

**White Paper 1** | Cognitive Impairment in Schizophrenia: Understanding Prevalence, Magnitude, and Scope**White Paper 2** | Cognitive Impairment and Poor Functional Outcomes in Schizophrenia**White Paper 3** | Cognitive Impairment in Schizophrenia: Understanding the Neurobiology and Its Implications for Future Management

# Cognitive Impairment in Schizophrenia: Understanding Prevalence, Magnitude, and Scope

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*“Cognition is what helps us negotiate, survive, and flourish.”*

— Peter J. Weiden, M.D., University of Illinois at Chicago

Despite significant advances in the medical treatment of schizophrenia over the past 50 years and the widespread use of antipsychotics, the disease is the third leading cause of disability worldwide among adults aged 15 to 44.<sup>1-3</sup> In fact, as few as 1 in 7 patients with schizophrenia achieve enduring and concurrent symptomatic and social/vocational improvements, and only an estimated 1% to 2% of patients qualify as “recovered” each year.<sup>1</sup>

A plethora of systematic research from the past 10 years highlights cognitive impairment as one of the most important barriers to recovery in patients with schizophrenia.<sup>4,5</sup> How do we define cognition, though?

“Cognition is how the brain adapts to its environment in a way that helps individuals fulfill their needs and achieve their desired goals,” Dr Weiden commented. It refers to a range of high-level brain functions, including the ability to learn and remember information; organize, plan, and problem solve; focus, maintain, and shift attention as necessary; understand and use language; accurately perceive the environment; engage in social interactions; and process new information (**Table**).<sup>4,6,7</sup>

Indeed, cognition is critically important for socio-occupational functioning in the world.<sup>4,8</sup> Yet, “it is rare to encounter a patient with schizophrenia who does not have clinically meaningful cognitive impairment in addition to positive and negative symptoms,” noted Sheldon Preskorn, M.D., of World-Wide Psychopharmacology Consultants in Wichita, Kansas, and the Laureate Institute for Brain Research in Tulsa, Oklahoma.

In fact, an estimated 98% of patients with schizophrenia have cognitive impairment, as demonstrated when their neurocognitive scores are compared with those predicted by maternal education levels.<sup>9</sup> Further, it has been well established that cognitive deficits in schizophrenia are predictive of impaired functioning.<sup>8,10-13</sup>

“It’s clear from studies that cognitive impairment among patients with schizophrenia is not something that’s confined to a subgroup. It’s something that’s relevant to virtually every individual with the disease,” said Stephen R. Marder, M.D., of the University of California, Los Angeles (UCLA), and the Desert Pacific Mental Illness Research, Education and Clinical Center of the VA Greater Los Angeles Healthcare System.

98% of patients with schizophrenia have cognitive impairment.<sup>9</sup>

## Cognitive Impairment as a Core Component of Schizophrenia

*“Explaining to patients and their families that schizophrenia affects cognitive functioning helps to decrease the stigma and blame that often accompanies the diagnosis.”*

— Alex J. Kopelowicz, M.D., UCLA;  
Olive View-UCLA Medical Center, Sylmar, California

Indeed, schizophrenia has been associated with profound and persistent cognitive impairment since the disorder was first identified by Emil Kraepelin in 1896 and Eugen Bleuler in 1908.<sup>14,15</sup>

“Kraepelin’s chosen nomenclature of *dementia praecox* literally translates into “cognitive decline with youthful onset,” Dr Preskorn noted. Further, Kraepelin’s definition stressed 2 “fundamental” disorders or problems in the disease state: a general decay of mental efficiency and a failure of executive functioning.<sup>14,16,17</sup>

Bleuler took a somewhat different approach, labeling the illness with its modern-day nomenclature of *schizophrenia*; however, he also identified cognitive impairment as a core component of the disease, noting that what we now recognize as *positive symptoms* were secondary to underlying cognitive dysfunction.<sup>14</sup>

Indeed, Dr Preskorn commented, “cognitive impairment is quite evident in most people with schizophrenia.”

