



SPECIAL ARTICLE

Heterogeneous trajectories in schizophrenia: insights from neurodevelopment and neuroprogression models

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The notion that schizophrenia is a neuroprogressive disorder is based on clinical perception of cumulative impairments over time and is supported by neuroimaging and biomarker research. Nevertheless, increasing evidence has indicated that schizophrenia first emerges as a neurodevelopmental disorder that could follow various pathways, some of them neuroprogressive. The objective of this review is to revisit basic research on cognitive processes and neuroimaging findings in a search for candidate keys to the intricate connections between neurodevelopment and neuroprogression in schizophrenia. In the complete panorama, schizophrenia is a neurodevelopmental disorder, possibly associated with an additional burden over the course of the disease through pathologically accelerated aging, and cognitive heterogeneity may explain the different trajectories of each patient.

Keywords: Schizophrenia; cognition; aging; neurodevelopment; neuroprogression

Introduction

Decades of extensive research have shed some light on one of the most challenging clinical conditions in psychiatry: schizophrenia (SZ).¹⁻⁴ A better understanding of the biological process of inflammatory response and oxidative stress in individuals living with the disorder has supported accelerated aging models in a neuroprogressive course.³ However, the understanding that there are different trajectories associated with premorbid alterations has resulted in a critical turnabout in the neuroscience of SZ, with an escalating emphasis on neurodevelopment.^{1,2}

Although this might sound conflicting at first glance, cumulative evidence has supported the notion that SZ first emerges as a neurodevelopmental disorder that could eventually follow a neuroprogressive course.⁵ Ultimately, neurodevelopment is suggested as a key variable for predicting outcomes associated with preserved functioning despite the disorder.⁶ We believe that cognitive processes and neuroimaging findings may unlock the intricate connections between neurodevelopment and neuroprogression in SZ.^{7,8}

Therefore, in this review, we summarize current neurobiological and cognitive knowledge about SZ, revisiting neuroimaging and peripheral biomarker research. We aim

to discuss the role of neurodevelopment and neuroprogression models in SZ as distinct trajectories, each associated with particular outcomes. Finally, we discuss the applicability of heterogeneous trajectories for personalized interventions.

Disease outcomes and health burden

With an estimated prevalence of about 1% of the population, SZ remains one of the top ten factors in the global health burden.⁹ Functionality could be impaired even prior to diagnosis. People who develop SZ tend to show slight cognitive, social, and motor deficits in early childhood during the premorbid phase.^{7,10} This is followed in adolescence and early adulthood by anxiety, depressive symptoms, and social withdrawal, and then by the emergence of prodromal symptoms, leading to the first episode of psychosis (FEP).⁵ Clinically speaking, it is logical to assume that a neurodevelopmental component is at least partially related to the premorbid and prodromal presentation and early deficits. However, it is difficult to determine its magnitude.⁵

After the FEP, the course of positive symptoms is marked by relapse and remission. Available treatments (antipsychotic medications) are effective against positive

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symptoms, although some patients can still present long-term residual manifestations.⁷ Negative and cognitive symptoms tend to be chronic and respond poorly to current treatment options,⁵ resulting in devastating deficits in social and occupational functioning.¹⁰ As many as 30 to 50% of individuals with the disorder follow a progressive course with cumulative residual symptoms, which suggests that there may be a neuroprogressive component in addition to the neurodevelopmental one.^{3,10} Unraveling the pathogenesis of the disorder is crucial to designing more appropriate and effective treatment strategies.^{11,12}

Better treatment might be a matter of life and death: compared to the general population, the life expectancy of individuals with SZ is reduced by 15 to 20 years,¹³⁻¹⁶ and the relative risk of all causes of death in SZ is 2.54, which is significantly higher than that of mood and anxiety disorders.¹⁷ The reasons for higher mortality in SZ patients may be related to late diagnosis and insufficient treatment of somatic diseases, the detrimental side effects of antipsychotics, and unhealthy lifestyle (smoking, poor diet, excessive alcohol consumption, and sedentarism), in addition to the risk of suicide and accidents.^{1,16}

