some of their cognitive deficits,^{5,6} insight into these deficits is often incomplete and, for at least half of patients, entirely absent.⁷

Several decades of increasingly focused investigations into the cognitive deficits of schizophrenia have cemented their status as a core component of schizophrenia (along with positive and negative symptoms). In many ways, this is a return to some of the earliest conceptualizations of the disorder. Kraepelin’s original work—and even his original name for the disorder, *dementia praecox*—emphasized cognitive deterioration^{8,9} during youth. Bleuler went so far as to suggest hallucinations and delusions were manifestations of the disorder secondary to core cognitive deficits.^{8,10} However, in the years after Kraepelin and Bleuler, the importance of cognitive impairment in diagnostic and research paradigms grew to be overshadowed by more dramatically visible and sometimes disruptive or frightening positive symptoms.^{9,10}

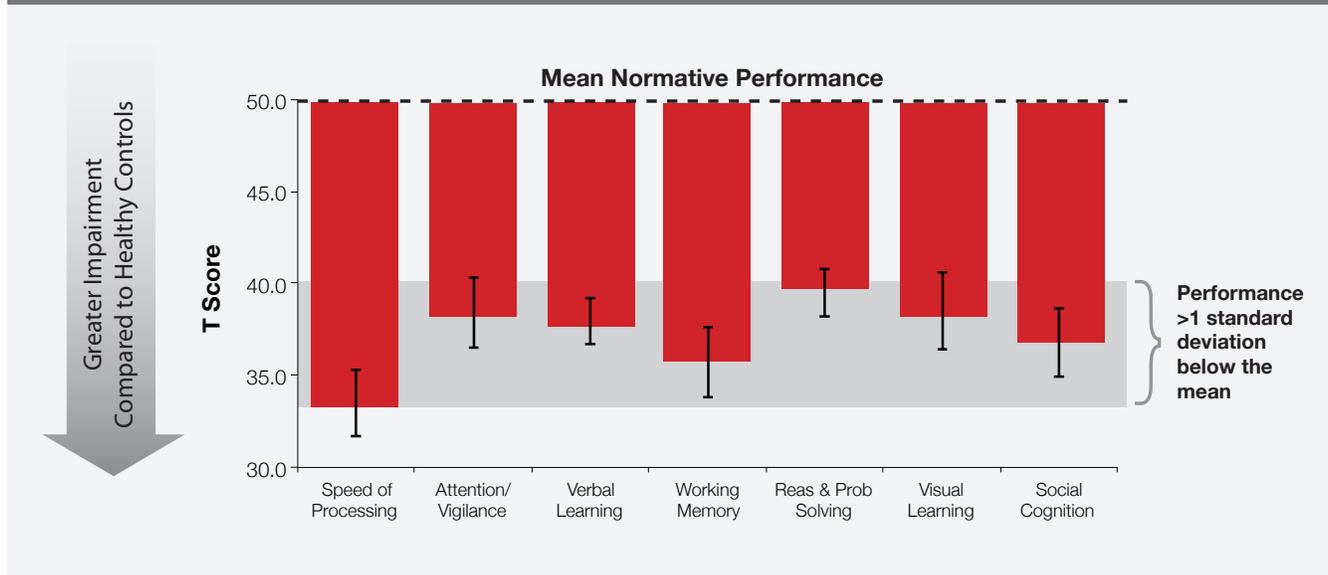
The last 30 years of research has led to the re-emergence of cognitive impairment as a core feature of

schizophrenia, as our cognitive probes have become more reliable and informative, and neuroimaging has demonstrated that impaired cognition in the disorder has clear correlates with neurobiological activity such as reduced frontal lobe volume or blood flow.^{9,10} The centrality of cognitive impairment in schizophrenia is further underscored by the pattern of deficits seen in patients and the association of these deficits with other clinical and developmental aspects of the disorder. In the sections that follow, we briefly review the nature, course, and correlates of cognitive impairment in schizophrenia.

Cognitive impairment is severe and extremely common

Cognitive testing is typically done across many important domains (such as memory, attention, and speed of processing). When most or all domains of cognition are compromised, the pattern of cognitive impairment is considered “generalized.” The severity of cognitive impairment is typically indexed by comparing the magnitude of the impaired test performance to typical performance on the same test by an age- and education-adjusted healthy population. In this context we know that cognitive impairment in schizophrenia is both severe and generalized, manifested by a widespread reduction in cognitive abilities across multiple domains of performance¹¹ (**Figure**). Patients with schizophrenia typically display cognitive performance that is greater than 1 standard deviation below that seen in the general population^{11,12}—putting these patients in the lowest 15% of the age-matched general population in terms of global intellectual ability. On cognitive testing, 98% of patients individually score below their anticipated cognitive performance as statistically derived from regression analyses using maternal education levels¹³ and other variables.