**Table.** Real-world Examples of Cognitive Domains<sup>18,19</sup>

Cognitive Domain	Definition	Real-world Example
<b>Attention/vigilance</b>	Responding correctly to targets while not responding to distractors during a series of rapidly presented stimuli	Being able to read a book or pay attention to a movie
<b>Working memory</b>	Maintaining and manipulating information in mind for brief periods of time (approximately 5-20 seconds)	Remembering a phone number just given to you
<b>Verbal learning and memory</b>	Remembering verbal information over longer periods of time (minutes to years)	Remembering the items someone told you to purchase at the supermarket
<b>Visual learning and memory</b>	Remembering visual information over longer periods of time (minutes to years)	Remembering where you put something in a closet
<b>Reasoning and problem solving</b>	The ability to apply strategies effectively	Arriving on time for work even though your bus schedule has changed
<b>Speed of processing</b>	Responding quickly and accurately when executing relatively simple tasks	Using a touch-screen computer to serve customers at a fast-food restaurant
<b>Social cognition</b>	Effectively processing social information, such as facial expressions and emotions and the meaning of social interactions	Knowing by looking at someone whether they are angry at you or not; being able to take someone else's perspective in a conversation

Despite these early insights, however, cognitive dysfunction was often overshadowed by the easily recognized positive symptoms.<sup>14,16</sup> “Today, however,” said Vivek Singh, M.D., of the University of Texas Health Science Center at San Antonio, “there has been a renewed focus on cognitive dysfunction as a core component of the illness—one that impacts both functionality and illness outcome.” Several factors have contributed to this reemergence, including advances in neuropsychological testing

and neuroimaging, a greater understanding of the true scope and magnitude of cognitive impairment in the disease, and the profound and pervasive effects of this dysfunction on function and recovery.<sup>14,16</sup>

### **COGNITIVE IMPAIRMENT OCCURS EARLY, REMAINS STABLE THROUGHOUT DISEASE COURSE**

*“I think many clinicians believe that cognitive deterioration continues throughout the course of the illness. They may not appreciate how bad it is at the onset.”*

— **John M. Kane, M.D., Hofstra North Shore-LIJ School of Medicine, Hempstead, New York; The Zucker Hillside Hospital, Glen Oaks, New York**

Signs of cognitive impairment may appear years before the first acute psychotic episode.<sup>20,21</sup> “For those of us who see children and adolescents, cognitive changes and educational challenges are often the earliest signs of the evolution of schizophrenia,” noted Gregory Mattingly, M.D., of the Washington University School of Medicine in St. Louis and the Midwest Research Group in St. Louis, Missouri. These signs include evidence of poor academic performance as early as first grade, which becomes more pronounced during middle and high school.<sup>22</sup> In adolescence, premorbid IQ levels in those who go on to develop schizophrenia are roughly 8 points below normal.<sup>20</sup>

“Cognitive impairment can be seen prior to the prodromal period, when patients begin to socially withdraw,” said Noel C. Gardner, M.D., of the University of Utah School of Medicine in Salt Lake City and the Polizzi Clinic in Holladay, Utah. “Before that, they may have been very bright, engaged, good students.”

Although less is known about the longitudinal course of cognition during the illness, cognitive impairment appears relatively stable after the initial decline, with neurocognitive test score deficits among first-episode populations already comparable to those in patients with chronic schizophrenia.<sup>23,24</sup>

“At the time of onset, it is not possible to know that the problem will eventually evolve into schizophrenia,” commented Dr Weiden. “Therefore, cognitive dysfunction is not part of the diagnostic criteria; however, as noted by my fellow panelists, it is almost always already there at the onset of psychotic symptoms.”

**COGNITIVE IMPAIRMENT IS SIGNIFICANT, CAN BE SEEN ACROSS MULTIPLE DOMAINS OF THE ILLNESS**

As a group, patients with schizophrenia are impaired on nearly all tasks assessing different domains of cognitive ability. This impairment is often quite severe, typically 1

This impairment is often quite severe, typically 1 to 2 standard deviations below normal.<sup>5</sup>

to 2 standard deviations below normal (Figure).<sup>5</sup> The seminal 1998 meta-analysis from Heinrichs and Zakzanis, which calculated effect sizes from more than 200 studies comparing the neurocognitive performance of patients with schizophrenia with the neurocognitive

performance of healthy controls, found moderate to large impairment in patients relative to controls for all test variables, including verbal memory, IQ, sustained attention, word fluency, and other parameters.<sup>25</sup>

Indeed, the panelists all noted that they could clearly recognize multiple domains of impairment in their patients, both with recent-onset and with chronic schizophrenia.

