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Cognitive Impairment Associated with Schizophrenia: From Pathophysiology to Treatment

Daniel C. Javitt[1,2]

[1]Department of Psychiatry, Columbia University Medical Center, New York, NY, USA; email: dcj2113@cumc.columbia.edu

[2]Schizophrenia Research Division, Nathan Kline Institute for Psychiatric Research, Orangeburg, New York, USA

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Abstract

Cognitive impairment is a core feature of schizophrenia and a major contributor to poor functional outcomes. Methods for assessment of cognitive dysfunction in schizophrenia are now well established. In addition, there has been increasing appreciation in recent years of the additional role of social cognitive impairment in driving functional outcomes and of the contributions of sensory-level dysfunction to higher-order impairments. At the neurochemical level, acute administration of *N*-methyl-D-aspartate receptor (NMDAR) antagonists reproduces the pattern of neurocognitive dysfunction associated with schizophrenia, encouraging the development of treatments targeted at both NMDAR and its interactome. At the local-circuit level, an auditory neurophysiological measure, mismatch negativity, has emerged both as a veridical index of NMDAR dysfunction and excitatory/inhibitory imbalance in schizophrenia and as a critical biomarker for early-stage translational drug development. Although no compounds have yet been approved for treatment of cognitive impairment associated with schizophrenia, several candidates are showing promise in early-phase testing.

INTRODUCTION

Schizophrenia was initially characterized by Emil Kraeplin in the 1890s as a dementia affecting younger individuals, termed dementia praecox, as opposed to Alzheimer's disease, which primarily affected older individuals. Kraeplin believed strongly in schizophrenia as a neurological disorder and cataloged disturbances in memory, attention, motor function, and perception that resonate with modern findings (reviewed in 1). Although this conceptualization of schizophrenia fell out of favor during the first half of the twentieth century under the influence of more psychodynamic concepts, the last 50 years have seen a revival of the conceptualization of cognitive dysfunction as a core feature of schizophrenia and a major cause of the long-term disability that is associated with the disorder. The interest in cognition has converged with the development of glutamate-based conceptualizations of schizophrenia, which derive from the fortuitous discovery of the psychotomimetic and cognition-impairing effects of *N*-methyl-D-aspartate receptor (NMDAR) antagonists in the early 1960s (reviewed in 2). These theories complement earlier dopaminergic (DA) models and permit a more holistic conceptualization of cognitive dysfunction patterns.

Over recent years, cognitive impairment associated with schizophrenia (CIAS) has become a mature clinical target based on increased understanding of underlying mechanisms at both the molecular and local-circuit levels, as well as the development of translational biomarkers that assist in clinical development. Nevertheless, no compounds are yet approved for this indication, and ideal translational drug development approaches are still being developed. Here, we review information related to patterns of neurocognitive impairment in schizophrenia relative to predictions of both glutamatergic and DA theories of schizophrenia, as well as the latest advances in biomarker-based paths for clinical development.

PATTERNS OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

The modern era of neuropsychological investigation of schizophrenia can be dated to the publication of the *Diagnostic and Statistical Manual of Mental Disorders III* in the early 1980s, which helped standardize diagnostic conceptualizations of schizophrenia, combined with maturation of widespread neuropsychological batteries such as the Halstead-Reitan or Luria-Nebraska battery that were originally developed to help localize and quantify deficits caused by structural brain lesions. During that time period, different research groups tended to focus on different functions. However, across groups, a clear picture emerged of generalized neurocognitive dysfunction across multiple cognitive domains and no clear hemispheric or focal abnormalities (3, 4).

MATRICS and Current Test Batteries

A major advance in the standardization of neurocognitive assessment in schizophrenia occurred with the development of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) in the early 2000s (5). As opposed to prior batteries that borrowed heavily from the brain damage literature, the MCCB was developed based on a RAND panel approach of schizophrenia experts. The panel considered not only the domains to be assessed but also the psychometric properties of specific tests and their suitability for use in drug development.

Based on consensus, seven domains were identified as being of relevance to schizophrenia: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. Moreover, domains were co-normed to assist in comparison of relative impairment across domains (6, 7). As with earlier studies, individuals with schizophrenia showed a relatively flat distribution of impairment across domains with effect sizes of approximately 0.75–1.5 SD (8). Other well-validated batteries are now also available,

including the Brief Assessment of Cognition in Schizophrenia (BACS) (9) and the Penn Computerized Neurocognitive Battery (PennCNB) (10). The batteries differ primarily based on the ease of administration and scoring and test-retest reliability rather than content.

Social Cognition

Social cognition refers to the psychological processes involved in the perception, encoding, storage, retrieval, and regulation of information about other people and ourselves (8). In the MCCB, social cognition is considered to be a single domain within the larger cognitive construct. However, social cognition may instead be viewed as involving separate processes from those involved in nonsocial cognition, which is increasingly termed neurocognition. Concepts of social cognition have expanded to include multiple domains, including emotion processing, social perception, attributional bias/style, and mentalizing (8).

In schizophrenia, social cognition deficits are best established in emotional perception/processing using tests of auditory (e.g., 11, 12) and visual (face) (e.g., 13–15) emotion recognition and in mentalizing using tasks such as The Awareness of Social Inference Test (TASIT) (16–18). Deficits in social cognition are of approximately equal magnitude to the deficits in neurocognition (i.e., ~1 SD). Social cognitive deficits in schizophrenia are strongly related to outcome. Nevertheless, batteries for repeated assessment of social cognitive function are underdeveloped compared to those that are available for neurocognition (16). Social cognition is also less studied to date in pharmacological intervention trials. To the extent that neural substrates for social cognition differ from those for neurocognition (see the sidebar titled Physiology Versus Behavior), incorporation of enriched social cognition measures in CIAS studies (or separate social CIAS studies) should be considered.