Figure. Cognitive Impairment Profile of Schizophrenia Individuals on a Consensus Cognitive Battery¹²



Age- and gender-corrected T-scores in 176 clinically stable individuals with schizophrenia and 300 healthy community residents. Performance scores converted into standardized T scores based upon mean performance by community residents. T scores provide information about score relative to average score; for T scores, the standardized mean is 50, and each difference of 10 points reflects a deviation of 1 standard deviation from the mean. For example, a T score of 30 is 2 standard deviations below the mean.

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Evidence that this impairment is nearly universal can be found in comparisons of patients against carefully matched control groups¹⁴ as well as comparisons against a twin discordant for the disease.¹⁵ Thus, while 70% to 80% of patients may qualify for a categorization of “cognitively impaired” based upon neurocognitive test scores that are a certain magnitude below normal performance (eg, 1 standard deviation below the mean in 1 or more areas of cognitive function),¹⁶ nearly all patients with schizophrenia exhibit cognitive impairment relative to what would be expected from them in the absence of disease.

The presence of cognitive deficits before the onset of illness

Cognitive impairment in schizophrenia differs from that found in individuals with developmental disability, in which the cognitive limitations are present at birth. For patients who develop schizophrenia, it seems that cognitive dysfunction starts somewhere between childhood and the eventual onset of psychotic symptoms. Cognitive problems almost always come before the onset of psychotic symptoms and are present well before a formal diagnosis of schizophrenia is possible. A recent longitudinal follow-up of a cohort of more than 1000 individuals born in New Zealand in 1972 and 1973¹⁷ confirms meta-analytic findings that those who develop schizophrenia have an intelligence quotient (IQ) prior to illness onset that is 8 to 9 points lower than that of their peers^{17,18} putting them at the lower end of average and slightly more than half of a standard deviation below normal. Other studies have shown academic performance that was poorer than that of peers as early as first grade¹⁹ with the difference becoming more pronounced as those who were to develop schizophrenia advanced into adolescence and middle and high school.^{19,20} Thus, subtle cognitive deficits are evident before the onset of psychotic symptoms for individuals who have yet to convert to schizophrenia; these deficits may serve as early biomarkers of vulnerability to schizophrenia.

The course of cognitive impairment after disease onset through chronic stages

Our understanding of the course of cognitive impairment from onset through chronic stages of illness in schizophrenia is still evolving. Still, available evidence suggests that the initial onset of psychosis is associated with a further decline in cognitive abilities from premorbid levels. For example, additional data from the New Zealand longitudinal cohort suggests,

on average, an additional 6-point decrement in IQ when IQ after illness onset is compared with that in the premorbid period.¹⁷ Following this initial decline at illness onset, cognitive impairment appears relatively stable: Cross-sectionally, neurocognitive test score deficits among first-episode populations are comparable to those of patients^{21,22} with more chronic illness, suggesting no further significant deterioration among nonelderly patients and supporting longitudinal analyses that demonstrate cognitive impairment is stable through the nonelderly course of illness²³ (ie, in those <65 years of age).^{24,25} Thus, because cognitive deterioration in schizophrenia is generally not progressive, cognitive impairment in schizophrenia should not be confused with the progressive cognitive decline that typifies Alzheimer’s disease.

Cognitive impairment is evident in first-degree relatives of patients with schizophrenia

Cognitive impairment can also be detected among some unaffected first-degree relatives of patients with schizophrenia who, as a group, show greater cognitive impairment than the

general population: There are reliable differences of small to medium effect size when nonpsychotic siblings, parents, and offspring of patients are compared to healthy, nonrelated controls.^{26,27} These differences in cognitive performance further support the notion that cognitive deficits index some level of vulnerability to schizophrenia, and that cognitive impairment may serve as an “endophenotype” (see sidebar) in the disorder, or an intermediate phenotype

Endophenotype

An **endophenotype**, or intermediate phenotype, is a quantifiable biological variation or deficit. These stable trait markers, not visible to the naked eye, but assessed by experimental, laboratory-based methods, aggregate in families and may be found in some unaffected relatives of individuals with the disorder, at a higher prevalence than seen in the general population. They serve as indicators of presumed inherited vulnerability to a disease and are thus “intermediate” between a clinical entity and the associated disease vulnerability genes. The hope is that endophenotypes may enable a more straightforward search for the etiology and pathology of a complex heterogeneous disorder like schizophrenia.²⁶

that, by virtue of being “less complex” than the full clinical syndrome, may be easier to investigate.^{26,27} In addition to reinforcing the centrality of cognitive impairment in the disorder, such work suggests that cognitive impairment in nonpsychotic relatives of patients may represent a risk factor for schizophrenia and may help uncover “carrier genes” or “susceptibility genes” responsible for some portion of the risk of developing schizophrenia.^{26,27}