**COGNITIVE IMPAIRMENT IS RELATED TO POOR FUNCTIONAL OUTCOMES**

For many patients, such as the first composite patient discussed in this article, cognitive impairment leads to poor functional outcomes.<sup>10</sup>

“Our understanding of the robust relationship between cognitive impairment and functional outcomes owes much to the work of Green and his colleagues, who published a pair of pivotal reviews and analyses on this topic in 1996 and 2000,” noted Anil K. Malhotra, M.D., of the Hofstra North Shore-LIJ School of Medicine in Hempstead, New York, and The Zucker Hillside Hospital in Glen Oaks, New York.

The analyses by Green and colleagues demonstrated consistent relationships between measures of cognitive ability, such as verbal memory, attention,

and executive functioning, with outcomes such as community functioning, skill acquisition, and problem solving.<sup>10,26</sup> Composite neurocognitive variables that

**Patient Profile: Ethan\***

AGE: 42

DIAGNOSED WITH SCHIZOPHRENIA: 16 years ago

STATUS OF EDUCATION/EMPLOYMENT: Never completed college; currently unemployed

Ethan currently resides in assisted living. He experienced an insidious onset of the disease at age 26 after years of faltering relationships, social withdrawal, and increasingly idiosyncratic behavior.

He was treated with a second-generation oral antipsychotic until 5 years ago, when he was hospitalized with active psychotic symptoms and transitioned to a long-acting second-generation antipsychotic to support adherence.

Ethan stopped working a year after his diagnosis. Four years ago, he began warehouse work through a supported employment program. That lasted just 3 weeks. He couldn't remember what some people told him and had trouble paying attention to other coworkers, as well as difficulty reading and interacting with his boss. He also had issues with activities of daily living and frequently missed work or arrived quite late.

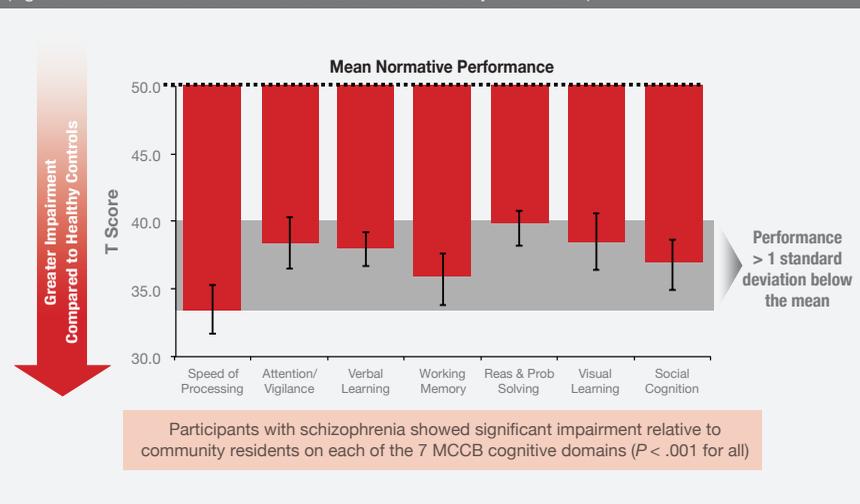
He currently watches television all day, although he never changes the channel. Although he can name some of the programs he watches, he can't really describe what happens on them. Ethan attends a day program 3 days a week but has no obvious friends there or in the assisted-living setting.

Ethan remains very dependent on his mother, who takes him shopping for his clothes and most of his groceries—experiences that overwhelm him.

The clinicians who care for Ethan are concerned that he appears to be “stuck.” He is stable but not making any moves toward recovery.

\*Composite patient.

**Figure.** Magnitude and Severity of Cognitive Impairment in Patients With Schizophrenia (Age- and Gender-Corrected T Scores, as Measured by the MCCB)<sup>5</sup>



MCCB, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery; Reas & Prob Solving, reasoning and problem solving.

indexed performance across multiple domains of intellectual performance were even stronger predictors of functional outcomes.<sup>10</sup> Little correlation was found between functional outcomes and positive or disorganized clinical symptoms.<sup>26</sup>

## The Importance of Recognizing Cognitive Impairment in Clinical Practice

*“Early recognition of cognitive impairment is relevant because if patients withdraw, that perpetuates deterioration. So it’s important to intervene early, pay attention to the impairment, and provide any interventions that may help.”*

— **Vladimir Maletic, M.D., M.S., University of South Carolina School of Medicine, Columbia**

It is important to recognize cognitive impairment because improved function is what patients want, the panelists said. “They want to go back to work,” said Chris Reist, M.D., of the University of California, Irvine, and the Long Beach VA Healthcare System. “They often want to attain independence. We need more tools to get them there.”