Inner Structure of Cognitive Dysfunction

Although cognitive deficits appear relatively uniform when viewed at a molar level, a specific inner structure can be discerned when tests are evaluated at a more molecular level. Thus, for example, both schizophrenia and structural hippocampal damage are associated with a reduced ability to

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A tacit assumption of many clinical development programs for cognitive impairment associated with schizophrenia is that because individuals have similar behavioral deficits, the underlying physiological mechanisms are the same. Recent comparative studies in schizophrenia and autism spectrum disorder (ASD) challenge this assumption. Thus, individuals with both schizophrenia and ASD have social cognitive difficulties as assessed using tests of face emotion recognition or theory of mind (e.g., TASIT). Nevertheless, the two groups differ substantially in underlying neurophysiology. Thus, individuals with schizophrenia as a group show underactivity of subcortical and cortical structures involved in visual stimulus processing. In contrast, individuals with ASD show hyperactivity in these regions (14, 15). In schizophrenia, the deficits are likely related to impaired input into the cortex via the magnocellular visual system. In ASD, the differences may reflect abnormal persistence of functions of the retinotectal system into adulthood (15). In both cases, the differences in early visual processing result in the underactivity of regions within superior temporal cortex and temporoparietal junction that are extensively involved in social cognitive functions (15, 18). Overall, these findings highlight the importance of using physiologically based measures (biomarkers), as opposed to behavior alone, in developing and applying new pharmacologically based treatment approaches.

learn new information. However, unlike individuals with hippocampal damage, individuals with schizophrenia show a relatively intact ability to retain information once it is learned within both declarative (8) and working memory (19) systems. Similarly, several aspects of attention such as the ability to switch back and forth between different tasks, as reflected in increased time to response (switch costs) (20), or the ability to orient to information presented at specific locations (spatial attention) (21) are paradoxically preserved, although other aspects such as the ability to process competing information (mixing costs) are significantly impaired (20). Processes that are intact tend not to differ from those that are impaired in terms of brain regions engaged but likely differ in terms of local-circuit mechanisms. The overall pattern of cognitive dysfunction may thus be considered to be regionally diffuse, but process specific, likely related to the involvement of specific neurotransmitter systems, as discussed below.

Natural History

Most studies in CIAS involve individuals with established schizophrenia. Nevertheless, cognitive decline in schizophrenia appears to predate illness onset and may be relatively stable once symptoms have appeared. For example, in follow-back studies using standardized scholastic testing (Iowa tests) as a proxy for overall cognition, individuals who went on to develop schizophrenia tested in the forty-fifth percentile at grades 4 and 8 but then declined to the fortieth percentile by grade 12, with language-related subscores being most affected (22). A similar reduction in adolescent reading ability was observed in follow-back studies of mandatory psychometric screening scores in Israeli military recruits (23).

Reading tests can also be used to assess the time course of cognitive decline. Premorbid reading ability can be assessed using tests of single-word reading ability, such as the Wide Range Achievement Test (WRAT), which assess the ability to recognize irregular sight words (e.g., "knight," "itinerary"). In contrast, current reading ability can be assessed using passage reading tests such as the Woodcock-Johnson or Gray Oral Reading Test batteries (24). Consistent with the follow-back studies, individuals with schizophrenia show an approximately 0.3-SD reduction in premorbid reading ability but an additional approximately 1-SD reduction in present versus premorbid ability, corresponding to about 4 grade levels in reading ability (25).

Reading deficits also correlate highly with the observed reduction in socioeconomic status between individuals with schizophrenia and their parents (24, 25). Similar deficits in premorbid function are observed in long-term prospective follow-up studies (26), including a decline in verbal ability from ages 13 to 18 (27). Small-to-moderate effect-size deficits in cognition are observed in individuals with high risk for developing schizophrenia based on either clinical or familial factors (28–30). To the extent that cognitive decline may begin as early as eighth grade in individuals who subsequently develop schizophrenia, ideal treatments for CIAS would target the decline that occurs during the late adolescent period.

Sensory Processing Dysfunction and Hierarchical Distributed Models

Deficits in sensory processing in schizophrenia were first documented in the early 1900s and were commented upon by Kraeplin in his textbook of psychiatry. However, Eugen Bleuler subsequently proclaimed that sensory functions were unaffected (reviewed in 1). This view persisted throughout much of the twentieth century before studies of eye tracking (31) and visual backward masking (32) in the early 1970s provided objective evidence of sensory processing deficits independent of other aspects of neurocognitive impairment (1). To date, sensory processing deficits are best operationalized within the auditory and visual processing systems, although analogous deficits likely exist within the somatosensory and proprioceptive systems (33).

Auditory System

Auditory stimuli are processed through the cochlea and midbrain auditory nuclei and conveyed via the medial geniculate nucleus (MGN)/body (MGB) of the thalamus to primary and secondary auditory cortex (reviewed in 34, 35). In schizophrenia, peripheral aspects of the auditory system appear unaffected. Nevertheless, significant deficits are observed in the function of the echoic memory system, which underlies the ability to compare tones across brief delay (36).

Despite the simplicity of the echoic memory process, individuals with schizophrenia as a whole show deficits in simple tone-matching ability that are similar in magnitude to those observed for more general neurocognitive impairment (34–36). Moreover, whereas most cognitive deficits are unimodally distributed within the schizophrenia population, tone-matching deficits show a bimodal distribution (37), suggesting that they may divide individuals with schizophrenia into etiologically distinct subgroups (**Figure 1*a***). Individuals with deficits in early auditory processing (EAP−) show significantly lower estimated premorbid IQ, educational achievement, and cognitive function, especially on tests of processing speed, and increased Positive and Negative Syndrome Scale (PANSS) cognitive disorganization scores relative to subjects with intact early auditory processing (EAP+) and lower functional connectivity between MGN and auditory cortex (37).

In Western languages, tonality (prosody) is used to convey affect and attitude. Thus, as expected, EAP deficits correlate highly with auditory aspects of social cognition, including auditory emotion recognition (11, 38) and sarcasm detection (35, 37), as well as auditory-based neurocognitive processes such as verbal learning (37) (**Figure 1*b***). Tonal discrimination also plays a critical role in formant discrimination and phonetic language processing, which are also impaired in schizophrenia (34, 38), contributing to impaired reading ability (25). In a tonal language (e.g., Mandarin), EAP deficits correlate with a reduced ability to identify words with similar phonetic content but altered tonality, which in turn predicts outcome (39). Auditory training may lead to improvements in general neurocognitive function (40) and may be especially effective in individuals with baseline EAP deficits (41).

At present, there are no gold standard tests for the assessment of auditory processing in schizophrenia. On the Montreal Battery for Amusia (tone deafness), individuals with schizophrenia show a significant deficit in melodic processing that correlates with their conceptual disorganization scores (42). The Test of Basic Auditory Capabilities (TBAC) evaluates multiple aspects of function and interrelates with more general neurocognitive impairment (43). The recently developed INTONATION test uses natural stimuli from spontaneous displays of emotion and may be more sensitive than earlier tests for the detection of affective prosodic impairment (44).

