

# Current understandings about cognition and the neurobiological correlates in schizophrenia

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## ABSTRACT

Schizophrenia is a severe mental disorder. Cognitive deficits are one of the core features of schizophrenia. Multiple domains of cognition (executive function, attention/vigilance, working memory, verbal fluency, visuospatial skills, processing speed, and social cognition) are affected in patients with schizophrenia. Deficits in cognition led to impairment in the real world functioning. Identifying the cognitive deficits and early intervention is required for better functional outcome. This review focuses on conceptual understanding of cognition with its neurobiological correlates in schizophrenia and its different clinical implications.

**Key words:** Cognition, cognitive deficits, neurobiological correlates, schizophrenia

## Introduction

Schizophrenia is a severe mental disorder with complex and multifactorial etiology. The prevalence of schizophrenia is about 1% worldwide. It is the most common psychotic disorder worldwide with point prevalence of about 4.6/1000 population.<sup>[1]</sup>

The symptoms of schizophrenia can be broadly categorized into – positive symptoms, negative symptoms, affective symptoms, cognitive symptoms, and aggressive symptoms. Cognitive impairment in schizophrenia causes impairment in real-world functioning and significantly impairs the quality of life.<sup>[2]</sup> Schizophrenia causes dysfunction of the prefrontal cortex by several mechanisms such as perfusion defect, defective metabolism, and defective synaptic pruning, which is responsible for the higher cognitive functions such as planning, regulation, and execution of goal-directed activities.<sup>[2]</sup>

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## Evolution of Understandings about Cognition in Schizophrenia

Previously, cognitive symptoms in schizophrenia are considered to be the major symptoms of schizophrenia, which led to the perception that probably schizophrenia is like premature onset dementia; hence, Benedict Morel and Emil Kraepelin acknowledged this disorder as "dementia precoce" and "dementia praecox," respectively. Subsequently (in the early part of the 19<sup>th</sup> century), this perception was rejected and schizophrenia is presented as a distinct mental disorder with quite different pathophysiology and psychopathology. Whatever, cognitive symptoms observed in patients with schizophrenia were considered to be secondary to positive or negative symptoms. However, very recently in the last two decades, it was understood that cognitive deficits in schizophrenia are primary and core deficits.<sup>[3-5]</sup> The reasons for which the cognitive deficits in schizophrenia were given special attention as a distinct domain of symptoms are, due to a characteristic pattern of the cognitive symptoms in schizophrenia, stable deficits in cognition persisting throughout the

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**How to cite this article:** Kar SK, Jain M. Current understandings about cognition and the neurobiological correlates in schizophrenia. J Neurosci Rural Pract 2016;7:412-8.

### Access this article online

#### Quick Response Code:



#### Website:

www.ruralneuropractice.com

#### DOI:

10.4103/0976-3147.176185

course of illness and persistence of cognitive deficits independent of remission of other symptoms of schizophrenia.<sup>[5]</sup>

It is also recently understood that the socio-occupational decline in patients with schizophrenia was mostly due to core cognitive deficits.<sup>[3,4]</sup> Even during the phases of symptomatic remission, these cognitive deficits persist, which can be explained by the persistent brain changes in these patients.<sup>[4]</sup> Structural brain changes in schizophrenia are frequently seen in the frontotemporal region, which attributes to the impairments in neuropsychological functions.<sup>[6]</sup>

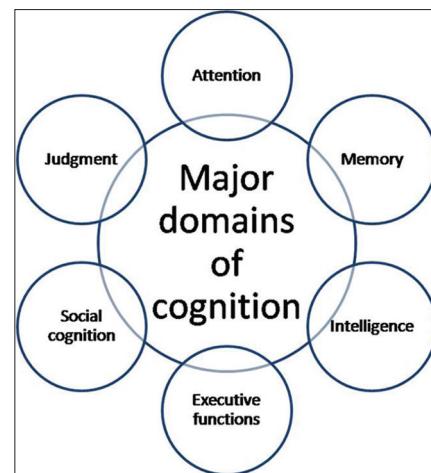
The impairment of cognition is not only limited to patients suffering from schizophrenia; research evidence are also suggestive of cognitive dysfunction in otherwise normal individuals with high risk of psychosis, first-degree relatives of patients with schizophrenia.<sup>[7-9]</sup> Cognitive deficits are found to exist in patients with schizophrenia as early as before the onset of illness, early phase of illness and remain stable over time in patients not receiving any specific intervention.<sup>[9,10]</sup> Few recent studies had revealed that cognitive deficits in schizophrenia depend on the age of onset; earlier is the onset, more will be the deficits.<sup>[11-13]</sup> Duration of schizophrenia has little impact on the already existing cognitive deficits.<sup>[11-13]</sup> The deficits in cognition persist even during the phase of remission.<sup>[9]</sup>

## Understanding Cognition and Cognitive Deficits in Schizophrenia

Cognition is an important brain function. It is the sum total of mental processes that enables us to acquire knowledge and keeps us aware of our surroundings and thus enable us to arrive at appropriate judgments. It is cognition that determines skills such as problem-solving, decision-making, and creativity. Some major cognitive domains are summarized in Figure 1.