There are options available that may help improve cognition and functioning, including cognitive remediation therapy and environmental supports,<sup>27-30</sup> both of which are discussed in more detail in the second paper in this series.

“Once patients’ positive symptoms are stabilized,” said Dr Marder, “those who have better cognitive functioning tend to have fuller recoveries and better social and vocational functioning.”

A greater awareness of a patient’s cognitive impairment is important in evaluating the risk-benefit profile of any concomitant medication that may impact cognition, including anticholinergics, benzodiazepines, antihypertensives, and antihistamines.<sup>31,32</sup> “Being aware of the cognitive dysfunction reminds me to choose the medications in such a way that I’m not adding to it,” said Roueen Rafeyan, M.D., of Northwestern University Feinberg School of Medicine and St. Anthony Hospital in Chicago, Illinois. Further, added Gerald Maguire, M.D., D.F.A.P.A., of the University of California, Riverside, School of Medicine, given that reimbursement is increasingly tied to outcomes, “there are lower costs

### Patient Profile: Samuel\*

AGE: 22

DIAGNOSED WITH SCHIZOPHRENIA: 2 years ago

STATUS OF EDUCATION/EMPLOYMENT: Withdrew from college; currently unemployed

Samuel previously attended a state university in his hometown, where he planned to major in chemistry. Premorbidly, he had trouble focusing and understanding test questions. In fact, this became so difficult for him that he thought he might have attention-deficit/hyperactivity disorder (ADHD). He began to withdraw from his friends and to experience transient periods of depression. He also began to develop some unusual thoughts, such as the belief that he could transmit ideas into other people’s minds. All of this distressed him.

Samuel was hospitalized early in his junior year after the residence advisors in his dorm observed an episode of frank psychosis and bizarre behavior. He was treated with a second-generation antipsychotic and experienced a significant reduction in positive symptoms.

Samuel moved home but returned to school. However, he struggled. He still couldn’t pay attention and follow lectures. He also found it difficult to plan an approach to his homework and complete his assignments. He dropped a few classes but continued to have problems. He withdrew from school after 6 months.

Samuel is currently living at home, where, his parents report, he “hides” in his room, refusing to participate in family functions. Samuel says that he “can’t handle” family functions, but he can’t articulate why. He doesn’t work or attend school, although he participates in group and family therapy. Otherwise, his time is completely unstructured. Right now, Samuel notes, “things are just not working.”

\*Composite patient.

to the system if the patient is functional”; Dr Maguire observed that this is particularly important in capitated models. As noted by Dr Reist, “Those outcomes are going to be those functional measures of things that we don’t typically think about.”

“It’s not enough to get people into traditional treatment,” said Ralph Aquila, M.D., of the Icahn School of Medicine at Mount Sinai and St. Luke’s-Roosevelt Hospital Center in New York, New York. “You’ve got to keep these patients engaged.”

## Patients’ Perceptions of Cognitive Impairment

*“Why wait for the patient to talk about cognition? Why not have the physician or the clinician proactively seek out cognitive deficits?”*

— **Vivek Singh, M.D., The University of Texas Health Science Center at San Antonio**

Although some patients with schizophrenia are aware of and report clear cognitive problems, at least half of those with demonstrable cognitive deficits have no insight into the existence of these problems or mistake them for signs of other mental disorders.<sup>33-35</sup>

College students, like the one featured in this paper, often complain of trouble reading, falling grades, and problems paying attention, said Dr Marder. Often, he and other panelists said, students think they have ADHD.

“Most of my patients say they can’t concentrate,” said Steven J. Siegel, M.D., Ph.D., of the University of Pennsylvania in Philadelphia. “We never really get past that. So when I think of the building blocks of how this comes into play, it really starts with ‘I can’t concentrate,’ and then everything unravels from there. ‘Since I can’t have a job, I have nothing to do. Since I have nothing to do, I have no friends. Since I have no friends, what’s the point?’”

## Identifying Cognitive Impairment

*“You really need to take the long view to be able to focus on cognition, because at any given moment, the positive symptoms are going to be the splashiest things, the things that have the most sense of urgency. Improvements in cognition will not be as splashy, and yet the effects on functioning and lifetime functioning are also important.”*

— Rona J. Hu, M.D., Stanford University School of Medicine; Stanford Hospital and Clinics, California

Given that less than 50% of patients with schizophrenia have insights into their cognitive deficits,<sup>35</sup> how might clinicians go about identifying these issues? Our panelists felt that asking the patient and caregiver a simple list of questions about the patient’s functioning could provide a good place to start (**Box**). “Asking the patient or the caregiver to describe the patient’s daily routine can provide valuable insight into how well the patient is functioning,” noted Dr Rafeyan.

