



A review of neurocognitive outcomes in early-onset schizophrenia spectrum disorders after treatment

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Abstract:

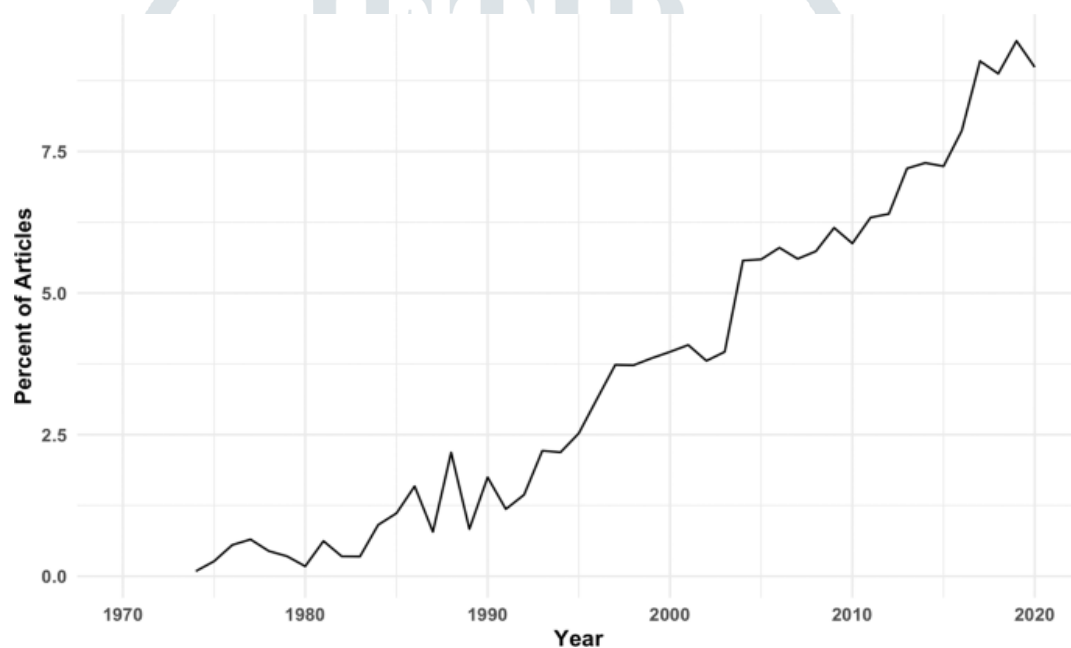
To understand the effectiveness and tolerance of psychosocial and psychopharmacological therapies for young people with early-onset schizophrenia spectrum disorders (EOS) in a better way, researchers have reviewed the literature. A justification for pragmatic psychopharmacology in EOS is observed, covering dose, switching, and the monitoring and control of side effects. These are linked to critical clinical variables such as scholastic performance, negative symptoms, and adaptive functioning. Adolescents with early-onset schizophrenia-spectrum disorders (EOS) offer special neurodevelopmental data that could advance the knowledge of schizophrenia across the lifespan as they are in a stage of substantial brain maturation. The literature on adults shows that compared to other disease aspects, neurocognitive impairments are a stronger predictor of social and role performance. One of the main characteristics of schizophrenia is cognitive impairment, which is more prominent in EOS than in later-onset cases. Nevertheless, little is known about

the long-term evolution of global cognition in EOS or the ways in which early disease symptoms impact cognition over time.

Keywords: Psychosocial, psychopharmacological, early-onset schizophrenia spectrum disorders (EOS), negative symptoms, neurocognition, adaptive function.

