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A REVIEW ARTICLE ON COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA

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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.

1. 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. 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. 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.

2. 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.

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. 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 As with earlier studies, individuals with schizophrenia showed a relatively flat distribution of impairment across domains with effect sizes of approximately including the Brief Assessment of Cognition in Schizophrenia (BACS) and the Penn Computerized Neurocognitive Battery (PennCNB). The batteries differ primarily based on the easebof 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 . 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 metallizing. In schizophrenia, social cognition deficits are best established in emotional perception/processing using tests of auditory and visual emotion recognition and in metalizing using tasks such as The Awareness of Social Inference Test (TASIT).Deficits in social cognition are of approximately equal magnitude to the deficits in neurocognition. 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 . 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.

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 . This view persisted throughout much of the twentieth century before studies of eye tracking and visual backward masking in the early 1970s provided objective evidence of sensory processing deficits independent of other aspects of neurocognitive impairment . 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.

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. By contrast, parvocellular neurons are specialized for slower but more graded analysis of fine spatial details and project primarily to ventral visual regions . 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 .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

1.Early auditory processing deficits in schizophrenia.

2.Distribution of tone-matching test (TMT) performance across controls versus schizophrenia (Sz) individuals.

3, 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. 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 (CC BY-SA 4.0), and panels cand d adapted from Reference (CC BY-SA 4.0).b deficits are observed preferentially in the detection of low-contrast (<16%), low–spatial frequency (<4 cycle/degree) , and motion 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). An important aspect of the magnocellular system's function is that it operates largely outside of conscious awareness. Thus, without specific testing bothndividuals with schizophrenia and clinicians will be unaware of the deficistDeficits in visual magnocellular function contribute to processes such as impaired contextual processing , cognitive control , object recognition , face emotion recognition, contour integration , and visual/oculomotor aspects of reading . 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 , may be useful but require further study.

3. NEUROCHEMICAL MODELS OF COGNITIVE IMPAIRMENT

Neurochemical conceptualizations of CIAS focus primarily on glutamatergic and DA brain systems. In addition, GABAergic systems may play a critical role in modulating local circuit activity, whereas anticholinergic side effects of antipsychotic medication may represent abconfound in CIAS studies.

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+/Ca2+-permeable ion channel and the Mg2+ 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 .Most pathological NMDAR mutations are associated with conditions that manifest during early development, including intellectual disability/developmental delay and epilepsy with aphasia. 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 . 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 . 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 . However, another is the shift in expression of GluN2B to GluN2A during development, leading to increased pathology as the changeover occurs . GluN2A subunits also regulate neuron-microglial interaction , providing a potential bridge between models.

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 inlclude 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.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. Moreover, meta-regression analyses suggest differential scaling with sample size, suggesting differences in biological effects between active and placebo treatments . 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. 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 .A more recent multicenter study evaluated effects of the glycine transport inhibitor BI 425809 across three doses 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 . Follow-up Phase III studies are investigating BI 452809 during long-term treatment, while a Phase II study is investigating the combined effects of BI 452809 and computerized cognitive remediation . Significant post hoc beneficial effects on cognition have also recently been reported for luvadaxista in association with improved MMN , but they require confirmation in larger trials.

4. CONCLUSION

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 presume comatic cognitive decline in the late adolescent period would permit a shift from rehabilitations prevention-based treatment and potentially a dramatic decline in the long-term disability associated with schizophrenia.

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