Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/60/20241404

Environmental risks and etiology for schizophrenia from the lens of neurodevelopment: A literature review

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Abstract. Schizophrenia is a chronic mental disorder marked by positive symptoms such as hallucinations and delusions, negative symptoms including aversion and withdrawal, and cognitive dysfunctions. Despite the preponderance of genetic influences, environmental factors have rarely been singled out in the past literature as significantly contributing to the development of the disorder. This paper focuses on major environmental risk factors, such as prenatal infections and malnutrition, urban living, childhood trauma, and substance abuse, which examines the impact from a neurodevelopmental perspective. Findings from epidemiologic and neuroimaging studies indicate that these environmental factors disrupt crucial neurodevelopmental processes and potentially increase the risk of developing schizophrenia. Neuroimaging advances have provided insights into brain abnormalities associated with schizophrenia that could facilitate early diagnosis and intervention. However, further longitudinal and interdisciplinary studies are currently required to adequately understand the role of environmental factors in the etiology of schizophrenia.

Keywords: Environment factor, Schizophrenia, Neurodevelopment.

1. Introduction

Schizophrenia is a severe chronic mental disorder characterized by positive symptoms including hallucinations and delusions, negative symptoms including aversions and withdrawal, and cognitive dysfunctions, especially in executive function, according to both the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) and the International Classification of Diseases 11th edition (ICD-11) [1,2]. These symptoms can change the way people think and behave and cause exhaustion, impaired concentration, and a tendency to self-isolate [3]. Consequently, individuals with schizophrenia may have difficulty working, performing daily tasks, and maintaining relationships. Epidemiological research suggests that 70-90% of people with schizophrenia are unemployed and often suffer from social and family isolation [4]. Between 10% and 15% of schizophrenics are likely to die by suicide [5].

While the causes of schizophrenia have yet to be conclusively established, previous research suggests that genetic, neurodevelopmental, and environmental factors may all be involved. According to a meta-analysis, the heritability of schizophrenia is 81% [6], indicating a strong genetic component. However, the discrepancy rate of 40-55% in the occurrence of schizophrenia among genetically identical twins suggests that environmental factors are also salient [7]. Therefore, environmental conditions appear to play an important and potentially modifiable role in the neurodevelopmental pathways that lead to schizophrenia[8,9].

DOI: 10.54254/2753-8818/60/20241404

To understand the complexity of schizophrenia development, the present paper presents a literature review focusing on key environmental factors implicated in schizophrenia, including prenatal exposure to infection/nutritional deficiencies, urban living, drug abuse, and childhood trauma. It will first review previous findings based on epidemiological and neuroimaging studies, then consider whether these findings support or refute the neurodevelopmental hypothesis. In contrast to previous literature reviews, this paper emphasises on explaining the etiology and environmental risk factors of schizophrenia from a neurodevelopmental perspective.

2. Literature Review

2.1. Neuroplasticity

The neurodevelopmental hypothesis proposed that one of the causes of neurological developmental abnormalities due to psychiatric disorders is the influence of environmental factors in the prenatal or early childhood period. Neuroplasticity is the brain's ability to change and adapt and is essential for learning and memory [10]. These changes may involve both the structure (size of brain regions) and function (how brain regions work) of the brain [11]. Dysplasticity in the brain originates from the lack of proper coordination between neuronal activities and the inability of brain cells to synchronize their responses to experiences, thereby leading to distorted perceptual and cognitive functioning [12]. Research has revealed that there are issues with the brain cells called Parvalbumin-expressing (PV) cells and their surrounding structures observed in psychotic schizophrenia. This indicates that the brain is still too flexible or not flexible enough when it should be stable [13]. It can affect normal cognitive and emotional functioning, such as inability to adapt to new information and emotional dysregulation. [14] also mentioned that there are issues with glutamate and GABA the brain chemicals that contribute to the communication of the brain cells. Research has demonstrated that chemicals in the brain contribute to the direction of neuronal growth and connectivity and are necessary to maintain certain receptors that are essential for synaptic plasticity [15]. Loss of synaptic plasticity causes thought and emotion regulation [16] and increases the risk of schizophrenia. Early pregnancy prenatal period are is critical periods for neuroplasticity in the brain [17]. The outer layers of the fetal brain are forming in the early stages of pregnancy, where disturbances from harsh environmental factors can affect the way brain cells grow and connect [18]. This involves the effects of environmental factors such as the factors of prenatal infections, malnutrition, urbanization, drug use and child trauma [19].