Visual System

The early visual system is divided into three distinct subcortical pathways that are specialized for processing different types of information. Both the magnocellular and parvocellular pathways are relayed to cortex via the lateral geniculate nucleus, whereas the retinotectal pathway is relayed through superior colliculus and pulvinar nucleus. Magnocellular neurons are specialized for the rapid detection of low-contrast, low–spatial frequency, and motion stimuli and are preferentially involved in attentional capture and framing of the visual scene (45, 46). By contrast, parvocellular neurons are specialized for slower but more graded analysis of fine spatial details and project primarily to ventral visual regions (46). The retinotectal system, which is evolutionarily older, plays an important role in guiding visual development and, in adults, may convey threat-related activity rapidly to visual cortical regions and amygdala (15, 46).

The relative function of the different subcortical pathways can be distinguished using visual stimuli with well-defined psychophysical parameters (e.g., Gabor patches). In schizophrenia,

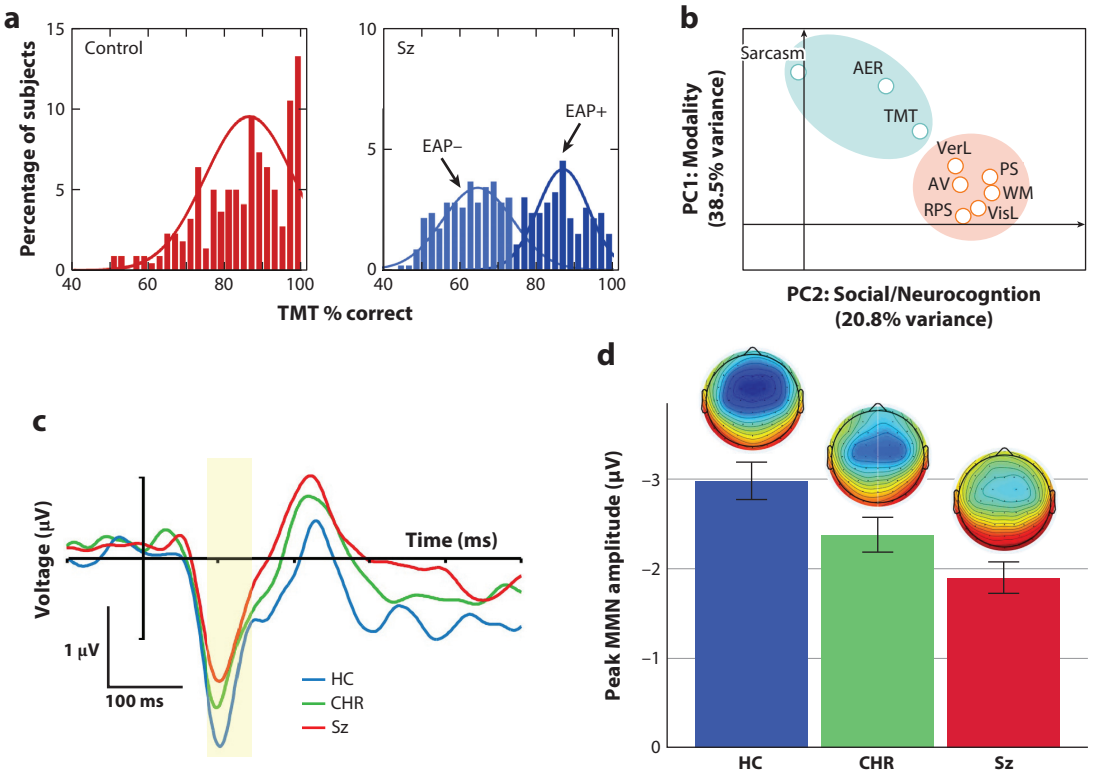

Figure 1

Early auditory processing deficits in schizophrenia. (*a*) Distribution of tone-matching test (TMT) performance across controls versus schizophrenia (Sz) individuals. In controls, few individuals score below 75% performance on this test. In contrast, in schizophrenia, performance shows a double (bimodal) peak, permitting the groups to be divided into those with intact versus impaired early auditory processing (EAP+, EAP−). To date, tone matching is the only cognitive measure that has been shown to have a bimodal distribution, suggesting that it may be useful as a stratification variable. (*b*) Principal components (PC) analysis of auditory-related processing versus Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery domains showing separate clustering of social cognitive deficits such as auditory emotion recognition (AER) and theory of mind (sarcasm) relative to nonsocial (neurocognitive) deficits such as auditory verbal learning (VerL), attention/vigilance (AV), processing speed (PS), working memory (WM), or reasoning/problem solving (RPS). The axes may be interpreted as reflecting primarily modality of task (auditory vs. visual) and relationship to social vs. neurocognition. As expected, TMT deficits were most closely interrelated to impairments in auditory-dependent components of working memory such as VerL. (*c*) Mismatch negativity (MMN) waveforms to location deviants in individuals with schizophrenia or at clinical high risk (CHR) relative to healthy controls (HC). (*d*) Mean (SEM) MMN amplitudes across groups, along with scalp distribution. Panels *a* and *b* adapted from Reference 37 (CC BY-SA 4.0), and panels *c* and *d* adapted from Reference 155 (CC BY-SA 4.0).

deficits are observed preferentially in the detection of low-contrast (<16%), low–spatial frequency (<4 cycle/degree) (47–49), and motion (14, 50–52) stimuli and have been linked most specifically to impairment in the NMDAR-dependent nonlinear gain functions of the magnocellular system (53). In contrast, the processing of high–spatial frequency stimuli is relatively intact, especially following control for potential differences in uncorrected visual acuity between groups (54). An important aspect of the magnocellular system's function is that it operates largely outside of conscious awareness. Thus, without specific testing, both individuals with schizophrenia and clinicians will be unaware of the deficits.

Deficits in visual magnocellular function contribute to processes such as impaired contextual processing (55), cognitive control (56), object recognition (57), face emotion recognition (14, 15, 52), contour integration (58), and visual/oculomotor aspects of reading (59, 60). Routine clinical testing (e.g., eye charts) are sensitive primarily to ocular and parvocellular function and thus are relatively uninformative regarding magnocellular visual dysfunction in schizophrenia. Methodologies developed for assessing magnocellular dysfunction in glaucoma, including optical coherence tomography (48, 61), may be useful but require further study.