Cognitive impairment is not secondary to psychosis or medication side effects

A large number of first- and second-generation antipsychotics have been examined to determine their efficacy for cognitive impairments in schizophrenia, and there is little evidence these

agents have significant cognitive-enhancing effects.²⁸ Some patients receiving high doses of antipsychotics may actually experience secondary cognitive blunting from excessive dopamine blockade,²⁹ as is often seen in Parkinson's disease.³⁰ In addition, some drugs commonly used concomitantly with antipsychotics, such as anticholinergic agents^{31,32} or benzodiazepines,^{33,34} may impair cognition. These secondary deficits aside, the primary and enduring cognitive impairment seen in patients with schizophrenia is found before any drug treatment is administered: Not only does subtle cognitive impairment date back to prior to the onset of illness in patients and cluster in unaffected family members; treatment-naïve patients also demonstrate serious cognitive impairment comparable to that of medicated patients.³⁵ It also appears that cognitive deficits are not secondary to positive symptoms of the disorder, as a treatment-related change in these symptoms is unrelated to cognitive change,³⁶ and cross-sectional correlations between positive symptom scores and cognitive deficits are negligible in both first-episode patients^{37,38} and those with more chronic disease.³⁹ Thus, a growing body of evidence suggests that cognitive impairment is an independent, core neurobiological feature of schizophrenia.

Cognitive impairment is associated with poor functioning and outcomes

Cognitive impairment in schizophrenia has been reliably and robustly associated with multiple limitations in functional outcomes, including problem-solving skills,⁴⁰ skills acquisition,⁴¹ work performance,⁴² community functioning,⁴¹ and recovery.⁴³ Seminal reviews and meta-analyses by Green and colleagues in the late 1990s consolidated a growing literature that demonstrated the strong association between cognitive test scores and functional outcomes, including “medium”-strong associations between individual test scores and functioning, and “large” effect sizes for the association of outcomes with composite scores of multiple cognitive domains.⁴¹ Somewhat surprisingly, in contrast to neurocognitive abilities, the presence and severity of psychotic symptoms such as delusions and hallucinations were unrelated to functional outcomes.⁴¹ These findings have been replicated numerous times in the last few decades across patients in all stages of illness, including recent-onset patients,⁴³ those with more chronic illness,⁴⁴ and even clinically high-risk prodromal subjects, in whom mild cognitive impairment predicted social and vocational functioning but attenuated positive symptoms did not.⁴⁵

Pharmacology to improve cognitive impairment in schizophrenia: an urgent unmet need

Given the severity of cognitive impairment seen in schizophrenia and the clear association between these cognitive deficits and poor functional outcomes, cognitive impairment in schizophrenia has been identified as a major health care priority, as has the development of pharmacologic

agents to alleviate such deficits.³³ The National Institute of Mental Health sponsored an initiative known as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project.^{33,46,47} The goals of this initiative were to encourage and support the development of drugs targeting cognitive impairment in schizophrenia.^{33,46} In collaboration with the US Food and Drug Administration (FDA), academia, and industry, this initiative developed a brief, reliable, and valid consensus cognitive battery (the MATRICS Consensus Cognitive Battery or MCCB)^{34,48,49} that the FDA has accepted as a primary end point for clinical trials in cognition.⁴⁷ The FDA has agreed that demonstrating significant improvement on the MCCB, along with significant improvement on a co-primary, functionally meaningful end point, may serve as scientific evidence to support the approval of a drug for cognitive enhancement in schizophrenia.⁵⁰

The MATRICS initiative also included the identification of several key molecular targets for cognitive enhancement in schizophrenia, including cholinergic (such as the $\alpha 7$ receptor), dopaminergic, and glutamatergic approaches.⁴⁷ Fortunately, there is currently a concerted effort in research and development to explore these mechanisms, utilizing the tools and guidance provided by the MATRICS initiative.⁴⁷ Targeting these novel mechanisms may hold the potential to improve outcomes for patients by improving core cognitive deficits that currently limit functional abilities.

Conclusions

Cognitive impairment is a core domain of dysfunction in schizophrenia, characterized by stable, broad, and enduring cognitive deficits that limit functional outcomes, rehabilitation, and recovery. Cognitive impairments are evident prior to illness onset in those who eventually develop schizophrenia, whereas mild deficits can be detected in nonpsychotic first-degree relatives, suggesting such cognitive compromise may be associated with fundamental etiologic factors such as susceptibility genes. In addition, these impairments, which worsen with the onset of psychosis but generally remain stable among patients younger than 65 years, are not secondary to either antipsychotic medications or positive symptoms, meaning they represent an independent, neurobiological target for treatment. Following the guidance developed by the MATRICS initiative, a number of development programs are exploring the abilities of drugs that target novel molecular mechanisms to improve cognition in the disorder.

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