INTRODUCTION

Schizophrenia, a chronic mental illness, is typified by a wide range of symptoms, such as hallucinations, delusions, disordered speech, or behaviour, and diminished cognitive function ^[1]. Schizophrenia patients frequently struggle in relationships, at workplace, in classroom, and in the society generally. They could appear to have lost contact with reality, feel scared, and withdrawn. These patients can be managed with the right care. For many patients and their families, the disease is incapacitating due to its early start and protracted duration ^[2]. Negative symptoms, which are defined by loss or deficiencies, and cognitive symptoms, which include problems with attention, working memory, or executive function, frequently lead to disability. Furthermore, positive symptoms including delusions, and hallucinations might lead to relapse ^[2,3]. Since schizophrenia is inherently heterogeneous, opinions on its genesis, pathophysiology, and diagnostic standards are divided. Researchers have been unable to determine the exact cause of schizophrenia for over a century ^[2]. However, it is generally acknowledged that a combination of factors, such as genetic predisposition and environmental impacts, lead to the different phenotypes of the condition ^[1].



Increase in incidence of cognitive impairment in schizophrenia ^[3]

ETIOLOGY:

GENETIC FACTORS:

The possibility that schizophrenia develops as a result of prenatal exposure is one theory. Six obstetric problems that have been linked to the development of schizophrenia in later life are haemorrhaging during pregnancy, gestational diabetes, emergency vaginal delivery, hypoxia, and low birth weight ^[1]. Researchers have been particularly interested in foetal abnormalities during the second trimester, which is a crucial stage in embryonic neurodevelopment. During this time, infections and high stress levels have been associated with a twofold increase in the likelihood that offspring may experience schizophrenia.

COGNITIVE CHEMISTRY:

Individuals suffering from schizophrenia may have uncontrolled release of chemicals called neurotransmitters in the brain, which regulate specific nerve cell pathways, or "circuits," that impact behaviour and thought processes. Considered as a polygenic disorder, schizophrenia arises from the co-occurrence of multiple genes with little effects that raise the likelihood of illness when specific alleles are present ^[3].

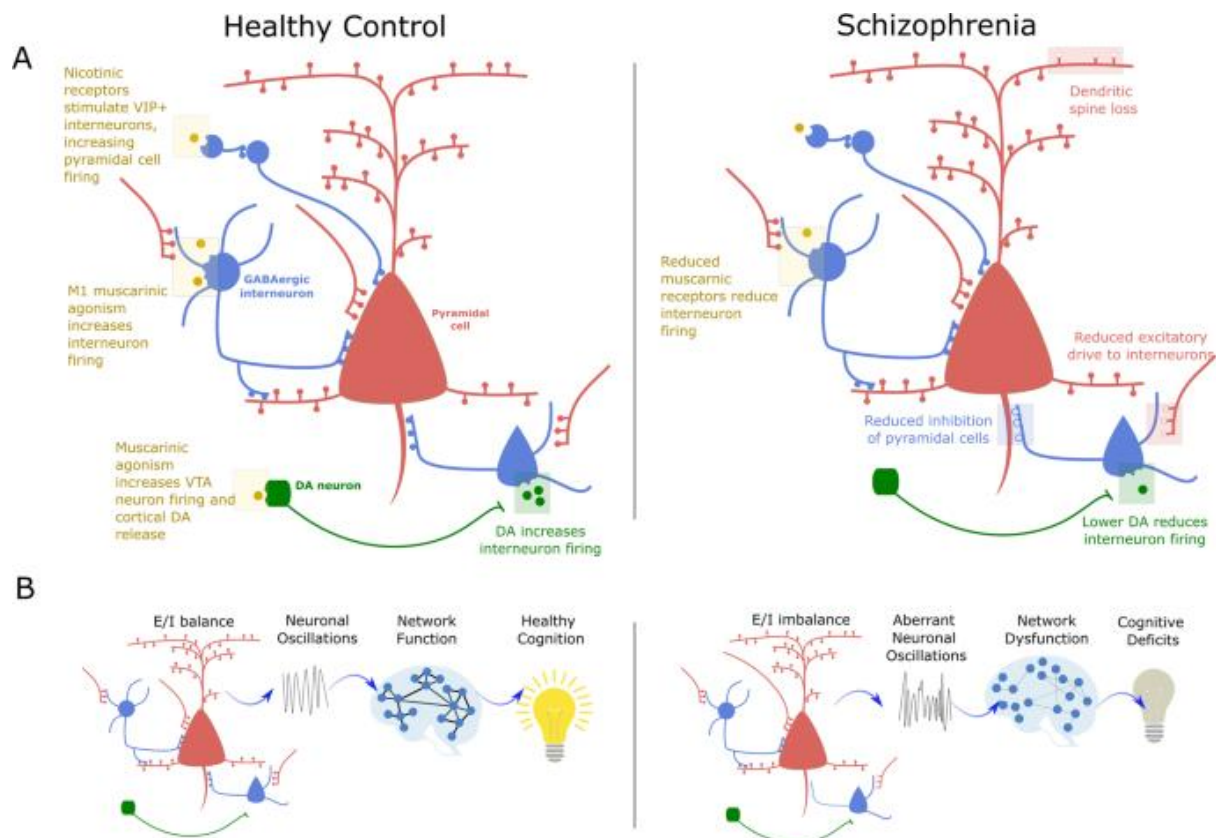
SOCIAL AND ENVIRONMENTAL FACTORS:

