

## COGNITIVE DEFICIT IN SCHIZOPHRENIA: AN OVERVIEW

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### SUMMARY

*Depressive mood, anxiety, delusions, hallucinations and behavioral disturbances have been traditionally recognized as leading symptoms of mental disorders. However, cognitive symptoms went under-recognized or declined. Today there is robust evidence that cognitive dysfunction is present in the majority of mental disorders and is also related to impairments in the functioning of the persons with mental illness. It is proposed that aberrant brain neuronal network connectivity, arising from interplay of genetic, epigenetic, developmental and environmental factors, is responsible for cognitive decline.*

*In schizophrenia, dysfunctions in working memory, attention, processing speed, visual and verbal learning with substantial deficit in reasoning, planning, abstract thinking and problem solving have been extensively documented. Social cognition – the ability to correctly process information and use it to generate appropriate response in situations, is also impaired. The correlation of cognitive impairment with functional outcome and employment, independent living and social functioning has emphasized the need for development of the treatments specific to cognition. It is considered that brain neuroplasticity allows for re-modulating and compensating the impairment process which could give opportunity to improve cognitive functions. Therefore, there is a need for comprehensive clinical assessment and follow-up of cognitive decline in mental illness. Implementation of specific treatment strategies addressing cognitive decline in mental illness, like new drugs, distinct cognitive-behavioural therapy, psychoeducation, social skills training and remediation strategies should be strongly endorsed targeting recovery and reduction of disability due to mental illness.*

**Key words:** cognition - cognitive deficits - schizophrenia

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### INTRODUCTION

Due to the apparent manifestation, symptoms like depressive mood, anxiety, delusions, hallucinations and behavioral disturbances have traditionally been recognized as the leading symptoms of mental disorder. Cognitive changes, however, were systematically neglected – either under-diagnosed or even ignored. Owing to the development of the specific neuro-cognitive diagnostic instruments and brain imaging techniques, it has been recognized that cognitive symptoms accompany the majority of mental disorders and, in some of them, have prominent impact. There is evidence that cognitive problems are most pronounced in the schizophrenia (Medalia & Revheim 2002). Almost 98% of people with schizophrenia will experience problems with cognition. Since schizophrenia usually starts in adolescence or young adulthood, at that time the most dramatic decline in cognition may be seen. Because of the psychotic symptoms, like delusions and hallucinations, cognitive problems may be overlooked, until the psychotic symptoms stabilize. Drop in school performance may be the first sign for children and adolescents that something is going wrong with cognitive abilities. Dysfunctions in working memory, attention, processing speed, visual and verbal learning with substantial deficit in reasoning, planning, abstract thinking and problem solving have been extensively documented in schizophrenia (Heinrichs & Zakzanis 1998.). Cognitive problems may be

evident even before psychotic symptoms start. One of the earliest cognitive symptoms of schizophrenia is poor attention, but difficulty with memory and visual motor speed may also be evident before the onset of psychotic symptoms. A large scale retrospective study showed cognitive deficits to be among one of the first signs in individuals who were later diagnosed with schizophrenia (Häfner et al. 1992).

In schizophrenia there is also a decline in the social cognition. Social cognition is ability to correctly process information and use it to generate appropriate response in situations. Impairments in social cognition have negative impact in overall functioning, resulting in behavioural and relationship issues. Difficulties in social functioning are leading to social isolation, exacerbate symptoms, and promote relapses. There is correlation between functional outcome of cognitive deficits and employment, independent living, social and community functions and treatment decisions (Janović & Bajs 2005, Fett et al. 2011, Mihaljević-Peješ et al. 2016.). That could further significantly interfere with rehabilitation processes (Prouteau et al, 2005).

Therefore, there are considerable activities to develop new treatments for cognitive impairment and recovery-focused approaches. Facing the development of new drugs and methods in the treatment of mental disorders, cognitive impairment should be addressed as one of the primary goals of treatment and rehabilitation.

## NEUROBIOLOGY OF COGNITIVE DEFICIT

Cognitive impairment is regarded to be induced by various interacting genetic, epigenetic, developmental and environmental factors. Changes are expressed both at the level of neurons and glia and at the level of neural networks (Millan et al. 2012). Cognition can be best understood in terms of complex networks operating over multiple temporal scales and incorporating diverse dimensions: from cellular cascades to cerebral circuits (Millan et al. 2012).

Schizophrenia is neurodevelopmental and neurodegenerative disorder. In schizophrenia, abnormality of brain development begins in the prenatal life, intensifies during childhood and continues during adulthood (Gross & Huber 2008). Brain changes can be explained as the cumulative effect of neurodevelopmental abnormality, change in neuroplasticity and alteration in neuronal maturation (Gourion et al. 2004). Neurodevelopmental changes in schizophrenia alter the BDNF (Brain derived neurotrophic factor) which mediated hippocampal neuroplasticity, attributing to the cognitive deficits (Nieto et al. 2013).