Vulnerability and somatic response to stress

There is growing evidence about the biological underpinnings of increased physical morbidity and early mortality in SZ. Since biomarkers are objective measures of these biological processes, they have potential for assessing diagnostic, prognostic, and therapeutic response.¹⁸ Despite the diversity and complexity of the changes observed in individuals diagnosed with SZ,¹⁹ there is consistent evidence of immune system dysfunction²⁰ and changes in oxidative stress.²¹ Such immune alterations have been reported from the FEP²² to chronic populations.²³

Inflammatory imbalance, which has been found even prior to FEP, is associated with impaired functioning in individuals with an ultra-high risk of developing psychosis.²⁴ Indeed, long before diagnosis, known risk factors for SZ may influence neurodevelopment and result in vulnerability to psychosis later in life, including pre- and

perinatal factors (infection, placental pathology, low birth weight) and premorbid exposure to stress (urban environment, childhood trauma, ethnic minority, and migrant status).² For instance, transcriptome and methylome studies in SZ point to alterations in immune-related genes, pathways, and cells involved in neurodevelopment and neural functioning.²⁵ Although heterogeneous, immune-related gene alterations could indicate potential diagnostic biomarkers, at least for a subset of patients.²⁶

The continuous pro-inflammatory state in SZ appears to be the result of a genetic vulnerability and somatic response to stress, which is described as the vulnerability-stress-inflammation model of SZ.²⁷ The serum oxidative stress and inflammatory cytokine patterns appear to be similar among patients early after diagnosis and late in the course of the illness, which supports the idea that an early degenerative component precedes SZ onset.²⁸ This low inflammatory status is a constant neurotoxic injury that could accelerate the biological aging of individuals with SZ according to telomere length^{29,30} (Figure 1). Telomeres, structures at the ends of chromosomes that are crucial to preserving DNA information, are consumed at each cell division. When the cells reach a minimum size, senescence or apoptosis begins. Therefore, telomere length can be understood as a “biological clock” related to the life span of cells and organisms. It indicates the speed of biological aging³¹ and the body’s ability to absorb damage over time.³² Such a process is consistent with a comprehensive meta-analysis which showed that telomere length is slightly lower in individuals with SZ than controls.³³ Although telomere length is an inherited trait, it can be influenced by epigenetics, the environment,³⁴ inflammation, and oxidative stress.^{35,36}

Moreover, short telomeres in individuals with SZ are associated with illness duration, memory deficit, less gray matter, and increased chemokine levels, which suggests that, at least to some extent, cognitive impairment in SZ is the result of accelerated aging of a neuroprogressive nature.³⁰ In summary, biomarker research has indicated that SZ has an early neurodevelopmental trajectory that leads to increased vulnerability to stress and follows a neuroprogressive course that involves imbalanced inflammatory response.^{27,30}

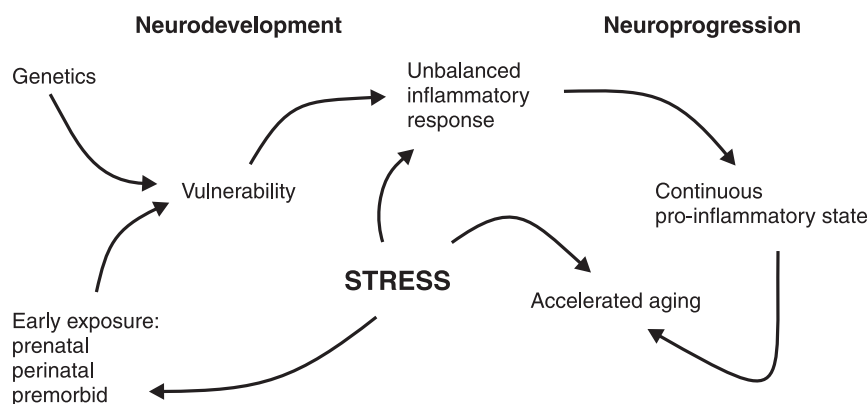


Figure 1 Accelerated aging as a result of a chronic unbalanced inflammatory response to stress.