Cognition helps an individual for functioning in the real world. Attention, concentration, memory, intelligence, judgment, executive functions, and social cognition are some major cognitive functions. These cognitive processes help in delivering various functions. Processing speed is the fastness to deliver these functions, which is dependent on the integrity of neuronal network as well as white matter. Impairment in cognitive processing results in difficulty in delivering different tasks leading to disability.

Cognitive impairments are one type of core symptoms in schizophrenia. Patients with chronic schizophrenia are impaired in a wide range of cognitive functions which



**Figure 1:** Major domains of cognition

include verbal memory, working memory, motor speed, attention, executive functions, and verbal fluency.<sup>[14-17]</sup>

Nearly four out of every five individuals suffering from schizophrenia exhibit some sort of cognitive deficits which hamper the normal functioning of the individuals.<sup>[18]</sup> The cognitive deficits in schizophrenia can be attributed to the under-activity of N-methyl-d-aspartate receptors.<sup>[19]</sup> Nair *et al.*, in a recent meta-analysis, established that insight for psychosis has strong correlation with the important cognitive parameters such as executive function, memory, and intelligence as well as total cognition.<sup>[20]</sup> Cognitive dysfunction in schizophrenia is believed to be an endophenotype which manifests across the schizophrenia spectrum disorders.<sup>[21]</sup> Most dysfunctional cognitive functions attribute to the disrupted cortico-striato-thalamo-cortical network.<sup>[21]</sup>

### Attention and vigilance

Attention refers to processes of how an individual becomes receptive for external or internal stimuli.<sup>[22]</sup> The critical attributes of attention are focus, selectivity, exclusiveness, and vigilance. Attention requires rapid encoding of information.

In schizophrenia, attention impairment is a core cognitive deficit.<sup>[23]</sup> Perhaps deficient rapid encoding of information is responsible for attention impairments in schizophrenia.<sup>[24]</sup>

### Learning and memory

Memory is the outcome of learning. The human memory is a complex system by which an individual registers, stores, retains, and retrieves information.<sup>[22]</sup>

In schizophrenia, different domains of learning and memory are affected. Studies suggest that working

memory, visuospatial memory, and verbal memory are common to be affected in schizophrenia.<sup>[3]</sup> In schizophrenia, there also occurs impairment of emotional modulation of memory and attention.<sup>[25]</sup> They initially take longer time to encode information than do normal people; however, they tend to perform better with repeated exposure.<sup>[26-28]</sup> They do not use effective learning strategies, such as semantic clustering, not even when told to cluster the information. However, they tend to show intact recognition memory<sup>[29]</sup> thus, suggesting more impairment in explicit compared with implicit memory.<sup>[30]</sup>

### **Working memory**

Working memory refers to a multicomponent cognitive system that is serving to hold a limited amount of information "online" for a short period of time and to simultaneously manipulate the information so that it is available for further cognitive processing, or to guide response selection relevant for a specific context.<sup>[31]</sup> The working memory system comprises the core executive domain with two short-term storage systems of information, visuospatial network for visual information, and the articulatory loop for phonological information.<sup>[32]</sup>

It has been argued that impaired working memory is the core cognitive deficit in schizophrenia, associating with the clinical picture and the functional consequences of the disorder.<sup>[33,34]</sup> Both verbal and nonverbal working memories are dysfunctional in schizophrenia.<sup>[29,35,36]</sup>

Working memory plays an important role during the encoding process. Seidman *et al.* found that during a verbal learning task in which the words can be semantically clustered, the differences between schizophrenia patients and healthy controls were eliminated when the results were controlled for scores in a working memory task.<sup>[37]</sup> It is likely that abnormalities in working and strategic memory contribute substantially to the verbal encoding deficit in schizophrenia as well as to other cognitive functions.

### **Executive function**

Executive functions involve the use of information rather than the fundamental processing of information and refer to the processes by which an individual realizes purposeful behavior.<sup>[22]</sup> The unique skills used for expansion, modulation, and implementation of goal-directed activities are the executive functions of the brain, which is the amalgamation of several complex mental abilities.