NEUROCHEMICAL MODELS OF COGNITIVE IMPAIRMENT

Neurochemical conceptualizations of CIAS focus primarily on glutamatergic and DA brain systems (**Figure 2*a***). In addition, GABAergic systems may play a critical role in modulating local-circuit activity, whereas anticholinergic side effects of antipsychotic medication may represent a confound in CIAS studies (62).

Glutamate Models

Glutamatergic conceptualization began with the synthesis of phencyclidine (PCP) and ketamine in the early 1960s, followed by characterization of their unique dissociative effects in monkeys and

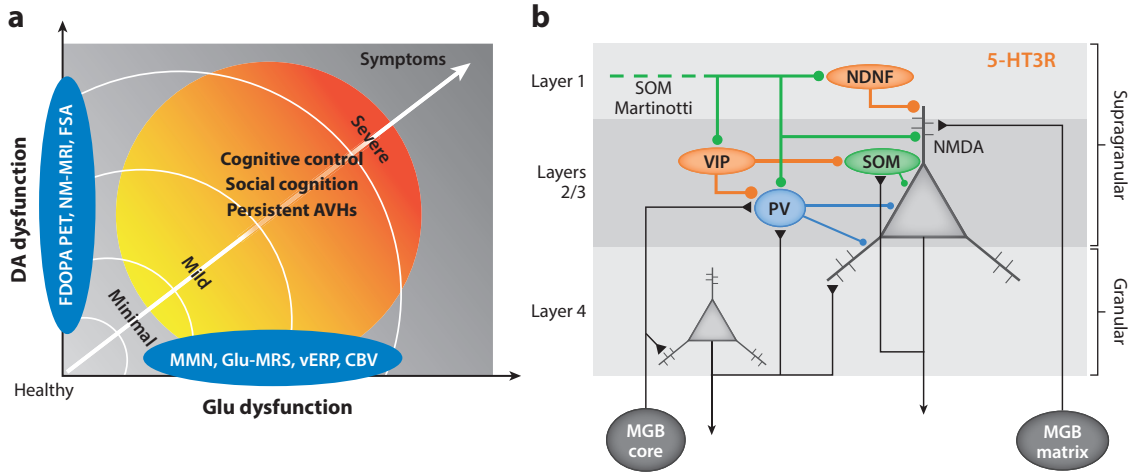

Figure 2

Models of cognitive impairments in schizophrenia: (*a*) Overall structure of symptoms and neurocognitive deficits in schizophrenia, suggesting parallel contributions from glutamatergic (Glu) and dopaminergic (DA) pathways. Measures such as mismatch negativity (MMN), visual event–related potentials (vERPs), local cerebral blood volume (CBV) (156), or glutamate MR spectroscopy (MRS) may be used to assess glutamatergic involvement across individuals, whereas [^{18}F]FDOPA positron emission tomography (FDOPA PET) (90) or neuromelanin (92) imaging (NM-MRI) index may be used to assess intrinsic DA contributions, while functional MRI–based measures such as functional striatal abnormality (FSA) (157) may be used to assess striatal dysregulation. The interaction of these pathways gives rise to cognitive impairments, including deficits in cognitive control and social cognition and symptoms such as persistent auditory verbal hallucinations (AVHs). (*b*) Schematic local circuit model of auditory cortex related to MMN impairment. MMN indexes *N*-methyl-D-aspartate receptor (NMDAR)-related cognitive impairments in schizophrenia. MMN is generated primarily in supragranular layers of auditory cortex. Inputs to auditory cortex derive from both the core and matrix of the medial geniculate body (MGB). Parvalbumin (PV) and non-Martinotti somatostatin (SOM) interneurons exert primarily local feedforward inhibition, while Martinotti-type SOM interneurons may cross columnar boundaries. Interneurons expressing neuron-derived neurotrophic factor (NDNF) or vasoactive intestinal peptide (VIP) target both excitatory (pyramidal) neurons and other interneuron types. Both NDNF and VIP interneurons express 5-HT3R, which may be a target for intervention. NMDAR involved in MMN generation may be localized to dendrites of layer-2/3 pyramidal neurons. For further information, readers are referred to several studies (112–116). Panel *b* adapted from Reference 34.

their schizophrenia-like psychotomimetic and neurocognitive effects in humans (63, 64). These agents were subsequently shown to induce their unique behavioral effects by blocking neurotransmission at NMDAR-type glutamate receptors (2, 65). Since then, effects of ketamine have been extensively documented across a range of neurocognitive domains (66, 67). Moreover, as in schizophrenia, specific deficits are observed on encoding but not retention of information (68, 69), context but not target processing (70, 71), and mixing but not switch costs during cognitive control (72). Cognitive profiles are also similar between chronic ketamine users and those with schizophrenia (73). The potential involvement of NMDAR in the pathophysiology of schizophrenia is also supported by genetic studies that show consistent enrichment of NMDAR genes in schizophrenia families (74, 75) and by autoimmune states such as systemic lupus erythematosus or anti-NMDAR encephalitis in which the presence of antibodies against NMDAR, but not those against other neuroreceptor types, correlates with the degree of neurocognitive dysfunction (reviewed in 76, 77). NMDAR dysfunction may also lead to compensatory upregulation in presynaptic glutamate release, as measured by magnetic resonance spectroscopy (MRS), cerebral blood volume imaging, or other approaches, which may contribute in parallel to symptoms and neurocognitive deficits (78).

Neural Mechanisms of NMDAR Dysfunction

Given the ability of acute treatment with NMDAR antagonists to reproduce both symptoms and neurocognitive impairments associated with schizophrenia, there has been increasing focus in recent years on potential causes of NMDAR dysfunction at both the molecular and local-circuit levels.

