Editorial

Time to Re-focus onto Cognitive Symptoms in Schizophrenia

INTRODUCTION

Clinicians always feel helpless when faced with a person with residual symptoms of schizophrenia. Though the available antipsychotic agents have definitely reduced the disease burden and disability due to positive psychotic symptoms, the cognitive symptoms keep the affected person disabled and lead to poor functional outcomes. It is a cause of concern in routine clinical psychiatric practice. It has led to the FDA/NIMH initiative of Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) in 2004.[1] The multidisciplinary group which convened for MATRICS initiative proposed the clinical trial guidelines for the development of novel cognitive-enhancing agents in schizophrenia. They also designed the MATRICS Consensus Cognitive Battery, as a measurement tool[2] in research to find novel procognitive agents. In this article, we will review the current status of research into cognitive symptoms of schizophrenia and their management.

CONCEPTUAL ISSUES

What's in a Name? An awful lot!

Recently, Kahn and Keefe[3] argued to call-a-spade-a-spade by reaffirming that schizophrenia is a cognitive illness. They discussed that the erstwhile name "Dementia Praecox" suited schizophrenia best and that both Kraepelin and Bleuler gave prominence to the cognitive decline or cognitive deficits in its diagnosis and gave only a secondary (or, accessory) status to what we today call as "positive symptoms." The later emphasis on psychotic symptoms as the core of schizophrenia was an outcome of factors such as push for a psychological explanation of schizophrenia by Freudian school, Kurt Schneider's proposal to give prominence to first rank symptoms to aid reliability, and the excitement related to symptom resolution by dopamine antagonists. Kahn and Keefe's proposal to refocus is based on four threads of evidence.

- Low IQ and poor scholastic performance increase the risk for developing schizophrenia in a dose-response fashion
- There is a progressive cognitive decline between the ages 7 and 13 in people who go onto develop schizophrenia, which starts at least a decade before the onset of psychotic symptoms
- There is significantly lesser increase in cognition in patients compared to controls and larger degree of cognitive impairment in patients than that is observed before the onset of psychosis suggesting that cognitive performance may continue to decline after the onset of psychotic symptoms
- The mean cognitive underperformance during adolescence and at the onset of psychotic symptoms differentiates schizophrenia from the other major psychotic illness and bipolar disorder.

The proposal to view schizophrenia as a cognitive illness will impact the way, we formulate the diagnosis, treatment guidelines, and risk phenotype in research. This perspective will radically influence the discourse on at-risk psychosis and also encourage the use of (and research into) early interventions such as cognitive and behavioral therapies.

Change in drug target

Dopamine hypothesis which was the focus of drug discovery over the last six decades has now given place to newer hypothesis such as the N-methyl-D-aspartate receptor (NMDAR) hypofunction hypothesis and the modified dopamine hypothesis which give importance to glutamine and serotonin function, respectively.

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Newer drugs which are studied for the potential benefit in relieving cognitive symptoms are either those who act on novel serotonin receptors like 5HT1A or those who act on NMDAR. There is also a serious consideration to develop drugs which can be combined for the treatment of schizophrenia, similar to the multidrug therapy in tuberculosis or cancer.[4]

Recovery model

The newer and nuanced use of the term "recovery" does not refer to the older clinical use which focuses only on the reduction of symptoms but refers to an emphasis on a renewed sense of self and encouragement to return to a more meaningful and self-directed life.[4] However, the models of clinical and personal recovery can be used complementarily. This model gave rise to the "recovery movement" which is a service user led the movement and has encouraged the restorative philosophy of cognitive remediation therapies.

COGNITIVE SYMPTOM DOMAINS AND NEUROBIOLOGICAL RESEARCH

According to MATRICS,[2] there are seven cognitive domains which have to be assessed. They are – processing speed, attention or vigilance, working memory, verbal learning and memory, visual learning and memory, problem-solving, and social cognition. As most of these are easily understood, social cognition requires a bit of explanation. Social cognition consists of mental operations which are behind the capacity to perceive the intention and disposition of others in a certain context. It includes theory of mind, emotional recognition, social perception, and attributional style. Social cognition acts as a mediator between neurocognition and social functioning. Social cognition is described as a heterogeneous construct; therefore, the factors of metacognition, basic neurocognition, and personality traits have to be accounted for in its research.[4]

Although current literature considers the negative and cognitive symptoms of schizophrenia as distinct entities, there is an alternative view which deems it appropriate to study them together.[5] The fact that both these symptoms are primarily residual phase symptoms and that there is an overlap in concepts is used to argue that they are considered together, at least in research.

Intelligence research has given insights into the cognitive impairment in schizophrenia.[6] In people with schizophrenia, the processing speed domain is disproportionately impaired, which is a part of performance IQ or fluid intelligence. New research suggests that there is an abnormal frontoparietal neural network in schizophrenia that impairs the processing function which is required ultimately for environmentally adaptive behavior. Later research may elucidate the modifiability of this network and thereby inform the methods of cognitive remediation.