Social and environmental variables may also contribute to the onset of schizophrenia, particularly in those who are predisposed to the illness. People living in an urban region, along with a member of minority ethnicity, experiencing childhood trauma, and social isolation are all environmental factors associated with schizophrenia. Furthermore, societal pressures like prejudice or financial hardship can make people more prone to delusional or paranoid thinking ^[1,3].

The assumption that genetic factors contributes significantly to the development of schizophrenia is supported by scientific evidence; two studies have indicated that the probability of illness is roughly 10% for first-degree relatives and 3% for second-degree relatives. If one of the twins is monozygotic, there is a 48% chance that the other will also have schizophrenia; with dizygotic twins, the risk is between 12% and 14%. The likelihood that a child with schizophrenia will be born is about 40% if both parents have the disorder ^[1].

PATHOPHYSIOLOGY OF COGNITIVE IMPAIRMENT:

Schizophrenia is linked to abnormalities in numerous neurotransmitters and brain circuits ^[3]. A common pathway that is essential to cognitive functioning appears to be shared by many of these, and it is the disturbance in balanced interactions between excitatory and inhibitory (E/I) neurons in cortical microcircuits that is hypothesized to play a role in causation of Schizophrenia. While inhibition fine-tunes neurons' responses to enable accurate neuronal representations, excitation permits neurons to activate in response to inputs. For the brain processes that underpin cognition, the two must be in harmony. The glutamatergic, GABAergic, cholinergic, and dopaminergic systems plays a crucial role in schizophrenia, and in normal cognitive function, and maintaining the balance between emotions and intelligence.



Neurocognitive dysfunction in Schizophrenia ^[3]

- A. E/I balance in healthy individuals and processes of disturbance in schizophrenia are influenced by glutamatergic, GABAergic, dopaminergic, and muscarinic pathway.
- B. E/I equilibrium and thinking. Gamma oscillations are produced in healthy people by interactions between excitatory pyramidal cells and inhibitory interneurons. These oscillations are linked to functional brain networks that can be seen using functional MRI imaging, and all levels of the networks are connected with normal cognitive function. Cortical disinhibition may be caused by intrinsic interneuron impairments or alterations to muscarinic and dopaminergic signalling in persons with schizophrenia. The disorder's abnormal gamma activity and functional networks would be explained by this disinhibition, which would also exacerbate cognitive deficits.

SIGNS AND SYMPTOMS:

Positive symptoms:

Delusions: These are erroneous, contradictory, and occasionally bizarre beliefs that a person has but will not give up despite being presented with the truth ^[2]. A person suffering from delusions could think, for instance, that others are trying to harm them, that they are God or the devil, or that others can hear their thoughts.

Hallucinations: Unreal sensations are a feature of hallucinations. The most prevalent hallucination in individuals with schizophrenia is hearing voices. The voices could criticize the person's actions, make fun of them, or provide directives. Less common forms include experiencing a funny taste in your tongue, sensing objects on your skin even when nothing is touching it, tasting strange aromas, and seeing things that are not there.