Molecular architecture of NMDARs. NMDARs are composed of variable combinations of NR1 (GluN1), NR2A-D (GluN2), and NR3A,B (GluN3) subunits, which are encoded by *GRIN* genes. In adults, GluN2A and GluN2B subunits predominate, with a developmental switch over from GluN2B to GluN2A subunits. GluN1/GluN2 subunits consist of (*a*) an amino terminal domain that is sensitive to effects of Zn^{+}, polyamines (e.g., spermine, ifenprodil), and protons; (*b*) a ligand binding domain that is sensitive to glycine/D-serine (GluN1) or glutamate (GluN2); (*c*) a transmembrane domain that incorporates the Na^{+}/Ca^{2+}-permeable ion channel and the Mg^{2+} and PCP binding sites; and (*d*) a C-terminal domain (CTD) that exhibits significant diversity among NMDAR subunits and that regulates trafficking of NMDARs within the cell as well as NMDAR interactions with proteins in the postsynaptic density (PSD) following their insertion into the dendritic membrane (79).

Most pathological NMDAR mutations are associated with conditions that manifest during early development, including intellectual disability/developmental delay and epilepsy with aphasia (80, 81). In contrast, most mutations associated with schizophrenia localize to the CTD of GluN2A subunits and in the N-terminal domain and CTD of GluN2B subunits (79, 82). The involvement of *GRIN* genes in the pathophysiology of schizophrenia is also supported by a recent whole-exome sequencing study that identified protein-truncating mutations of the *GRIN2A* gene that increase risk for schizophrenia but not for other developmental disorders (74).

One of the unexplained features of CIAS is its onset during the second and third decades of life. One potential explanation for this delayed onset is the extensive synaptic pruning of glutamate terminals that occurs during late adolescence (83, 84). However, another is the shift in expression of GluN2B to GluN2A during development, leading to increased pathology as the changeover occurs (74). GluN2A subunits also regulate neuron-microglial interaction (85), providing a potential bridge between models.

Intra- versus extrasynaptic compartments. NMDARs are initially inserted into the dendritic membrane at extrasynaptic sites. They then diffuse laterally before eventually entering the synapse

and docking with PSD proteins via the CTD. Interestingly, both dopamine D1 and D2 receptors (D1R, D2R) fall within the NMDAR interactome (86). Although both intra- and extrasynaptic NMDARs have similar gating characteristics, their contributions to cell function are distinctly different. In general, Ca^{2+} flow through synaptic NMDARs exerts effects that favor long-term potentiation and cell survival, whereas Ca^{2+} entry though extrasynaptic NMDARs leads to mitochondrial dysfunction, loss of integrity of neuronal structures, neurotoxicity, and cell death (86).

GluN2A and GluN2B subunits also differ in their docking properties, with GluN2B showing greater exchange between synaptic and extrasynaptic compartments. The potential importance of NMDAR localization is supported by findings from NMDAR encephalitis, in which anti-NMDAR antibodies appear to induce their psychotomimetic effects by altering the distribution of NMDARs between intra- and extrasynaptic compartments rather than by affecting their function or absolute number (86). Gene clusters relating to synaptic function, plasticity, and Ca^{2+} channel function are also implicated in schizophrenia and likely act in parallel with disturbances of NMDARs (87–89). Nevertheless, many of these genes code for structural proteins or other targets that are difficult to leverage for treatment development.

Dopaminergic Contributions and Assessment

Abnormalities in DA neurotransmission have been documented in schizophrenia using multiple imaging approaches, including D2 radioreceptor displacement (90), [^{18}F]FDOPA PET (91) and, most recently, neuromelanin (92) imaging, and have been shown to correlate especially to positive symptoms. However, acute administration of psychostimulants, if anything, tends to improve rather than worsen cognitive functioning, suggesting that acute DA hyperactivity is unlikely to underlie cognitive impairments. Current revisions of the DA model of schizophrenia therefore tend to focus not on subcortical hyperactivity, accounting for symptoms, but on cortical underactivity, accounting potentially for specific aspects of neurocognitive dysfunction (reviewed in 93).

At present, the strongest support for DA contributions to cognitive dysfunction comes from the study of neurocognitive effects of chronic methamphetamine abuse. Across studies, the greatest abnormalities are observed in cognitive control (impulsivity) as measured by tests such as the Stop-Signal or Go/No-Go tasks and in social cognition as measured using tests of facial affect recognition and theory of mind (**Figure 2*a***), with more moderate effects on domains of attention, executive function, verbal fluency, speed of processing, working memory, and visual functions (94). Moreover, D2R-NMDAR dimers are increased by chronic psychostimulant administration (95), providing a mechanism for potential cross talk between systems.

Translational Biomarkers for New Treatment Development

Given the potential heterogeneous contributions to CIAS, there is a critical need for biomarkers that can be used both phenotypically in individuals with schizophrenia to identify homogenous subgroups and translationally across preclinical and clinical studies to refine dosing and demonstrate functional target engagement. As with behavioral tests, critical issues for biomarkers include not only the constructs that are assessed but also the stability and reliability of the measure when applied to clinical populations.

Mismatch negativity. The best-established translational biomarker for NMDAR dysfunction and CIAS is an auditory event-related potential (ERP) component termed mismatch negativity (MMN). In the ERP approach, continuous electroencephalographic (EEG) activity is recorded along with digital timing tags for specific events such as stimulus presentation. Responses to repeated stimuli (typically 50–200) are then averaged together to differentiate event-related activity

from background EEG and to calculate the ERP. MMN is elicited most commonly in a passive auditory oddball paradigm in which a sequence of repetitive standard stimuli is interrupted infrequently by physically deviant oddballs. MMN reflects the additional brain activity elicited by deviant, as compared to standard, stimuli and so is defined based on the deviant-standard difference wave. Principal generators for MMN are located in supratemporal auditory cortex (96), although deviance-related activity may be observed in both subcortical structures such as inferior colliculus and thalamus and higher-order structures such as inferior frontal cortex (97). An advantage of MMN is that it can be obtained in monkey (96, 98) and rodent (99) models as well as in humans, making it well suited for translational treatment development.

In schizophrenia, deficits in MMN generation have been extensively documented, particularly for location-, duration-, and frequency (pitch)-deviant stimuli (100) (**Figure 1*c*,*d***). Duration MMN, which is decoded predominantly at the cortical level, is impaired across individuals drawn from both inpatient and outpatient settings, with a large effect size (d = 0.8) across studies (100). In contrast, impairments in frequency MMN appear to be more severe in individuals drawn from inpatient versus outpatient settings and correlate with behavioral EAP deficits (101). In functional MRI studies, activation deficits are observed at all stages and propagate from subcortical to cortical nodes in a feedforward fashion (102). Across populations, deficits in MMN correlate strongly with cognitive dysfunction and poor functional outcome (103). MMN-like activity can be elicited in both nonhuman primates (96, 98, 104, 105) and rodents (99, 106) using paradigms homologous to those used in humans. Moreover, ketamine induces schizophrenia-like MMN deficits in humans (107, 108), nonhuman primates (96, 98, 105), and rodents (99, 106, 109), supporting both the link to NMDAR dysfunction and the potential translational utility.