Patients with schizophrenia have deficits in executive function and theory of mind.<sup>[38]</sup> The deficits of executive function and theory of mind seem to be

independent of each other.<sup>[38]</sup> Dysfunction of the executive function is not only limited to patients of schizophrenia but also reported in their healthy first-degree relatives.<sup>[39,40]</sup> Executive dysfunction in schizophrenia leads to impairment in maintenance and shifting of the responses according to situation and dysfunctional goal-directed activity.<sup>[23,41,42]</sup>

### **Information processing and processing speed**

The term information processing is used to describe the process of taking information and encoding it in such a way that it can be understood and recalled when appropriately cued. Memory and perception are stages in information processing.<sup>[43]</sup> Processing speed is the rapidity by which information processing occurs.

Many neurocognitive tests require subjects to process information rapidly and can be compromised by impairments in processing speed. Standard examples of this type of task are the coding tasks, which have been found to demonstrate the most severe deficits in schizophrenia.<sup>[44]</sup>

### **Problem-solving**

Problem-solving is the complex mental processes of using previously learned information to identify solutions to new problems. Patients with schizophrenia, who are impaired on measures of executive functions, have difficulty adapting to the rapidly changing world around them.

Poor problem-solving ability in schizophrenia can be a core deficit or may be secondary to deficit in other major areas of cognition such as task initiation, attention, concentration, and working memory; core deficits in executive functions such as difficulty in shifting task (due to impaired ability to think alternatively), repetition of the errors (perseveration), and slower rate of processing speed may prolong the problem.

### **Social cognition**

Social cognition refers to "the ways social events are interpreted, analyzed and mentally represented." It also provides an information-processing framework for understanding how the construal of self and others affects social discourse and psychological life.

In studies, social cognitions such as recognition and discrimination of faces and emotions are found to be impaired in patients with schizophrenia, which compromises the socio-occupational life significantly.<sup>[45,46]</sup> McCleery *et al.*, in their study, found that there was no difference in the severity, pattern, and involvement of different cognitive domains in patients with the

first-episode schizophrenia and chronic schizophrenia; however, social cognition and working memory were relatively preserved in the early phase of illness.<sup>[47]</sup> Compromised cognitive function in schizophrenia results in wrong self-appraisal of empathetic abilities.<sup>[48]</sup>

Recently, activity of mirror neurons in patients with schizophrenia has been focussed in several studies and it is believed that mirror neurons have a unique role in social cognition though robust evidences are lacking.<sup>[49]</sup> In schizophrenia, there is dysfunction of the mirror neuron system which may attribute to deficits in social cognition.<sup>[49]</sup> Impaired cortical inhibition may also have role in impairment of social cognition in patients with schizophrenia.<sup>[50]</sup>

In several studies, it was found that patients with schizophrenia had gross decline in general intellectual ability on the neuropsychological assessments.<sup>[17,23,51-54]</sup> Deterioration of intellectual functioning is not only attributable to decline in performance IQ or verbal IQ, but rather more related to deficits in specific cognitive domains such as attention, processing speed, and working memory.<sup>[23,51]</sup>

## Cognition Assessment Tools in Schizophrenia

Cognitive deficits in patients with schizophrenia cause significant impairment in real world functioning. Identifying cognitive deficits will help in planning for specific therapeutic intervention as well as rehabilitation. Early identification of cognitive deficits helps in early intervention and better outcome.

Several tools have been developed to assess cognition comprising of different cognitive tasks employed, especially for patients with schizophrenia. Numerous batteries have been developed which are comprehensive and give detailed description of the multiple domains of cognition. However, such batteries are difficult to be applied in many settings because of the time constraints. The kind of test to be used depends on the research question to be answered. For example, if the research questions want to assess the effectiveness of an intervention, then a detailed evaluation needs to be done while if it involves assessing a particular domain, then a brief battery will do.<sup>[55]</sup> The details of some of the cognitive test batteries are given below in Table 1.

There are several computerized batteries such as the Cambridge Neuropsychological Test Automated Battery,<sup>[62]</sup> the Cognitive Drug Research Cognitive

Assessment System,<sup>[63]</sup> and the CogTest Battery<sup>[64]</sup> which have been applied to patients suffering with schizophrenia, but they have certain operational difficulties such as cost, portability, regular software, and hardware version change.