Catatonia: A person suffering from this illness may cease talking and remain motionless for extended periods of time.

Cognitive Symptoms: Impairments in

- Knowing information and applying it to decision-making (what a physician could refer to as weak executive functioning)
- Concentrating or being attentive
- Utilizing their newly acquired knowledge as soon as possible (this is known as working memory)
- Acknowledging the existence of any of these issues.

Negative symptoms:

- Absence of feelings or a restricted emotional spectrum
- Retraction from social interactions, family, and friends
- Decreased enthusiasm, Speaking less, Decreased drive
- loss of enjoyment or life enthusiasm
- Inadequate personal grooming and hygiene practices.

Neurocognitive impairment in early-onset of schizophrenia

The clinical condition of schizophrenia is complex and has a wide range of manifestations, comorbidities, and outcomes [4]. According to the network hypothesis of psychiatric diseases, certain systems of symptoms either directly cause other symptoms to manifest or are linked to other symptoms. The diagnosis of early-onset schizophrenia (EOS) is made if symptoms appear before the age of eighteen. Schizophrenia has a 1% lifetime prevalence, and many people are diagnosed before the age of 18. The literature on adults shows that compared to other disease aspects, neurocognitive impairments are a stronger predictor of social and role performance. In a similar vein, baseline neurocognitive parameters were linked to social and community functioning at follow-up in a recent 13-year follow-up study of EOS. Adolescents with early-onset schizophrenia-spectrum disorders (EOS) offer special neurodevelopmental data that could advance our knowledge of schizophrenia across the lifespan because they are in a stage of substantial brain maturation. The findings imply that the core components of the network of symptoms are cognition, social functioning, and occupational functioning. One of the main characteristics of schizophrenia is cognitive impairment, which is more prominent in EOS than in later-onset cases. Nevertheless, little is known about the long-term evolution of global cognition in EOS or the ways in which early disease symptoms impact cognition over time.

Discussion:

Study 1: According to **Charlotte. M et al., [2018]** [5] at baseline, clinical characteristics (PANSS, duration of untreated psychosis [DUP], hospitalizations, suicide attempts, and remission) were assessed in thirty-one EOS patients and seventy-three controls (age 12–18). At baseline and after one and two years, neuropsychological evaluations using the MATRICS Consensus Cognitive Battery (MCCB) were carried out, and composite scores of overall performances were computed. For the analysis, a linear mixed model was used. According to the current study, global cognition in EOS patients had a steady trajectory during the early stages of the illness, but it was noticeably poorer in EOS patients than in controls. On the one hand, PANSS-general and history of suicide attempts at baseline were found to be risk factors of longitudinal cognitive function; on the other hand, they were unable to find any correlation with DUP, remission, positive/negative symptoms, hospitalizations long-term cognition. Over two years, the EOS group and the controls saw a comparable cognitive path, but at different levels. During the first two years of the illness, several baseline features (psychotic symptoms, DUP, remission, and hospitalization) did not affect cognition. In contrast, general symptoms and a history of suicide attempts at baseline were found to be more powerful predictors of the cognitive course than symptoms specific to psychosis. As a result, individuals with early-onset psychosis should receive extra attention during their diagnosis and treatment.

Study 2: According to **Daniel Gabriel et al., [2017]** [6] the TEOSS trial studied the effectiveness of three antipsychotic medications in treating early-onset schizophrenia and schizoaffective disorder in 119 children and adolescents aged 8 to 19 over eight weeks. Patients with more severe symptoms and a history of mood stabilizer prescription were more

likely to respond to treatment. Anhedonia and low community functioning were predictors of symptom reduction. The study found that aggressive children may need extra help to increase treatment adherence and that youth with severe psychotic symptoms are more likely to benefit from antipsychotic medication.

