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# CNS SPECTRUMS

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## CME Review Article

### Cognitive Impairment in Schizophrenia: The Great Unmet Need

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- Assess and monitor cognitive impairment in patients with schizophrenia over time
- Incorporate evidence-based treatment strategies for the management of cognitive impairment in schizophrenia
- Describe the underlying neurobiology of cognitive impairment in schizophrenia
- Describe novel mechanisms under investigation for the treatment of cognitive impairment in schizophrenia

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# Cognitive impairment in schizophrenia: the great unmet need

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Cognitive impairment in schizophrenia is present in almost all persons with the disorder and can be a substantial obstacle to efforts in the recovery process. In clinical research, cognition is assessed through neuropsychological testing as well as by different types of structured instruments focusing on function. Although nonpharmacological interventions such as cognitive remediation have been therapeutic, particularly in combination with vocational rehabilitation and supported employment, these modalities are not always easy to access. Pharmacological interventions are in development and have principally focused on the dopamine, glutamate, and acetylcholine neurotransmitter systems, aiming to target the dorsolateral prefrontal cortex and its interactions with other brain regions.

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## Introduction

Innovation and technology have played a significant role in improved outcomes in medical illnesses. From antibiotics to laparoscopic surgery and beyond, new innovative approaches have saved lives and decreased suffering. For psychiatric disorders, newer medications have shown improved efficacy with better side effect profiles, but when it comes to schizophrenia, which is considered by many to be one of the most devastating illnesses, our success remains limited. Although we have moved beyond symptom management to the concept of recovery or reintegration,<sup>1</sup> cognitive impairment associated with schizophrenia continues to be a significant obstacle. Presently, cognitive impairment is recognized as a core, stable feature of the disease that limits patient functioning and well-being. Almost all persons diagnosed with schizophrenia have some degree of cognitive impairment.<sup>2</sup>

## Cognitive Domains

Cognition includes several domains<sup>3</sup>: (i) working memory: the ability to maintain and manage information for brief

periods of about 5–20 seconds; (ii) verbal learning and memory: recalling verbal information for longer periods of time; (iii) attention/vigilance: the ability to stay focused on the task at hand without being distracted by other stimuli; (iv) processing speed: quickly responding to simple tasks; (v) social cognition: recognizing facial expressions and understanding their meaning; (vi) problem solving: effective strategy application; (vii) visual learning and memory: the ability to remember visual information for longer periods of time, from minutes to years.

## Cognitive Integrity and Psychiatric Rehabilitation

Cognitive integrity can be the difference in keeping someone in treatment or losing him or her to isolation, despair, and homelessness. Optimizing cognitive functioning can help with adherence to treatment, enable rehabilitative efforts, and help prevent further deterioration and relapse.

Nonpharmacological modalities to ameliorate cognitive dysfunction have included cognitive remediation,<sup>4–6</sup> which can be integrated into a comprehensive recovery plan, together with vocational rehabilitation and supported employment.<sup>7,8</sup> However access to these labor-intensive interventions is limited in many locales. Mental health specialists who are not working in an environment with access to these modalities may not even be aware of them. Unfortunately, psychiatric residencies often do not offer their trainees education or practical experience with this.

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Nonetheless, it is clear that nonpharmacological rehabilitative interventions can make a substantial impact. In a meta-analysis of nine prospective controlled trials ( $N = 740$ ) that evaluated computer-assisted cognitive remediation on productivity outcomes, patients receiving the intervention demonstrated a 20% higher employment rate, worked 19.5 days longer in a year, and earned US \$959 more in total annual earnings than those not receiving cognitive remediation.<sup>5</sup>

An area of potential clinical interest would be the combination of a specific psychopharmacological intervention to treat cognitive dysfunction in patients with schizophrenia, together with a nonpharmacological intervention such as cognitive remediation. Should synergy be demonstrated for both cognitive and functional outcomes, this would be a substantial advance in our therapeutic armamentarium.<sup>6</sup>

## Measurement

Neuropsychological testing, such as with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB),<sup>3</sup> has been the gold standard in assessing cognition in research, and has generated interest in the development of shorter and simpler instruments. Unfortunately at present, the most well-known, clinician-friendly bedside tests are the Mini-Mental State Examination (MMSE)<sup>9</sup> and the Montreal Cognitive Assessment (MCA),<sup>10</sup> which tend to assess only gross measures of cognitive ability.