PHARMACOLOGICAL RESEARCH FOR COGNITIVE ENHANCERS IN SCHIZOPHRENIA

As discussed, the newer targets of drug action are being hypothesized to discover new drugs. One of them is the NMDA (glutamate) receptor hypofunction hypothesis. Findings of association between neuregulin-1 and schizophrenia, phencyclidine, and psychotic symptoms, and a subset of schizophrenia patients expressing anti-NMDAR antibodies have strengthened the glutamate or NMDA hypofunction hypothesis. This has led to the search for drugs which target NMDAR, which are currently in phase II or III trials.[7] Some of them are:

- Glycine site agonists such as Glycine and D-serine
- Glycine reuptake inhibitors like bitopertin
- Metabotropic type 5 receptor agonists
- α7 nicotinic agonists.

The second group of drugs is the newer atypical antipsychotic agents which are supposed to act through the serotonin receptors and enhance cognition in schizophrenia, based on the modified dopamine hypothesis. Researchers are aiming to find more than 0.5 standard deviation improvement in cognition which is known to substantially improve the quality of life for patients. Some of these drugs are – asenapine, lurasidone, aripiprazole, ziprasidone, perospirone, blonanserin, and tandospirone, apart from the earlier atypical agents such as olanzapine and clozapine. Proponents[8] of this view suggest that there are three threads of evidence. They are:

- Electrophysiological evidence: Olanzapine and perospirone have been found to increase P300 amplitudes (P300 is used as marker for attentive cognitive processes) and also concomitantly increase verbal memory and quality of life
- Neural network which mediates atypical antipsychotic action: 5HT1A receptor agonist is suggested to enhance cognition. Tandospirone, which is a 5HT1A partial agonist, has been shown to improve executive function and verbal memory in patients who were treated with typical antipsychotic agents. The mechanism of this effect has been suggested selective stimulation of 5HT1A receptors on gamma-aminobutyric acid (GABA) interneurons diminishes GABA neuronal activity which in turn disinhibits glutamate neurons. Glutamate activity

is credited with increased dopamine release in the prefrontal cortex
- Animal models of energy metabolism in the brain: Lactate dependent energy metabolism is associated with glutamatergic activity and energy supply in prefrontal cortex which is crucial for cognition. Tandospirone has been shown to inhibit the suppression of stress-induced lactate increase in prefrontal cortex in a rat model of schizophrenia.

Apart from 5HT1A receptors, other receptors such as 5HT7 receptors (e.g., lurasidone) are suggested to be important in influencing cognition in schizophrenia.[9] Other drugs such as donepezil and modafinil have been tested but showed no benefits.

In spite of this promising pharmacological research, many still argue that cognitive dysfunction in schizophrenia is unaffected by pharmacotherapy. They opine that the effect size rarely reaches more than 0.3 in both first-episode and chronic schizophrenia, and even this can be accounted for by placebo response and practice-related (or test-retest) response. It has been observed that though the pharmacological research is supported by basic science and small pilot trials, it fails to show any effect in larger replication trials.[10] This might be due to publication bias toward initial positive studies which lack methodologic and statistical rigor, biological heterogeneity, high placebo rates in psychiatry, high attrition, poor compliance with treatment, and concurrent substance use. Animal models might also fail to represent the complex neurodevelopmental and neurodegenerative abnormalities underlying cognitive impairment.

COGNITIVE REMEDIATION

Cognitive remediation therapies have consistently shown benefit in the treatment of cognitive symptoms. Multiple meta-analyses have demonstrated a robust medium effect size around 0.41 or 0.51 with the highest effects sizes with executive function and verbal working memory, which are fundamental components of cognition.[4] Cognitive remediation can be described as top-down approaches which use more complex skills to improve individual components of neurocognition or as bottom-up approaches which work on basic neurocognitive skills such as attention and advance to more complex skills such as problem-solving. They can also be described a compensatory or restorative approaches.

Compensatory approaches emphasize adaptation to environment by circumventing neurocognitive deficits. Cognitive Adaptive Training is one such therapy where behavioral principles of antecedent control and environmentally directed activity are used to cue and sequence adaptive behaviors. Restorative approaches, on the other hand, emphasize the plasticity of the brain and propose various methods to improve cognitive functions. Various therapies such as neuropsychological Educational Approach to Remediation, Neurocognitive Enhancement Therapy, Cognitive Remediation Therapy, and Cognitive Enhancement Therapy are used with an aim to restore the possible neurocognitive functions. These approaches are based on "recovery movement" philosophy which focuses on personalized recovery as opposed to clinical recovery. They creatively use computer-based interactive training methods in remediation. Many suggest that the procedural learning and targeted reinforcement in an individualized way helps improve cognitive impairment in schizophrenia. However, these interventions are difficult to implement due to their need for expertise, issues with patient adherence, and lack of standard approaches.[7]

CONCLUSION

Cognitive symptoms of schizophrenia cause huge disease burden and disability. Various pharmacological and remediation therapies are being used and explored to address cognitive impairment. Cognitive remediation has consistently shown benefit in this regard as opposed to minimal benefit from pharmacological procognitive agents. Negative symptoms have to be assessed whenever cognitive symptoms are assessed as these two phenomena overlap. Return of the focus onto cognitive symptoms in schizophrenia might help further research.

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