Neuroimaging insights

In addition to blood tests, neuroimaging results could also act as biomarkers. Although they are not yet sufficiently specific to be of diagnostic value, substantive evidence of structural, functional, and neurochemical brain alterations in SZ corroborates both the neurodevelopmental and neurodegenerative models of this disorder.³⁷

A comprehensive meta-analysis of more than 18,000 people found that those with SZ had lower brain volumes than controls, both globally (total volumes) and in several specific cortical and subcortical structures. Curiously, the findings were similar regardless of antipsychotic use.³⁸ Optimized treatment with antipsychotic medication appears to reduce such processes, having a neuroprotective effect,⁴ although there is also evidence of decreased gray matter with chronic antipsychotic exposure.³⁹

Brain change is most severe during the early stages of the disorder and is not homogeneously distributed among patients.⁴⁰ The greatest effect sizes have been found for total gray matter, cortical gray matter reduction, and lateral ventricle enlargement.³⁸ Subcortical structure analysis has shown that the hippocampus, amygdala, thalamus, and accumbens of individuals with SZ were smaller than those of healthy controls,⁴¹ while the caudate, putamen, and pallidum were larger.^{41,42} Moreover, the brain age of patients with SZ can be eight times that of other people, which reinforces the hypothesis of accelerated aging.⁴³ Progressive brain loss over time is highly variable among patients and is more pronounced shortly after onset, with the acceleration rate slowing to almost zero in five years.⁴⁴

There is also evidence of functional change in neural networks in individuals with SZ.⁴⁵ The ENIGMA consortium has compiled data showing that global structural connectivity is significantly compromised in SZ patients compared to healthy controls, and that such alterations are associated with impaired cognitive ability.⁴⁶ Nevertheless, it is unclear whether such alterations are markers of compromised neurodevelopment or of the cumulative damage of neuroprogression.

There are subtle distinctions in brain volume reductions with respect to intellectual and cognitive performance. Although SZ patients with current cognitive impairment may have a lower volume of gray matter, only those with a lower estimated premorbid crystallized intelligence quotient (IQ) have a lower total intracranial volume (ICV). Those with an intact estimated premorbid IQ, even when presenting with cumulative cognitive deficits after diagnosis, do not differ from controls in ICV.⁴⁷ This suggests that abnormal neurodevelopment is associated with brain hypoplasia, while neuroprogression leads to localized atrophy in gray matter volume consistent with cerebral dysmaturation.⁴⁸

In typical development, ICV and whole-brain volume (WBV) increase between early childhood and early adolescence. The ICV then remains relatively stable throughout adulthood, although whole-brain volume begins to reduce. Thus, changes in ICV vs. whole-brain volume relative to ICV can be thought of as neurodevelopmental

and neurodegenerative impairment indexes, respectively.⁴⁹

Cognitive trajectories

Individuals with SZ can present global and heterogeneous impairment in several cognitive domains.^{50,51} These changes appear similar to those of other severe mental illnesses, such as bipolar disorder, but with a greater extent and severity.^{52,53} The literature consistently reports that most cognitive impairment seems to originate during neurodevelopment, i.e., during skill acquisition rather than loss. However, different events during development could affect individuals with SZ heterogeneously.⁵⁴ One possible marker of this change in development would be intellectual functioning, which can be reduced in these patients.^{55,56}

General cognition is impaired in individuals who later develop SZ even before the FEP,⁵⁷⁻⁵⁹ resulting in consistent IQ deficits.^{60,61} A previous study⁵⁵ and meta-analysis⁶² found that the risk of developing SZ increases approximately 3.8% per 1-point decrease in IQ. In addition, the risk of SZ was strongly related to school performance decline according to family cognitive aptitude rather than cognitive performance,⁶³ which indicates the environment's impact on neurodevelopment. Specific cognitive functions are also impaired prior to the onset of psychosis, such as executive functioning, attention, memory, and processing speed.^{60,64} Processing speed seems to be a particularly crucial function, since it has been implicated as a central component of cognition in SZ⁶⁵ and could mediate other cognitive domains, such as executive functioning.⁶⁶

Verbal episodic memory, another domain widely studied in SZ due to its relationship with functional outcomes, may be considered an endophenotype for SZ.^{67,68} This ability is potentially vulnerable to aging and is responsible for storing facts and events. It has a crucial role in different aspects of everyday life, such as study, work, independent living, and interpersonal relationships.^{68,69} Verbal episodic memory is impaired early in SZ and worsens with time.⁵³ This pattern of deficit progression is corroborated by neuroimaging and biomarker studies, which have found that signs of accelerated aging are associated with such impairment.^{30,47,70} Notwithstanding this progressive course of memory deficit, according to a more comprehensive assessment of cognition in SZ, it appears to be already moderately impaired long before diagnosis, which supports the neurodevelopmental model of the disorder.⁴³ Since these results are reported even in drug-naïve individuals,⁷¹ the association between neurodevelopment and cognition and their role in psychosocial functioning in SZ are virtually undeniable.⁶⁹