Research of cognitive impairments in schizophrenia have historically been focused on cortical deficits, but subcortical areas are also involved in cognition. Impaired memory performance in schizophrenia is associated with striatum and thalamus (Anticevic et al. 2011), and poor executive function in schizophrenia is partially connected with dysfunction of thalamus (Minzenberg et al. 2009). Furthermore, Koshiyama et al. (2018) investigated association between volumes of subcortical structures and neurocognitive and socio-functional indices in a large sample of patients suffered from schizophrenia with a mean duration of illness of 11 years. In the patient group, the study showed correlation between the volume of the right nucleus accumbens and the Digit Symbol Coding Score, which is known as a distinctively characteristic index of cognitive deficits in schizophrenia.

Cognition is also largely influenced by genetic factors. Among the various domains of cognition, heritability has maximum impact on working memory and intelligence (Touloupoulou et al. 2007). There are several genes associated with schizophrenia that could affect the neuroplasticity. *DISC1* (The disrupted in schizophrenia 1) gene regulates the process of neuronal growth, expansion and migration in the developing brain. *NRG1* (*Neuregulin 1*) is candidate gene have some role in regulating synaptic plasticity in schizophrenia. *Akt1* is found to play an important role in neurogenesis in hippocampus and *DTNBP1* (dystrobrevin binding protein 1) gene influences the cognitive ability in patients. (Tripathi et al. 2018).

Genome-wide association studies (GWASs) of general cognitive function and association between cognitive function and genetic susceptibility to schizophrenia were also reported. In the last decade, large-scale GWASs (n>30,000) of general cognitive function and

schizophrenia have shown that substantial proportions of the heritability of the cognitive function and schizophrenia are explained by a polygenic component consisting of many common genetic variants with small effects (Ohi et al. 2018).

In the persons with schizophrenia, development of aberrant connection in the brain is resulting from abnormal synaptic plasticity and dysconnectivity in neuronal network. Some important neuromodulatory neurotransmitters like dopamine, acetylcholine and serotonin play a major role in abnormal synaptic plasticity (Stephan et al. 2009). Imbalance in dopaminergic, glutamatergic and gamma-aminobutyric acid (GABA) activity are proposed to be responsible for working memory deficits in schizophrenia (Van Snellenberg et al. 2016).

Cognition displays considerable redundancy and pleiotropy at all levels of integration: from intracellular signals, to neurons, to cerebral nuclei (Bullmore & Sporns 2009). The disruption of many elements can be compensated by others with similar roles. This organization affords considerable resilience to disruption (Bullmore & Sporns 2009). The fact that some disruptions could be compensated gives the opportunity to renovate cognitive functioning in patients with schizophrenia.

## TREATMENT OF COGNITIVE DEFICIT

Increasing awareness of the seriousness of cognitive dysfunction in schizophrenia, and recent insights into its potential causes, have triggered substantial efforts to discover new drugs specific for restoring cognitive function (Wallace et al. 2011). The array of drugs under investigation, target cellular signals, LTP (long-term potentiation) and LTD (long-term depression), network synchrony, transmitter release and dendrite spine formation. Still, there has been limited positive clinical feedback so far for many of the putative pro-cognitive drugs.

Apart from new drugs, other more available interventions like cognitive-behavioral therapies, psychoeducation and social skill training, could be used to improve cognitive disability in schizophrenia. However, the conventional psychological interventions have failed to adequately address the cognitive deficits in schizophrenia. Yet it seems that cognitive remediation therapy could have promising results.

The recent definition of cognitive remediation emphasizes an improvement of functional outcomes by addressing the cognitive deficits through the scientific principles of learning enhancement. The effectiveness of cognitive remediation can be achieved through delivering the therapy in various contexts to improve functioning of daily activities (Medalia & Saperstain 2013).

Cognitive Remediation Experts Workshop (2010) defines cognitive remediation for schizophrenia as “a behavioural training based intervention that aims to improve cognitive processes (attention, memory, executive

function, social cognition or metacognition) with the goal of durability and generalisation” (Cognitive Remediation Experts Workshop, Florence, 2010) (Barlatti et al. 2013). Cognitive remediation strategies have two models: compensatory and restorative (Medalia & Saperstain 2013). The compensatory treatments aim at eliminating or bypassing the specific cognitive deficit. Residual cognitive abilities are combined with individual environmental resources, for example simplifying daily routine and improving adherence (Velligan et al. 2008). Restorative methods are based on neuronal plasticity, allowing for the capacity of the brain for repairing and correcting a specific deficit (Medalia & Saperstain 2013). Finally, the combination of pharmacotherapy and cognitive remediation or similar approaches could have best result in overall recovery in schizophrenia.

## CONCLUSION

Cognitive impairment is prominent and persistent clinical feature in schizophrenia with high impact on life-long disability of the persons suffering from schizophrenia. In recent years major advances in the understanding of the cellular and neuronal network mechanisms controlling cognition have been achieved. Identification of novel drugs and psychological and other non-pharmacological treatments underpin the hope that it should be possible to improve declined cognitive performance in schizophrenia. Restoring cognitive function or bypassing cognitive impairment could significantly contribute to better outcome and recovery in schizophrenia.

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### Contribution of individual authors:

All authors contributed equally to the preparation of the manuscript.

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