Arguably, functional impairment is more clinically relevant than focusing exclusively on the results of cognitive testing alone. Scales to measure functioning include the Personal and Social Performance (PSP) scale<sup>11,12</sup> to assess routine social functioning and the UCSD Performance-based Skills Assessment (UPSA).<sup>13</sup> The PSP includes 4 domains: socially useful activities, including work and study; personal and social relationships; self-care; and disturbing and aggressive behaviors. Although not focused on cognition *per se*, the PSP has been used in antipsychotic drug development to illustrate changes that are otherwise not well described by scales that measure only psychopathology. More related to cognitive outcomes, the UPSA is performance-based, with 5 domains of functioning: household chores, communication, finance, transportation, and planning recreational activities.

Although it is generally acknowledged that cognitive impairment and functional disability are viewed as equally important treatment targets, there is little consensus on the best methods for assessing cognitive change in clinical practice.<sup>14</sup> Arguments are made that performance-based measures are essential for measurement of cognitive change, but they may be impractical because of their cost and time requirements. Interview-

based measures of cognitive and functional change are simpler to implement, but they can lack validity without informant involvement or frequent contact from clinicians. Examples of comprehensive cognitive performance assessments other than the MCCB include the CogState computerized assessment and the Cambridge Neuropsychological Test Automated Battery (CANTAB).<sup>14</sup> Briefer cognitive performance assessments include the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Brief Assessment of Cognition in Schizophrenia (BACS), the Brief Cognitive Assessment, the Brief Cognitive Assessment Tool for Schizophrenia, and the Brief Neurocognitive Assessment (BNA).<sup>14</sup> Examples of performance-based measures of functional capacity other than the UPSA include the Test of Adaptive Behavior in Schizophrenia (TABs) and the Independent Living Scales (ILS).<sup>14</sup> Examples of interview-based measures of cognition include the Cognitive Assessment Interview (CAI), the Measure of Insight into Cognition, and the Schizophrenia Cognition Rating Scale (SCoRS).<sup>14</sup> An example of an interview-based assessment of real-world functioning is the Specific Levels of Functioning (SLOF).<sup>14</sup> Some of the above instruments are reasonably brief and in theory should take no longer than the MMSE; however, their use in routine clinical settings is uncommon.

## Pragmatic Outcomes and Psychiatric Rehabilitation

A pragmatic outcome is graduation from higher learning institutions. The Center for Reintegration<sup>1</sup> has been administering scholarships for patients with schizophrenia for 18 years and has shown a graduation rate of 82% compared to the national average for the general population of 55.5% (Figure 1). Moreover, reintegration scholars evidenced grade point averages (GPA) of 3.7 compared to the national average of the general population of 3.2 (Figure 2). These numbers are skewed by the program picking “the best and the brightest,” but the fact remains that persons with a diagnosis of schizophrenia are able to graduate and do well in their scholastic education.

Employment is another pragmatic outcome. Historically, competitive employment for persons with schizophrenia is uncommon. Among the participants of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, 14.5% of the patients reported participating in competitive employment in the month before the baseline assessment, 12.6% reported other (non-competitive) employment activity, and 72.9% reported no employment activity.<sup>15</sup> Poorer neurocognitive functioning was identified as a barrier to employment; however, the availability of rehabilitative services may be helpful. Clubhouse models of community support, such as Fountain House, can facilitate competitive employment.<sup>1,16,17</sup>

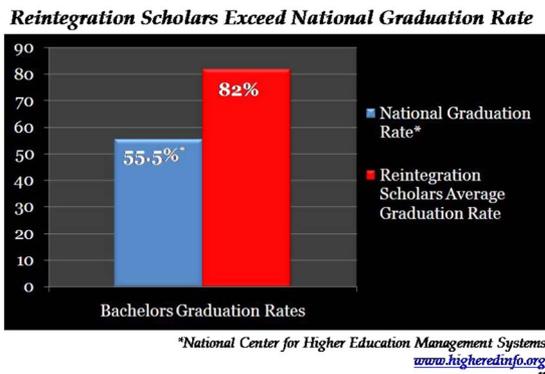


FIGURE 1. Reintegration Scholars Exceed National Graduation Rate.

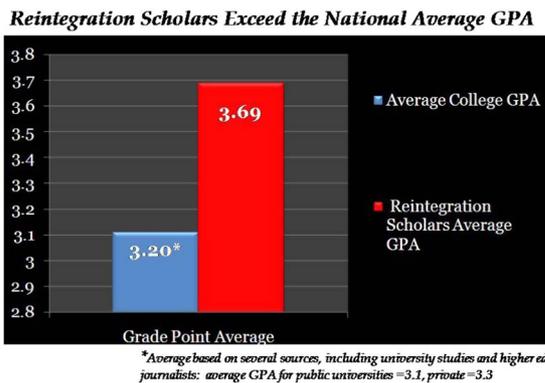


FIGURE 2. Reintegration Scholars Exceed the National Average GPA.