At the local-circuit level (**Figure 2*b***), MMN depends on current flow through open, unblocked NMDAR channels located on the apical dendrites of supragranular pyramidal neurons (96, 98). In time-frequency analyses, the power of MMN maps predominantly to the theta (4–7 Hz) frequency range, suggesting that it reflects an interaction between pyramidal neurons and local somatostatin (SOM)-type interneurons (110–112). MMN is known to depend primarily on the establishment of a disinhibitory memory trace in cortex. One potential substrate for this is inhibition of neuron-derived neurotrophic factor (NDNF)-expressing interneurons in layer 1 of auditory cortex by SOM+ Martinotti cells, which in turn exert tonic inhibition of superficial cortical pyramidal neurons as well as local-circuit PV interneurons (113, 114). Vasoactive intestinal peptide (VIP) interneurons, which also primarily target other classes of inhibitory interneuron (114–116), may also contribute. Both VIP and NDNF interneurons express serotonin 5-HT3 receptors (5-HT3Rs), (114) which may therefore represent a target for intervention (117). MMN is not affected by either psychostimulants (118) or hallucinogens (119–121), suggesting relative specificity for glutamatergic processing and the excitatory/inhibitory (E/I) balance within auditory cortex.

Additional paradigms. In the auditory oddball paradigm, additional ERP components are elicited when subjects are asked to attend the auditory stimulation stream, including the auditory P300 potential. As with MMN, P300 deficits are extensively replicated in schizophrenia and may predict outcome of CHR individuals (122). Generators for P300 are distributed throughout frontal and parietal regions and may reflect engagement of the frontoparietal networks. Unlike MMN, P300 is influenced not only by ketamine but also by hallucinogens (121). In schizophrenia, approximately 50% of the variance in P300 amplitude is driven by MMN, while 50% is independent, supporting the distributed hierarchical processing concept (123). P300 may thus be useful as a biomarker particularly for treatments that are targeted at the selective modulation of higher-order cognitive components.

Additional sensory-level paradigms include the auditory steady-state response, which is thought to index the function of parvalbumin (PV)-related circuits across cortical regions (124–126) and the long interstimulus-interval auditory N1 potential (127, 128). Physiological contributions to working memory deficits may be indexed by ERP measures in tasks such as the N-back or AX-CPT paradigms in which individuals must attend to a series of letters on the screen and press in response to specific letter sequences (55). Cognitive control deficits may be assessed using response inhibition paradigms such as the Stop-Signal task (56), although these paradigms remain underdeveloped compared to sensory-based approaches.

Pharmacological Approaches

To date, no compounds have been approved for CIAS. Nevertheless, promising results have been obtained with a number of compounds representing separate mechanisms. These studies, moreover, take advantage of the latest biomarker and assessment opportunities to help refine dose selection and remove sources of variance within large-scale clinical trials.

NMDAR-based treatments. A straightforward prediction of NMDAR models is that agents that potentiate NMDAR neurotransmission should be therapeutically beneficial. The main target for such treatments has been the glycine/D-serine allosteric modulatory site of the NMDAR, which is protected from ambient glycine levels within but not outside of the synaptic cleft due to the action of glycine transporters. Compounds used to date include the direct agonists glycine, D-serine, and D-cycloserine; the glycine (GlyT1) transport inhibitors sarcosine, bitopertin, AMG747, and BI-425809; and D-serine modulators such as luvadaxistat (129).

These compounds have been most extensively tested as adjunctive medications for individuals with significant residual symptoms following adequate antipsychotic treatment. Despite some high-profile negative multicenter trials, recent meta-analyses suggest beneficial overall effects (130, 131). Moreover, meta-regression analyses suggest differential scaling with sample size, suggesting differences in biological effects between active and placebo treatments (129).

Fewer studies have assessed cognition. Nevertheless, one study of D-serine showed a significant, large effect size (1.0 SD) on the MCCB composite score that correlated with peak D-serine concentration (132). In a second study, pairing of acute D-serine administration with auditory training led to a significant improvement in both the ability to detect the trained tone and the related generation of MMN (133) (**Figure 3**).

A more recent multicenter study evaluated effects of the glycine transport inhibitor BI 425809 across three doses (2, 10, and 25 mg) versus placebo for 12 weeks. Significant but small effect-size changes (~0.3 SD), corresponding to an approximately 2-point change in the MCCB overall cognition score, were observed for both of the higher doses (134). Follow-up Phase III studies are investigating BI 452809 during long-term (26 weeks) treatment, while a Phase II study is investigating the combined effects of BI 452809 and computerized cognitive remediation (135). Significant post hoc beneficial effects on cognition have also recently been reported for luvadaxistat (136) in association with improved MMN (137), but they require confirmation in larger trials.

Excitatory/inhibitory balance. Because NMDARs are embedded within a local-circuit framework, intervention elsewhere within the circuit may help restore the imbalance created by dysfunction of excitatory mechanisms. $GABA_A$ receptor types are mostly shared across interneuron types, potentially contributing to negative findings with $GABA_A$ receptor–based treatment (138). The recent observation that 5-HT3Rs are selectively expressed on NDNF- and VIP-expressing GABA interneurons (114), however, has prompted increased interest in this mechanism.