He suggested giving patients a 3-step instruction and asking them later to repeat it. “This can be a quick way of evaluating their deficit or at least recognizing the deficit.”

In addition, the MCCB—or the Measurement and Treatment Research to Improve Cognition in

### Box. Faculty Recommendations for Assessing Impaired Functioning Likely Related to Cognitive Deficits in Patients With Schizophrenia

#### Sample patient questions

1. Do you sometimes find that you can’t remember where you put items you need when you are getting ready for work or school?
2. Do you encounter any difficulties when your morning routine is altered?
3. Do you have any difficulty keeping track of your medications and taking them on time?
4. How easily can you follow your lectures at school? Have you experienced any difficulties keeping track of and completing assignments?
5. Do you have any trouble following instructions at work? Do you have any difficulties understanding what your supervisor means?
6. When you watch television programs, do you have difficulty following the plot?
7. Are you able to stay focused when reading a book?

Note: This is not a validated instrument for assessing cognitive impairment in schizophrenia.

Schizophrenia (MATRICS) Consensus Cognitive Battery—was developed specifically as part of a national initiative convened to support the development of pharmacologic agents aimed at improving cognition in schizophrenia.<sup>36</sup> This unique collaboration between the National Institute of Mental Health, the US Food and Drug Administration,

### Cognitive Impairment and Confounders

Although there may be some additional cognitive impact of excessive dopamine blockade, studies have demonstrated a similar magnitude of cognitive impairment in both treatment-naïve patients and those treated with antipsychotic medication.<sup>37</sup>

Cross-sectional analyses also demonstrate little to no relationship between cognitive performance and positive symptoms, suggesting that these deficits are not the result of psychosis.<sup>38-40</sup>

academia, and the pharmaceutical industry designed the MCCB to include tests in the key domains of cognition in schizophrenia, with excellent psychometric properties and strong relations to functional outcomes.<sup>18,36</sup>

## Moving Beyond “Treatment Nihilism”

*“There is some degree of therapeutic nihilism around cognitive impairment in schizophrenia. Clinicians probably do recognize it more than they’re able to articulate, but they don’t know what to do about it.”*

— **John M. Kane, M.D., Hofstra North Shore-LIJ School of Medicine, Hempstead, New York; The Zucker Hillside Hospital, Glen Oaks, New York**

As the next 2 papers in this series will demonstrate, there are effective psychosocial treatments available for cognitive impairment in schizophrenia.<sup>41</sup> In addition, the MATRICS initiative identified numerous molecular targets for potential pharmacotherapy treatments, several of which are in late-stage development.<sup>42</sup>

The next 2 papers in this series will highlight the impact of cognitive impairment in schizophrenia on functional outcomes, the neurobiology of cognitive impairment in the disease, and molecular mechanisms of interest currently being investigated for cognitive enhancement in the disease.

**For more information, please see [www.CurrentPsychiatry.com/Cognition](http://www.CurrentPsychiatry.com/Cognition).**

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“We can address the nihilism mindset with cognitive remediation therapy right now,” noted Naveed Iqbal, M.D., of Advanced Bio-Behavioral Sciences in Elmsford, New York; Montefiore Medical Center in Bronx, New York; and the Hudson Valley Hospital Center in Cortlandt Manor, New York. “The idea that if you can improve someone’s cognition and function, that you can change the bar ... that shows there is hope.”

“I think part of the mindset has to be that diagnosis of schizophrenia can’t be seen as a dead end with the expectations bar set low,” said Dr Aquila. “We have to be able to say, ‘Okay, my patient has schizophrenia. We can help him. He doesn’t have to end up being in a group home smoking cigarettes and drinking coffee all day.’”

“We can make an impact,” Dr Aquila continued, noting that therapeutic alliances among clinicians, patients, families, and caregivers (also referred to as a *clubhouse model*) help drive medication compliance and assist patients with living, working, and learning by fostering an environment of mutual support.<sup>43,44</sup> “It takes a community to engage persons with cognitive deficits. The clubhouse model has been shown to be effective in helping patients with functional outcomes.”

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CURRENT PSYCHIATRY is pleased to present this educational resource. It did not participate in the development or peer review of its content.