2.2. Prenatal Exposure to Infection

The prenatal period is critical for brain development, marking the onset of crucial processes such as synaptogenesis, glial cell proliferation, and myelin formation [20]. Maternal infections during pregnancy can affect brain structure features linked to schizophrenia, such as increased ventricular volume, reduced cortical volume, and lengthening of the cavum septum pellucidum [21]. Recent epidemiological studies have associated prenatal exposure to various infections with a heightened risk of schizophrenia [16]. For example, [22]for example, calculated a 1.5- to 5.3-fold increased risk of schizophrenia in pregnant women after perinatal exposure to rubella, genital or reproductive infections, influenza, toxoplasmosis, respiratory infections, and the herpes simplex virus. These viral infections trigger the release of cytokines (interleukin-6, IL-8), which mediate the effects of infection on schizophrenia [23,24]

Studies also suggest that exposure to maternal immune activation (MIA) can cause behavioral and dopamine-induced neurochemical abnormalities that are consistent with neurochemical markers associated with schizophrenia [25]. Early studies found that prenatal maternal infections in mice cause various behavioral changes in offspring, many of which are linked to schizophrenia and related disorders [26]. Activating the immune system of pregnant rodents by injecting a substance that mimics a viral infection causes behavioral and brain changes in the offspring that resemble those associated with schizophrenia [22,27]. This may suggest a direct relationship between MIA and the development of schizophrenia-related traits. [28] found that MIA is associated with impaired salience function due

DOI: 10.54254/2753-8818/60/20241404

to a neurotransmitter release mechanism. However, the salience changes did not cause neuronal death, which is consistent with observations in postmortem brain studies of individuals with schizophrenia [25]. Prenatal infections have also been implicated in verbal IQ deficits in children and adults [22].

Besides environmental factors, genetic factors also contribute to schizophrenia. Several studies have investigated the risk of developing schizophrenia from prenatal infections by measuring herpes simplex virus type 2 (HSV-2), but found no correlation between schizophrenia and HSV-2 antibodies [29]. According to [30], a history of psychiatric disorders on the paternal side may be a key factor in neurological deterioration, implicating parental psychiatric illness as a potential risk factor for schizophrenia [27]. Notably, [24] give evidence of an interaction between family history of psychiatric illness and prenatal infections, reporting a 5-fold difference in the risk of prenatal exposure to infections in those with previous family history of psychiatric disorder.

2.3. Prenatal Nutritional Deficiencies

The impact of prenatal malnutrition on neurodevelopment may also increase the risk of schizophrenia [31]. For instance, [32] found that maternal malnutrition during pregnancy can increase the chance of the child developing schizophrenia by a factor of 2.7. This is consistent with [33] research on the Dutch famine of 1944-1945 and [34] study of the 1959-1961 famine in China, both of which found that children born to women who were malnourished during pregnancy were more than twice as likely to develop schizophrenia [33].

These findings are consistent with research suggesting that prenatal deficiencies in micronutrients, such as folic acid, omega-3 fatty acids, and various vitamins, can cause central nervous system defects [35,36]. Iron deficiency, for example, impairs the formation of connections between nerve cells and protective myelin sheaths, which may increase the risk of schizophrenia [37]. Conversely, [32] found that supplementation with folic acid significantly reduced the prevalence of microcephaly and alleviated several other developmental anomalies. Similarly, [38] found that folic acid prevents neural tube defects (NTDs), which may protect against schizophrenia by improving the nutritional environment of the developing brain.

2.4. Urban Living

Urban living environments have been associated with a heightened risk of schizophrenia. This may be related to long-term stress exposure [39,40] which is known to contribute to a range of psychiatric disorders [41]. [42] tracked people with schizophrenia born in the Netherlands between 1972 and 1978, comparing those living in densely populated urban areas with those from less crowded places. The results confirm the importance of early living environment, suggesting that the influence of urban living on schizophrenia risk takes place around or before the time of birth, rather than the time of disease onset [42]. Early development is a critical period for neuronal plasticity and various neurocognitive and emotional functions [43]. Neurodevelopmental disorders early in life may increase susceptibility to unfavorable environmental conditions, thus increasing the associated risks of long-term environmental stressors [42,39]. [44] also found that being born or raised in an urban environment raises the risk of schizophrenia in adult life. Early development is a critical period for neuronal plasticity and various neurocognitive and emotional functions [43].