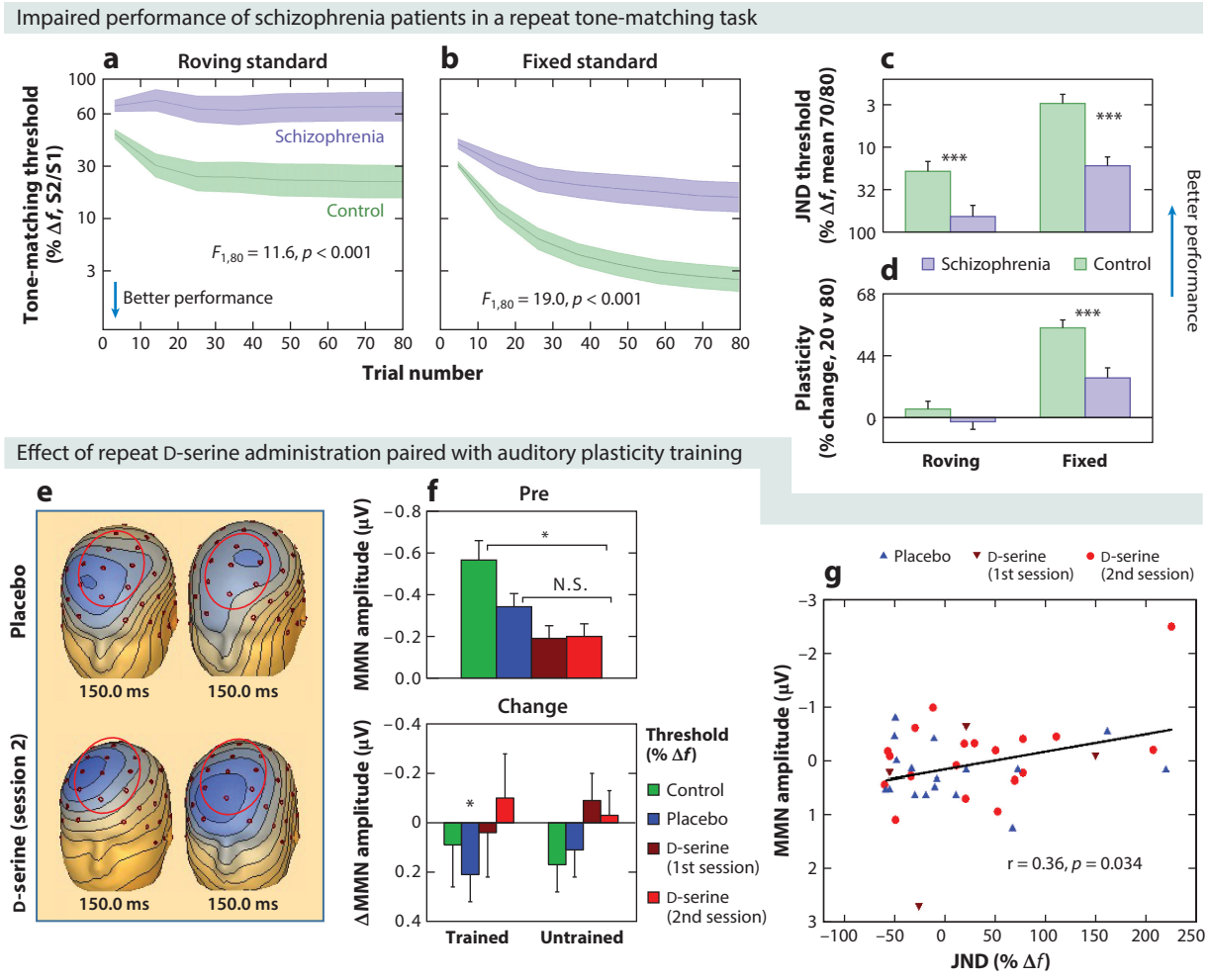

Figure 3

Illustration of the biomarker-based approach for treatment development in cognitive impairment associated with schizophrenia. The impaired performance of individuals with schizophrenia is shown in a repeat tone-matching task using either (*a*) random or (*b*) fixed standards, as reflected (*c*) in the need for greater between-tone pitch differences (Δ*f*) to create just-noticeable differences (JNDs) and (*d*) showing reduced auditory plasticity as well. (*e*–*g*) The effect of repeat D-serine administration paired with auditory plasticity training on MMN responses and tone-matching performance is shown. (*e*) MMN (*red circles*) is shown prior to and following plasticity training paired with placebo or D-serine. (*f*) MMN amplitudes for all treatment groups relative to controls and selective change in MMN in response to paired plasticity and D-serine treatment are shown. (*g*) Correlation between changes in JNDs and MMN is shown. Figure adapted with permission from Reference 133; copyright 2016 Oxford University Press.

5-HT3R agonists, including ondansetron and tropisetron, are US Food and Drug Administration (FDA) approved for the treatment of chemotherapy-related nausea and emesis. Initial studies with 5-HT3R antagonists were motivated based on concepts of serotonergic hyperfunction in schizophrenia but may be interpreted at present within the context of E/I imbalance. Across studies, significant beneficial clinical effects of these compounds have been observed, especially for persistent negative symptoms and total psychopathology (139). Significant beneficial effects of ondansetron were also observed on visual and auditory sensory memory processes and in the

auditory P50 gating paradigm, which measures decreases in the response amplitude during repeat tone presentation (140). In contrast, other aspects of cognition were not affected.

A recent study evaluated the effects of CVN-058, a novel, high-affinity 5-HT3R agonist, on MMN and other auditory biomarkers in an acute, within-subject cross-over design. At the highest dose tested (150 mg), CVN-058 significantly enhanced MMN generation, with a moderate effect size ($d = 0.48$) when only duration MMN was considered but a somewhat larger effect ($d = 0.57$) when a multivariate approach was conducted across MMN types (117). This study thus supports earlier findings with repurposed 5-HT3R agonists and supports the concept of E/I-based treatment.

Nondissociative NMDAR antagonists. While most NMDAR antagonists such as PCP or ketamine worsen both symptoms and neurocognitive function in schizophrenia, an interesting finding has been that the low-affinity NMDAR antagonist memantine may have beneficial effects against both symptoms and cognition. These findings converge with neurophysiological studies demonstrating that, unlike other NMDAR antagonists, memantine improves, rather than worsens, MMN (141, 142), suggesting that subpopulations of NMDARs may contribute differentially to cognition.

Memantine was first tested in schizophrenia based on its reported beneficial effects against both cognitive impairment and ongoing neurodegeneration in Alzheimer's disease. Although the results in schizophrenia have been somewhat variable across studies, a recent meta-analysis found significant effects on both persistent negative symptoms (SMD = −0.7) and total psychopathology (SMD = −0.56) (143). Three studies were identified that used the Mini-Mental State Examination (MMSE) with a mean difference of 3.09 points between drug and placebo ($p < 0.0001$). However, no significant effect on cognition was observed in a study using the BACS (144). Similarly, a recent study did not find a significant beneficial effect of acute memantine challenge on the MCCB (145). Nevertheless, a recent study found significant augmentation of auditory plasticity when memantine was paired with auditory training (146), similar to effects previously observed with D-serine (133).