Study 3: According to Schimmelmann *et al.*, [2013] [7] the study examines the effectiveness and tolerance of psychosocial and psychopharmacological therapies for early-onset schizophrenia spectrum disorders (EOS). Researchers suggest that pragmatic psychopharmacology covering dose, switching, and side-effect monitoring is necessary. Psychosocial therapies have value, but no clear differentiation is found between them. Six randomized controlled studies have demonstrated that risperidone, paliperidone, olanzapine, and quetiapine are more effective than placebo in treating EOS while ziprasidone is not. Clozapine has been found to be superior for treatment-refractory EOS. Tolerability factors should inform antipsychotic selection. Longer-term studies are necessary to examine pharmacologic and nonpharmacologic augmentation techniques.

Study 4: According to Jean. A *et al.*, [2012] [8] the design, methodology, and findings of the TEOSS investigation have been reported. Subjects in the TEOSS trial were randomized to receive one of three active treatments (olanzapine, molindone, or risperidone). The treatment-related changes in neurocognition from baseline to weeks 8 and 52/termination, as well as in between weeks 8 and 52/termination, are the main emphasis of this paper. Neurocognitive tests were conducted at baseline and at week eight, the end of the acute period. Following acute care (week 8), individuals 77 (66%) of the 116 participants in the TEOSS treatment group had analyzable post-baseline neurocognitive data. The average age of the sample constituting two-third of men of 14.3 ± 2.5 years. The non-neurocognitive group (young people lacking baseline or post-baseline neurocognitive data; $n = 39$) and the youth included in these analyses did not vary substantially. This is the first EOS study to prospectively evaluate neurocognitive functioning during a 52-week double-blind treatment trial with antipsychotic medication in a significant well-characterized sample of young people. Between the initial phase of the study and weeks 8 and 52, they saw that neurocognition, as measured by a neurocognitive composite score, improved somewhat with antipsychotic treatment; the majority of the minor benefit appeared during the acute period of the trial.

Study 5: According to Stephen. R *et al.*, [2010] [9] the study included 2,119 children and adolescents with a mean age of 14.25 years. The Majority of the sample were male, white, right-handed, and belonged to a low-middle socioeconomic strata. Almost 45% were receiving special education services and over half had been previously admitted to a mental health facility or received pharmaceutical treatment. Completion rates for the neuropsychological assessment battery tests were high. No significant cognitive differences were observed between young people with SZ and those with SA disorder, except for the academic skill category where the SZ group underperformed on a single-word spelling challenge. Weak to moderate relationships were found between the neurocognitive functions and the degree of illness and adaptive behavior. Research has shown that neurocognitive functioning is a critical area of vulnerability in young people with schizophrenia spectrum disorders.

Study 6: According to Jeffrey. R *et al.*, [2008] [10] thirty-six participants aged 10-17 with diagnoses of schizophrenia, schizoaffective disorder, schizophreniform disorder, and psychosis were included in the study. A neuropsychological battery was given to the patients, and ratings on the Positive and Negative Syndrome Scale were performed at baseline and after a year ($n=14$). The majority of subjects were inpatients, and 13 out of 14 were taking an atypical antipsychotic during both sessions. Young patients with schizophrenia spectrum disorders showed deficits in their neurocognitive abilities at baseline, including working memory, processing speed, executive function, and language learning. No significant changes in cognition were observed after a year, but positive symptoms improved while overall clinical symptoms varied. A lower baseline IQ was associated with more unpleasant symptoms after a year, but no other significant associations were found between clinical and cognitive symptoms.

