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Addressing Cognitive Deficits in Schizophrenia: Toward a Neurobiologically Informed Approach

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"Baseline." What do we mean by this term? It can signify progress: the patient has returned to his previous level of functioning and is safe to discharge home. At the same time, for many with schizophrenia, the term can be heartbreaking: "this is the best we can do." And when we send the patient away, we know that this "baseline" level of functioning has little to do with his level of "functioning" at all. Yes, the patient is no longer responding to internal stimuli. Yes, the patient is no longer exhibiting bizarre behavior. Ultimately, though, this may mean less than we hope if he is still unable to hold down a job, go to school, or even carry on a meaningful conversation with those who love him. For many people living with schizophrenia, this may result in the inability to support themselves, forcing them to rely on caregivers, or, if they do not have such social supports, to fend for themselves on the streets.

With an estimated prevalence of 1%, schizophrenia is a multifaceted burden on families, caregivers, businesses, and economies. Financially, it is helpful to conceptualize schizophrenia in terms of direct and indirect costs. Direct costs can be attributed to measurable health care expenses, such as provider visits, laboratory monitoring, and medications. Indirect costs include those charged to society, such as care-givers, loss of productivity, housing, food, and transportation. In the United States, schizophrenia costs an estimated $60 billion annually (1). Even small gains in patients' function or productivity could translate into large financial savings.

Cognitive deficits are now considered a core feature of schizophrenia; 90% of patients with schizophrenia have deficits in ≥1 cognitive domain, including working memory (WM), attention, processing speed, reasoning and problem solving, social cognition, visual learning and memory, and verbal learning and memory (Table 1) (2,3). In addition, though cognitive symptoms are more predictive of functional outcomes, such as maintaining employment, current pharmacotherapy for schizophrenia focusing on dopamine D_2 receptor antagonism primarily addresses positive (psychotic) symptoms of the illness while leaving cognitive symptoms virtually untouched (2). To address this critical gap in our current care, new

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treatment development must be informed by a sophisticated understanding of the relevant neurobiological systems underlying cognitive deficits in schizophrenia. Non-pharmacological strategies, such as cognitive remediation, may be effective instead of—or in conjunction with—pharmacotherapies. However, this commentary focuses on pharmacologic treatment development.

WM serves as an interface between our knowledge base and the world around us. WM is unique in that it does not rely on stored information; WM is a prefrontal cortex (PFC) function that allows an individual to process and manipulate ongoing information. Although there are other brain regions relevant to cognition in schizophrenia (e.g., the hypothalamus and the rest of the PFC), much WM research has centered on the dorsolateral PFC (dlPFC), an evolutionarily recent brain area whose function is primarily to generate the mental representations required for abstract thought. It is also involved with self-monitoring and self-regulation. Impaired dlPFC function impacts not only WM but also emotion regulation and reward response. Four principal neurochemical targets have been explored as possibilities for enhancing dlPFC function: nicotinic acetylcholine receptors (nAChRs), *N*-methyl-D-aspartate receptors (NMDARs), gamma-aminobutyric acid (GABA) receptors, and, most recently, dopamine receptors.

nAChRs are widespread throughout the cortex and thalamus and are critical for cognition. One reason nicotinic acetylcholine was considered relevant to cognitive difficulties in schizophrenia was the long-noted observation that individuals with schizophrenia smoke more than the general population and other institutionalized populations. This led to speculation that individuals with schizophrenia may self-medicate with nicotine to improve cognitive, negative, or positive symptoms or overcome the side effects of antipsychotic medications (4).

The nAChR is a complex receptor with multiple/variable subunits; the two most important to the present discussion are α4β2 and α7. The higher-affinity α4β2 subunit of nAChR is thought to regulate reward properties of nicotine, while the lower-affinity α7 subunit is thought to regulate cognitive and sensory gating phenomena. Unfortunately, strategies targeting nAChRs have had poor success in improving cognition in schizophrenia. Administering nicotine itself shows no robust effects. Cholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine) have little to no clinically significant effect. Varenicline, a partial agonist at α4β2 and full agonist at α7 subunit nAChRs, is effective in nicotine addiction, but its effects on cognition in schizophrenia are mixed, and it may worsen psychotic symptoms. Specific α7 subunit nAChR agonists (e.g., DMXB-A, TC-5619, and tropisetron) are under investigation, but initial clinical trials have yielded disappointing results (4).