## Filling the Gaps

Many strategies have been attempted to improve cognition in patients with schizophrenia. Earlier studies revealed that antipsychotics improve cognition in patients with schizophrenia.<sup>[65]</sup> Inada *et al.* in their study on animal models found that antipsychotics stabilize the processing of emotion and cognition.<sup>[65]</sup> The improvement of cognition due to antipsychotic treatment may be due to improvement of positive symptoms, affective symptoms, or few negative symptoms and unlikely due to improvement of core cognitive deficits.<sup>[3]</sup> Keedy *et al.* (2015), in a recent study, concluded that antipsychotic medications improve the functioning of dorsal cortical attention network.<sup>[66]</sup>

Large studies found that antipsychotics have little role in cognitive deficits due to schizophrenia.<sup>[67-69]</sup> and supplementation of cholinergic, antiglutamatergic, and serotonergic agents may have some role in cognitive enhancement.<sup>[69]</sup> As per the recent understanding, atypical antipsychotics are not different from typical antipsychotics; so far, the cognitive improvement in schizophrenia is concerned.<sup>[70]</sup> The above findings suggest that antipsychotic treatment may bring some sort of cognitive improvement indirectly by controlling the positive symptoms, affective symptoms and to some extent the negative symptoms; however, the possibility of improvement in core cognitive deficits are unsatisfactory.<sup>[70]</sup> Probably some more innovative approach is required to fill this gap.

Several nonpharmacological strategies such as cognitive remediation, exercise, and social skill training are now being used for the management of cognitive deficits in such patients. Cognitive remediation therapy is a highly effective modality of intervention which improves the cognitive performance and social functioning.<sup>[71,72]</sup> This intervention modality can also be effectively used in early-onset schizophrenia in adolescents.<sup>[72]</sup>

Currently available medications used for the treatment of schizophrenia are unable to address the cognitive deficits.<sup>[19]</sup> Recent evidence suggest that adenosine and its receptors have role in neuromodulation and brain homeostasis which has a significant role in neuroprotection and cognitive processing.<sup>[73]</sup> Drugs

**Table 1: Summary of important cognitive test batteries**

Test	Developed by	Areas measured	Time taken to complete the test
Measurement and Treatment Research to Improve Cognition in Schizophrenia <sup>[56]</sup>	NIMH (2006)	Speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning, problem-solving, and social cognition	65 min
The Schizophrenia Cognition Rating Scale <sup>[57]</sup>	Keefe <i>et al.</i> , (2006)	Speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning, and problem-solving	12 min to complete
The University of California San Diego Performance-Based Skills Assessment <sup>[58]</sup>	Patterson <i>et al.</i> , (2001)	Skills for daily living Household chores (communication finance, transportation, and planning recreational activities)	30 min
Brief Cognitive Assessment <sup>[59]</sup>	Velligan <i>et al.</i> , (2004)	Verbal fluency (letters and categories), attention/vigilance, processing speed, verbal learning	15 min
The Repeatable Battery for the Assessment of Neuropsychological Status <sup>[60]</sup>	Randolph, (1998)	Mainly test for dementia comprising tests of memory, language and visual perception	45 min
The Brief Assessment of Cognition in Schizophrenia <sup>[61]</sup>	Keefe <i>et al.</i> , (2004)	Executive functions, verbal fluency, attention, verbal memory, working memory, and motor speed	35 min

acting through adenosine receptors likely to influence the cognitive performance and have a great scope for enhancing cognition and neuroprotection in schizophrenia and other disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease where cognition is commonly effected.<sup>[73]</sup> Other agents, which promote neurogenesis and neuroprotection (e.g. anti-inflammatory agents, antioxidants, etc.,) are also likely to offer procognitive effect.<sup>[74,75]</sup> Research evidence are also in favor of galantamine and memantine for the treatment of cognitive deficits in schizophrenia.<sup>[19]</sup>

Kalache *et al.* (2015), in their study, attempted to explore the correlation of cognitive impairment in schizophrenia with functional outcomes across lifespan and found that communication skills, comprehension and planning of recreational activities skills, financial skills, transportation skills, and household management skills depend upon the intactness of cognitive functioning.<sup>[76]</sup> Hence, improvement of cognitive functioning in schizophrenia is likely to cause improvement in these life skills across life time.<sup>[76]</sup>

## Conclusion

Targeting the cognitive deficits in the early phase of psychosis is likely to be more effective in preventing disability.<sup>[4]</sup> Insight about cognitive deficits has a lot of clinical implications. Patients with insight to cognitive deficits may have better treatment adherence and are more amenable for cognitive rehabilitation.<sup>[77]</sup> Cognitive domains have specific neurobiological correlates. Involvement of specific brain regions attributes to the unique pattern of cognitive deficit in patients with schizophrenia. Though there is significant overlapping of the brain areas involved

in other psychiatric disorders (e.g. mood disorder, dementia), which also produces overlapping in the mold of cognitive deficits.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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