Study 7: According to Kelly. L *et al.*, [2007] [11] the study conducted an assessment of the cognitive abilities of 52 patients with early-onset schizophrenia and compared the findings with those of healthy control subjects. Their research indicated that certain cognitive domains were more closely linked to functional outcomes than a general measure of intelligence. Specifically, attention/vigilance, working memory, and verbal memory at the start of the study showed a

significant correlation with follow-up social/communication, personal living, and communal living abilities. These outcomes suggest that there is a link between neurocognitive performance and functional outcomes in individuals with EOS. The study evaluated the cognitive performance of 52 patients with early-onset schizophrenia, comparing them to healthy control subjects. They found that certain cognitive domains were more strongly associated with functional outcomes than a general measure of intelligence. Specifically, attention/vigilance, working memory, and verbal memory at baseline exhibited a significant correlation with follow-up social/communication, personal living, and communal living abilities. These results suggest a connection between neurocognitive performance and functional outcomes in individuals with EOS.

Study 8: According to **Jean A. et al...**, [2007]^[12] the TEOSS study was a complex research endeavor that involved multiple parts and variables. To streamline the report, only the most relevant aspects of the study were covered. The study received a total of 478 applications from households interested in participating, but only 119 young people were ultimately enrolled. These individuals were all diagnosed with Schizophrenia and schizoaffective disorder, and their average age of onset was 11.1 ± 3.5 years. The patients' symptoms were evaluated using several standardized scales, such as the Positive and Negative Symptom Scale, the Brief Psychiatric Rating Scale for Children, and the Clinical Global Impression-Severity Scale. Remarkably, the symptom profiles of the young people were found to be comparable to those of adults with similar disorders, but more severe. In addition, the study found high rates of overall psychopathology and symptoms, which significantly impacted the participants' social and functional abilities. Overall, the TEOSS study represents one of the most extensive assessments of young people with schizoaffective disorder and SZ spectrum disorders to date.

Study 9: According to **JON Mc CLELLAN et al...**, [2007]^[13] the study involved youths aged 8-19 with EOSS and aimed to assess the efficacy and safety of risperidone, olanzapine, and molindone. The 8-week acute study was conducted at four sites, using a randomized, double-blind, parallel-group design. The primary end measure was responder status, with secondary measures including assessments of psychopathology, disability, quality of life, and drug safety. Neuropsychological tests were administered at baseline, week 8, and week 52. The study revealed significant safety issues, such as higher-than-expected rates of suicidality and difficulties decreasing thymoleptic drugs prior to randomization. Overall, the study findings are valuable in determining the use of antipsychotic drugs in clinical settings for young people with early-onset schizophrenia spectrum disorders.

Study 10: According to **Joseph P. et al...**, [2005]^[14] a comprehensive study was conducted on 106 individuals aged between 10 to 18 years who participated in the Early-Onset Schizophrenia Neuroimaging Studies at the Zucker-Hillside Hospital in Glen Oaks, New York by May 2004 (Kumra et al 2004). The Institutional Review Board of the North Shore-Long Island Jewish Health System authorized all procedures, including recruitment and consent, ensuring that the study was conducted with utmost adherence to ethical standards. Written informed consent was obtained from both the participants and their legal guardians. The results of the study revealed that 43% of the 54 patients who underwent neuropsychological testing and met DSM-IV criteria for schizophrenia, schizoaffective disorder, and schizophreniform disorder were determined to have COS. The study further suggests that adolescents with EOS have a significant and widespread deficiency in executive functioning, similar to that seen in adult patients during their initial episode of severe illness. Additionally, the study revealed various abnormalities in different neurocognitive domains, pointing to extensive brain dysfunction in EOS.

Conclusion:

Schizophrenia is a complex mental health condition that can result in neurocognitive impairment, particularly in individuals with early-onset conditions. In order to mitigate the effects of this impairment, early diagnosis and targeted treatment are essential. Cognitive impairment is a crucial aspect of this condition that requires specific attention and is often targeted for treatment. Studies have shown that antipsychotic medication can significantly enhance neurocognition in young people with schizophrenia spectrum disorders. However, it is important to note that abnormalities in multiple neurocognitive domains suggest that widespread brain dysfunction may be present in early-onset schizophrenia. As such, antipsychotic medications should be used with caution in clinical settings for young individuals with early-onset schizophrenia spectrum disorders.

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Conflict of interest

The content of this article is free of conflicts of interest, according to the authors.

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