Glutamate is the principal excitatory neurotransmitter in the human brain. It acts on a range of metabotropic and ionotropic receptors, including NMDAR—a receptor thought to be especially critical for learning and memory (5). Drugs that block the NMDAR produce symptoms remarkably like those of schizophrenia, including positive and negative symptoms and deficits in WM. The pathway through which NMDA blockade leads to psychotic symptoms is thought to involve 1) decreased NMDA-mediated drive on GABA interneurons

(which normally inhibit cortical pyramidal cells) and 2) decreased GABA inhibition on pyramidal cells leading to increased glutamate release in nearby areas, such as the hippocampus, promoting disorganized cortical activity (6).

Based on this model, varying approaches have attempted to modify the effect of glutamate at NMDARs using medications that act as NMDA modulators. In clinical populations, however, studies targeting the glycine modulatory site of the NMDAR complex to facilitate glutamate's action or lamotrigine to attenuate glutamate release have had inconsistent, inconclusive, or negative findings or have not yet been subject to double-blind clinical trials. A metabotropic glutamate receptor agonist recently showed initial promising results in treating schizophrenia, but these failed to be replicated. Future efforts are aimed at developing and testing allosteric modulators of other glutamate receptors (7).

Dovetailing with this, another proposed model to account for cognitive deficits in schizophrenia is supported by studies showing a primary deficit in the GABAergic signaling pathways in the PFC. The precise mechanisms behind these findings are being elucidated (8), but the resulting model is that low intrinsic activity of layer 3 pyramidal cells in schizophrenia leads to a compensatory reduction in inhibition to these neurons to try to rebalance excitation/inhibition in layer 3 of the dlPFC. This leads to a net lowering of excitation/inhibition that is inadequate for maintaining the synchronous firing of pyramidal neurons necessary to support effective dlPFC functions, such as WM.

The neurodevelopmental origin of these changes offers the exciting potential that this model may identify specific developmental targets and more effectively correct them. As this work progresses, it remains critical to develop pathophysiological models of illness and deficits to inform the rational treatment of people currently suffering from schizophrenia. One such therapeutic target, suggested by both the glutamate and GABA models, may be the dopamine D_1 receptor (D_1R).

Dopamine is critical to the functioning of the dlPFC. Integrating the glutamate and GABA models, the function of the dlPFC depends on the interplay between primarily glutamatergic pyramidal neurons in layer 3 of the cortex and GABAergic interneurons. Stimulation of D_1Rs on excitatory pyramidal neurons generates the synchronous persistent firing that underlies WM while inhibitory interneurons "fine-tune" the circuits. An optimal and low level of D_1R stimulation is needed to increase the firing of the layer 3 pyramidal neurons, while high levels of D_1R stimulation suppress firing (inverted-U dose-response curve).

In this issue of *Biological Psychiatry*, Arnsten *et al.* thoroughly chronicle the research efforts to find a drug that improves cognitive deficits in schizophrenia via the D_1R (3). Roadblocks have included drugs with poor blood-brain barrier penetration, nonselectivity for D_1R, partial instead of full agonism, poor oral bioavailability, short duration of action, rapid tolerance, or intolerable side effects. However, the first selective, centrally available D_1R full agonist (dihydrexidine) and related compounds are already being tested in humans, and the results are encouraging for future studies. The article offers intriguing thoughts on other possible therapeutic approaches, including D_1 positive allosteric modulators (to enhance endogenous dopamine), functionally selective D_1 ligands (that work poorly in some

pathways but great in others), and D_1R-selective compounds carefully dosed to capitalize on the inverted-U dose-response curve.

Ultimately, while we may be years away from effective, safe pharmacological treatments for cognitive symptoms of schizophrenia, there remains enthusiasm for targeting D_1R, with several avenues worthy of further exploration. Understanding of the neuroscience underlying psychopathology must continue to grow to maximize use of research resources. Given the toll cognitive deficits take on functional outcomes and quality of life, clinicians must be aware of these symptoms, know why current pharmacologic treatments are ineffective for them, and be on the lookout for future developments. Eventually the term “baseline,” and the lives themselves of people with schizophrenia, will be able to take on even greater meaning.

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Table 1

Cognitive Domains Affected in Schizophrenia

Cognitive Symptom	Associated Abilities
Working Memory	Temporarily store information for immediate recall and manipulation
Attention	Complete tasks requiring sustained focus
Processing Speed	The speed with which an individual performs perceptual or motor tasks, including verbal fluency
Reasoning and Problem Solving	Complete verbal and nonverbal tasks that require complex planning or decision-making skills
Social Cognition	Theory of mind (i.e., ability to infer intentions or mental states of others), social and emotional perception
Visual Learning and Memory	Acquire and recall visual information, such as faces or scenes, or reproduce simple images such as line drawings
Verbal Learning and Memory	Encode and recall verbal information, such as word lists, short narratives, or instructions

Data from Schulz and Murray (9).