## Neurobiology of Cognitive Impairment

The neurobiology of cognitive impairment in schizophrenia is complex and involves the interplay of a number of neurotransmitter systems, including, among others, dopamine, glutamate, and acetylcholine.<sup>18-20</sup> A locus of impairment is the dorsolateral prefrontal cortex (DLPFC) and its interactions with other brain regions.<sup>21</sup> In the DLPFC, dopaminergic transmission is mainly mediated by dopamine D1 receptors, and chronic low levels of dopamine in the DLPFC in patients with schizophrenia have been demonstrated.<sup>18</sup> This is quite different from our understanding of the positive symptoms of schizophrenia, which are thought to be due to excess amounts of dopamine in the striatum, and where the dopamine D2 receptor is the target of antipsychotic medications.<sup>18</sup> Almost all second-generation antipsychotics also possess strong antagonism at the presynaptic serotonin 5-HT<sub>2A</sub> receptor on the dopamine neuron, which facilitates release of dopamine and theoretically boosts dopamine in the DLPFC; however, effects in ameliorating cognition by second-generation antipsychotics have been inconsistent and generally small in magnitude.<sup>22</sup>

Of increasing interest is the glutamate system, with its connections with dopamine circuitry.<sup>23</sup> Glutamate is a widely distributed excitatory neurotransmitter in the human central nervous system. Experimentally, glutamate been

shown to be involved in fast synaptic transmission, neuroplasticity, and higher cognitive functions, such as memory; pharmacologic studies with glutamate receptor antagonists, such as phencyclidine and ketamine, have demonstrated induction of positive, negative, and cognitive symptoms in healthy individuals and worsening of these symptoms in patients with schizophrenia.<sup>24,25</sup> Although there are several types of glutamate receptors categorized into 2 “families,” metabotropic and ionotropic, it is specifically the ionotropic N-methyl-d-aspartate (NMDA) glutamate receptor that has attracted the most attention. In the DLPFC, NMDA receptors are involved in high-level processes such as executive processing. NMDA receptors are also located in the visual cortex and are involved in magnocellular function and motion detection.<sup>26</sup> Moreover, auditory sensory memory involves NMDA receptors in the auditory cortex, and in the hippocampus, NMDA receptors initiate processes that form the basis for learning and memory.<sup>26</sup> The final common pathway is dopamine, with cortical glutamate neurons regulating dopamine neurons either directly acting as accelerators, or indirectly acting as brakes.<sup>27</sup> For example, glutamate will act as a direct accelerator by means of glutamatergic fibers that project to brainstem neurons, where glutamate will promote activity at the dopamine neuron, thus allowing additional dopamine to be released in areas such as the DLPFC. Glutamate can also act as a brake in the presence of gamma-aminobutyric acid (GABA) interneurons. Because excitation by glutamate of a GABA interneuron results in the release of GABA, an inhibitory neurotransmitter, this will inhibit the dopamine neuron down the chain, decreasing the release of dopamine. A possible explanation for the symptoms of schizophrenia is the NMDA receptor hypofunction hypothesis.<sup>28,29</sup> When a lack of tonic excitation occurs, such as with NMDA receptor hypofunctioning (no acceleration), insufficient dopamine reaches the cortex, resulting in cognitive (and negative) symptoms. This differs in the mesolimbic dopamine pathway, where the presence of GABA interneurons results in glutamate acting as an indirect brake on dopamine release. With NMDA receptor hypofunctioning at the GABA interneuron, the GABA interneuron is unable to release sufficient amounts of its inhibitory neurotransmitter, which results in excess dopamine being released in the mesolimbic pathway and thus producing the positive symptoms of schizophrenia.

## Neurobiological Treatment Approaches

Because the hypofunction of NMDA glutamate receptors appears to have an important role in the cognitive impairments observed in schizophrenia, several attempts have been made to target this receptor in order to enhance its function and potentially lead to amelioration in cognitive symptoms. Administering glutamate directly is not feasible, but the NMDA receptor also requires the

presence of glycine in order to function. Thus, strategies have included increasing the availability of glycine at the synapse exogenously (by oral administration of glycine or other agents that bind at the glycine site on the NMDA receptor) or endogenously by inhibiting the reuptake of glycine, akin to the mechanism of action of serotonin-specific reuptake inhibitors that enhance the availability of serotonin at the relevant synapses for the treatment of depression.<sup>30</sup> Unfortunately, in a meta-analysis of 17 studies that included 1391 patients, glutamate-positive modulators were not superior to placebo in terms of overall cognitive function, nor on each of 8 cognitive domains.<sup>31</sup> Moreover, subgroup analyses by diagnosis (schizophrenia only studies) and by concomitant antipsychotics yielded the same disappointing results.