One classic debate over the years is whether cognitive deficits in SZ are stable or progressively worsen over time, with studies tending to support the former.^{64,72} For example, performance on the MATRICS Consensus Cognitive Battery early in the course of SZ is similar to that of individuals with a chronic course of illness.⁷³ No progressive course was found among SZ patients who

had an exceptionally long duration of untreated psychosis, i.e., a chronic sample with no treatment effect.⁷⁴ Likewise, a study with a 10-year follow up after onset found stable cognitive functioning over time.⁷⁵ On the other hand, longitudinal studies have found some evidence of cognitive decline after onset,⁶⁰ even in individuals already impaired at baseline. Further findings indicate a difference of 10 points or more between estimated premorbid and current IQ in over half of the individuals with SZ.^{76,77} However, the course of cognitive change is still controversial in the literature, mainly due to the heterogeneity of the presentations.⁷⁸

Indeed, different cognitive profiles in SZ have been established,⁷⁹ even among individuals with high premorbid intellectual functioning.⁶⁵ A recent systematic review showed that the results vary widely and can be grouped into several cognitive subtypes, ranging from 3 to 5 clusters with different profiles. The most consistent findings point to 3 clusters (Figure 2): 1) global impairment, 2) intermediate impairment, and 3) a subtype close to normal, with little impairment and a more preserved cognitive profile.⁸⁰ Based on estimated premorbid IQ, similar categories were observed in a large sample of individuals with SZ (n=534). Nearly half of the sample (44%) presented a decline from premorbid cognitive functioning, followed by preserved intellectual functioning (29%) and a compromised group (26%).⁸¹ Thus, cognitive heterogeneity seems to be an essential aspect of SZ, and certain markers during development might explain the different trajectories.

Functional outcomes

Individuals with SZ have been consistently reported to experience impairment in everyday functioning and lower quality of life, including difficulties with cognitive, social and real-world activities.^{82,83} Functioning reflects objective measurement of health and health-related domains, while quality of life is the individual's perceptions of these domains.⁸⁴ Although the onset of SZ is known to occur during adolescence or young adulthood, social functioning changes appear even earlier, long before the first episode.¹⁰

A couple of decades ago, associations with social adjustment were reported in young children many years before SZ onset. A higher incidence of poor premorbid social adjustment in childhood was associated with an increased risk of SZ.⁸⁵ During this period, one of the first studies to compare social functioning in childhood and adolescence among SZ and bipolar disorder patients and healthy controls found that both patient groups exhibited functional deterioration during adolescence. The results established a clear association between poor social functioning in childhood and adult psychosis, as well as significant differences in premorbid social ability and school performance between patients with SZ and healthy controls. Individuals with SZ were found to have social impairments since early childhood and experience significant deterioration during adolescence, including poor school adjustment, even considering differences in premorbid IQ between groups.⁸⁶ Since that time, the neurodevelopmental aspect of SZ has been well researched and established, having an important role in predicting functional outcomes, which has led to the suggestion that poor social adjustment in childhood and adolescence is an early manifestation of vulnerability to psychotic illness in adulthood.

Thinking forward to disease onset, premorbid impairments can later be affected by symptom severity, disease course, and the side effects of medication. Both the negative and positive symptoms of SZ are long-lasting and are associated with the diagnosis since the first episode, negatively impacting cognitive and social functioning, in addition to the side effects of some antipsychotics.^{82,87} More specifically, cognitive deficits and negative symptoms have been found to be stable over time and have a persistent impact on functional outcomes.⁸⁸ It appears that as the disease progresses, functional outcomes are even more closely related to neurocognitive deficits than before onset.^{89,90}

In past decades, the literature demonstrated a connection between cognition and everyday functioning, with cognitive deficits being relevant determinants of impairment in most functional domains.^{91,92} For example, impaired verbal memory has been reported to impact