At present, memantine is sui generis as it is the only known NMDAR antagonist that improves, rather than exacerbates, symptoms in schizophrenia. It is also the only known NMDAR antagonist without significant psychotomimetic effects in healthy volunteers at therapeutic doses and the only NMDAR antagonist without clinical antidepressant efficacy (147). The basis for the differential effects of memantine versus other NMDAR antagonists is presently unknown. However, its unique combination of affinity, Mg^{2+} sensitivity, NR2B versus NR2A specificity, and second-site binding may result in memantine having predominant effects on extra- versus intrasynaptic NMDARs (148). To the extent that impaired tethering of synaptic NMDARs is a critical issue in schizophrenia, blockade of extrasynaptic NMDARs may help restore balance.

The fact that memantine enhances rather than inhibits MMN (141, 142) reiterates the importance of incorporating functional biomarkers early within the drug development process rather than relying on in vitro assays for pharmacological characterization. To the extent that memantine effects are confirmed, it would encourage development of future compounds that differentially target extra- versus intrasynaptic NMDARs, either by mimicking memantine's specific properties or through alternative strategies.

Given the positive findings with glycine/D-serine-targeted therapies, which preferentially enhance synaptic NMDAR function, and with memantine, which preferentially inhibits extrasynaptic function, the potential for synergistic benefit between these mechanisms should be explored. In the interim, while memantine is often simply termed an NMDAR antagonist based on its in vitro effects, subdividing NMDAR antagonists based on either their abilities to produce

dissociative reactions in humans and monkeys or their relative effects at intra- versus extrasynaptic NMDARs would help clarify present nomenclature.

Dopaminergic intervention and the NMDAR interactome. The NMDAR interactome includes both D2Rs, which inhibit NMDARs, and D1Rs, which potentiate activity. NMDARs and D1Rs interact via their intracellular C-terminal tails, leading to increased D1R insertion into the cell membrane and increased NMDAR migration from extra- to intrasynaptic compartments (86). D1R agonists have also been shown to reverse antipsychotic-induced working memory deficits in monkeys (149). Studies of D1R modulators in schizophrenia have not shown beneficial effects to date (e.g., 150). Nevertheless, newer compounds with improved pharmacological properties are currently undergoing clinical testing (151).

Other proteins within the NMDAR interactome include α_7 nicotinic receptors, which are known molecular targets for potential CIAS treatments, and mGluR1 and mGluR5, which potentiate NMDARs. Although some positive results have been observed for α_7 compounds, results have not been replicated in larger-scale trials (152). mGluR5 variants have shown effects on cognition and hippocampal volume in schizophrenia (153). To date, however, no formal studies of mGluR1/5 agonists have been conducted. Other less-explored targets within the interactome include μ opiate, ephrin B2, apolipoprotein E2, sigma-1, histamine 3, interleukin 1, purinergic P2X receptors, and TRPM4 cation channels (86).

CONCLUSION AND FUTURE DIRECTIONS

In the original MCCB project, several candidate mechanisms were proposed for the treatment of CIAS. These included NMDAR agonists in general as well as glycine reuptake antagonists in specific, along with D1 receptor agonists, and other glutamatergic mechanisms (154); these remain among the most promising candidates. In the 15 years that have elapsed since the meeting (154), there have been significant developments in compounds and methods available to test the hypotheses, including the development of biomarkers such as MMN that permit cross-species translation and dose selection in early-stage clinical trials. There has also been increasing understanding of glutamatergic/NMDAR and DA function at the molecular level that may permit development of next-generation approaches.

At the local-circuit level, there has been increasing focus on concepts of E/I imbalance. Moreover, there has been improved categorization of GABA interneuron subtypes, which has permitted more refined approaches to E/I-based intervention. Large-scale trials are now underway for some of the most promising mechanisms, including GlyT1 antagonists and D1R agonists. The next few years will thus prove critical in determining whether results from promising Phase II studies can be translated into FDA-approved compounds. Improved methods for detecting presymptomatic cognitive decline in the late adolescent period would permit a shift from rehabilitation- to prevention-based treatment and potentially a dramatic decline in the long-term disability associated with schizophrenia.

SUMMARY POINTS

1. Cognitive impairment is a critical component of schizophrenia and contributes to impaired functional outcomes.
2. Social cognition may represent an independent construct from nonsocial cognition (neurocognition) in schizophrenia.

3. Deficits in *N*-methyl-D-aspartate receptor (NMDAR) function play a critical role in cognitive impairments associated with schizophrenia and are a primary target of current drug development programs.
4. Processes both upstream of NMDAR function, such as presynaptic glutamate release, and downstream, such as calcium homeostasis, may also contribute.
5. Intra- versus extrasynaptic NMDARs may play differential roles in cognitive function.
6. The NMDAR interactome may provide additional targets for clinical development.
7. Deficits in both subcortical and cortical neurophysiological processing may contribute to the overall pattern of cognitive impairment in schizophrenia.
8. Neurophysiological biomarkers such as mismatch negativity are critical for investigating mechanisms underlying cognitive impairment in schizophrenia, defining homogeneous subgroups, and assisting in early-stage clinical development.

FUTURE ISSUES

1. Current approaches for cognitive impairment associated with schizophrenia focus primarily on restoring function in individuals with established illness.
2. Ideal treatments may combine pharmacological approaches with cognitive remediation.
3. Noninvasive brain stimulation–based approaches, including transcranial electrical stimulation, may provide additional methods to target excitatory/inhibitory imbalance in schizophrenia.
4. More research is needed to define aspects of cognitive function that may continue to decline even during the initial stages of the illness.
5. More research is needed to develop methods to identify individuals showing presymptomatic cognitive decline.

DISCLOSURE STATEMENT

D.C.J. holds equity in Glytech, AASI, and NRx Pharmaceuticals. He has served as a consultant for SK Life Science, Biogen Cyclerion, and Boehringer Ingelheim. He has received research support from Cerevance. He holds intellectual property for use of NMDAR agonists in the treatment of schizophrenia, NMDAR antagonists for the treatment of depression, neurophysiological measures for detection of amyloid deposition, and parcel-guided approaches to brain stimulation.

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