Acetylcholine has long been a target of treatments for cognition, as pioneered by anticholinesterase inhibitors for the treatment of dementia.<sup>32</sup> Although these agents have also been studied adjunctively with antipsychotic medications in patients with schizophrenia, the supporting evidence for this strategy is weak.<sup>33</sup> Another mechanism of action that has been tested is that of agonism at the acetylcholine receptor itself, and in the case of schizophrenia, specifically at the  $\alpha 7$  nicotinic receptor.<sup>34</sup> The  $\alpha 7$  nicotinic receptor is distinct from the  $\alpha 4\beta 2$  nicotinic receptor, the latter affected by smoking.<sup>35</sup> The  $\alpha 7$  receptor has >100-fold lower affinity for nicotine than does the  $\alpha 4\beta 2$  receptor, and unbound brain concentrations of nicotine achieved by smoking are too low to either inhibit or desensitize the  $\alpha 7$  receptor. The  $\alpha 7$  receptors are located in several brain areas including the hippocampus and cortex that are involved in cognitive domains, such as attention and long-term and working memory. Activation of  $\alpha 7$  receptors enhances dopamine, acetylcholine, and glutamate efflux in rat cortex and in the nucleus accumbens.<sup>36</sup> In Phase III of clinical development is encenicline, a  $\alpha 7$  nicotinic receptor agonist that appears to “prime” the receptor by potentiating the response to the natural agonist acetylcholine, and thus existing acetylcholine is used more efficiently.<sup>37</sup> In a Phase II double-blind, randomized, placebo-controlled, parallel-design study, patients with schizophrenia on chronic stable atypical antipsychotics (N = 319) were randomized to encenicline 0.27 or 0.9 mg once daily or placebo for 12 weeks.<sup>38</sup> Notable trends in improvement were demonstrated across all cognition scales. Encenicline is also being assessed for the treatment of mild-to-moderate Alzheimer’s disease;<sup>39</sup> however, studies of encenicline for this disease state are currently on clinical hold because of serious gastrointestinal safety events reported in the Alzheimer’s disease studies.<sup>40</sup> Although central muscarinic acetylcholine receptor agonists have also been examined as potential treatments for cognitive impairment in patients with schizophrenia,<sup>20,41</sup> no agents modulating the muscarinic acetylcholine receptor are currently in advanced clinical testing for schizophrenia.<sup>42</sup>

Other agents of potential interest are under investigation, some of them driven by the MATRICS initiative<sup>43</sup> and the Treatment Units for Research on Neurocognition in Schizophrenia (TURN) network that has been a testbed for potential pro-cognitive compounds.<sup>44</sup> Through the efforts of TURN and others, compounds tested have included psychostimulants; dopamine D1 receptor agonists; agents that work at glutamate receptors other than NMDA; GABA-A receptor agonists; agents that target serotonin 5-HT1A, 5-HT2A, and 5-HT6 receptors; and miscellaneous agents such as modafinil and pregnenolone.<sup>45</sup>

## Conclusions

Cognitive impairment associated with schizophrenia is common, and it is also unfortunately a substantial obstacle to successful recovery. It is imperative that clinicians develop an understanding of the domains of cognition and how they may affect functioning. Although nonpharmacological interventions have been available, they are not always easy to access. Work is in progress to elucidate the biological underpinnings of cognitive impairment associated with schizophrenia and identifying potential pharmacological targets.

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## Optional CME Posttest and Certificate

*CME Credit Expires: November 30, 2018*

### CME Posttest Study Guide

**NOTE: The posttest can only be submitted online.** The below posttest questions have been provided solely as a study tool to prepare for your online submission. **Faxed/mailed copies of the posttest cannot be processed** and will be returned to the sender. If you do not have access to a computer, contact NEI customer service at 888-535-5600.

1. The current “gold standard” for assessing cognition in schizophrenia in clinical practice is:
  - A. MATRICS Consensus Cognitive Battery (MCCB)
  - B. Mini-Mental State Examination
  - C. Montreal Cognitive Assessment
  - D. There is no gold standard for assessing cognition in schizophrenia in clinical practice
2. A leading theory for the development of cognitive impairment in schizophrenia is hypofunction of what receptor?
  - A. 5HT<sub>2A</sub>
  - B. AMPA
  - C. D<sub>2</sub>
  - D. NMDA
3. In a 2015 meta-analysis of 17 studies, glutamatergic strategies to treat cognitive impairment were superior to placebo in terms of:
  - A. Overall cognitive function
  - B. Some but not all cognitive domains
  - C. A and B
  - D. Neither A nor B
4. Investigational treatments that target acetylcholine are currently being studied for the treatment of cognitive impairment in schizophrenia; specifically, actions at:
  - A. Acetylcholinesterase
  - B. Alpha 4 beta 2 receptors
  - C. Alpha 7 receptors

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