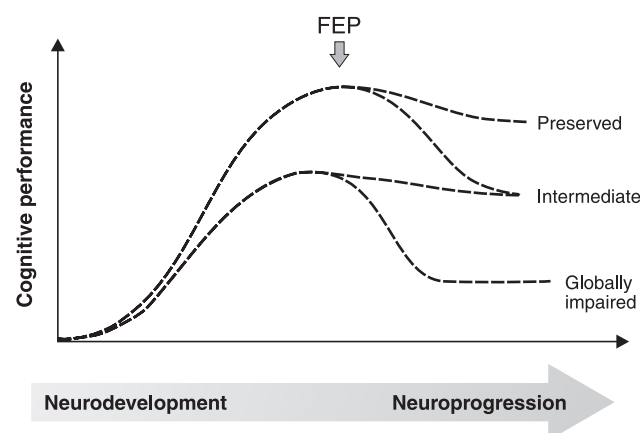


Figure 2 Heterogeneous cognitive trajectories in schizophrenia. FEP = first episode of psychosis.

real-world functioning. Processing speed has been correlated with several measures of functioning, including activities of daily living, occupational functioning, and independent living status.⁹³ Additionally, impaired social cognition has been shown to largely mediate the effects of neurocognition on functional outcome.⁹⁴ Longitudinal studies have explored the disease's neuroprogression regarding the association between cognition and functioning. In a Norwegian longitudinal study of FEP, the relationship between neurocognition, remission, and recovery was assessed at multiple follow-up points (baseline, 6 months after FEP, and once a year for 10 years). The study found that attention/vigilance and working memory scores at baseline significantly predicted social functioning outcomes, since adapting to social settings requires flexibility and the ability to process and maintain a large amount of information, skills for which these cognitive domains are essential. It was also found that attention and vigilance were related to role functioning at follow-up (activities of daily living, school or work performance or managing a home), demonstrating the crucial role of attention in daily problem solving and skill acquisition, as well as its progress throughout the illness.⁸⁹

Personalized interventions

The characteristics of neurodevelopment and neuroprogression in SZ and the relationships between them are being explored, studied, and evaluated continuously to search for the best possible treatment for the patients who live with the disease. According to Beck et al.,⁹⁵ higher functioning was achieved by some patients with SZ when they were motivated to engage in meaningful, enjoyable, and social activities. Another study found that exercise had beneficial effects on clinical symptoms, quality of life, global functioning, and depressive symptoms in patients with SZ.⁹⁶ Therefore, current treatments should go beyond the remission of psychotic symptoms, aiming to facilitate recovery by improving the patient functioning, focusing on the patient's subjective well-being, quality of life, real-world adaptation, and addressing motivation and beliefs, as well as social functioning, including independent living skills and the capacity for work or study.^{97,98}

Individuals with SZ, even those with moderate disabilities, maintain the ability to learn.⁵³ A recent systematic review reported that an increased cognitive reserve, which is the ability to maintain skills developed throughout life, could be a protective factor in SZ and decrease symptom severity, being related to better functional outcomes.⁹⁹ To that end, cognition in SZ should not be viewed as a "lost cause" but a potential target for rehabilitation and remediation techniques.¹⁰⁰

Such interventions tailored for a specific cluster of patients could only be properly tested if we recognize the concept of different trajectories in SZ.⁷⁸ Further research could help consolidate this concept and test targeted interventions for each trajectory. This idea is in consonance with stratified psychiatry or personalized medicine, seeking the best treatment possible for each patient rather than an average treatment response.¹⁰¹ Nevertheless, there is not

yet enough evidence to endorse particular interventions according to cognitive trajectory.

Conclusion

In conclusion, it is suggested that SZ is a neurodevelopmental disorder which leads to early impairments. However, there is also an additional burden over the years that could lead to accelerated aging. Different possible influences could explain the heterogeneity in the development and aging processes. These differences could lead to distinct trajectories of the disorder.

The present review aimed to contribute to a better understanding of the pathophysiology of SZ, considering biological and cognitive variables. We hope that proper comprehension of such variables leads to the development of individualized treatments and more effective interventions for each patient.

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Disclosure

The authors report no conflicts of interest.

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