Urban living appears to disrupt brain development at an early age. Urban living increases activity in the amygdala perigenual anterior cingulate cortex, which is involved in the regulation of stress and negative emotions [45]. [40] used nuclear magnetic resonance imaging (NMR) to scan the brains of 110 participants, finding a strong negative correlation between urban upbringing and the amount of grey matter in the right dorsolateral prefrontal cortex, which is involved in stress management and decision making. However, since [40] did not explicitly state whether participants had experienced significant stress at a young age, their study does not confirm the hypothesis that urban living affects the brain via stress response. A later study by [46] analyzed patients with schizophrenia in cities via video conferences, video recordings, and interviews, concluding that urban noise and pollution exacerbate stress in schizophrenia patients.

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2.5. Early Life Trauma

Neuroplasticity research has shown that adolescence is a crucial period for brain development associated with cognition and decision-making. Environmental disruptions to the remodeling process that occurs during this period can result in schizophrenia symptoms [12,47]. For instance, stress can affect cell proliferation and synapse formation, thereby impairing the development of the prefrontal cortex [17]. Research has also shown that schizophrenia patients with experiences of early childhood trauma have impairments in cognitive functions such as memory and attention [48]. In their meta-analysis on the relationship between childhood trauma and neurocognition in adults with psychiatric disorders, [49] confirmed that childhood trauma is associated with impaired working memory. Exposure to environmental stressors can also cause shrinkage of brain regions in the hippocampus, with negative effects on memory [50]. Therefore, early traumatic and stressful experiences may have long-term effects on brain function in schizophrenia. This is consistent with the findings of [51], who used a traumatic neurodevelopmental model to associate schizophrenia with childhood trauma.

Childhood trauma has also been associated with reduced grey matter in the brain, particularly in the prefrontal cortex, which is involved in decision-making and emotion regulation [52].[50] suggest that overactivity in brain regions associated with fear and stress, and impaired connections between the amygdala and the rest of the brain, will have difficulty regulating emotions. [53] investigated the stress system and brain changes in patients at risk of psychosis with the use of stress hormone and brain patch scans. The study found that when the stress system (HPA axis) becomes overactive, cortisol levels rise; this, in turn, increases dopamine activity, which can cause symptoms such as hallucinations and delusions [54,55] However, it is worth stressing that childhood trauma is not a direct pathway to schizophrenia, as genetic and other factors also play a role.

2.6. Drug use

The use of drugs, both illicit and controlled, can increase the risk of schizophrenia. [56], for example, used brain imaging techniques to show that cannabis use during adolescence may cause a reduction in grey and white matter in the brain, leading to changes in endogenous cannabinoids, neurotransmitters involved in brain cell communication and the formation of brain cellular structures. Cannabis disrupts these processes, thereby affecting the way neurons connect and communicate [43]. Furthermore, the use of drugs such as D-amphetamine can affect the brain's production of and sensitivity to dopamine [18], which can disrupt normal brain function [9,16]

[57] conducted a meta-analysis comparing cognitive functioning in individuals with and without a history of cannabis use. Patients with a history of cannabis use showed only selective cognitive deficits, while patients with no history of cannabis showed generalized deficits. This implies that cognitive deficits may be less common in cannabis users. However, [57] study may have been biased in its selection of participants, particularly in the group of first-episode psychosis patients with a history of cannabis use. This group may have included patients with only mild symptoms or good premorbid functioning, which could explain the appearance that cannabis users had better cognitive functioning. Indeed, research suggests that prolonged and frequent cannabis use increases the risk of impaired cognitive functioning [56,58]. [59] concluded that 44.9% of patients met criteria for lifetime substance abuse/dependence and 14.0% met criteria for present abuse/dependence. [60] used interviews to investigate the causes of substance abuse in patients with schizophrenia, finding that patients with psychosis are often medicated to decrease their anxiety, which can lead to a vicious cycle of drug dependence and worsening symptoms.

Several studies have demonstrated the potential of antipsychotics (e.g., clozapine, olanzapine, quetiapine, and risperidone) to alleviate substance abuse disorders [61]. For example, [62] found that 79% of patients with alcohol misuse disorders who took clozapine were able to achieve remission. However, while antipsychotic medication can improve symptoms in the short term, long-term use can cause various side effects, including dyskinesia and weight gain [63]. While medication response rates are generally stable, the proportion of psatients reporting significant improvement, or a "good"

DOI: 10.54254/2753-8818/60/20241404

response is comparatively low. Moreover, the excessive use of antipsychotics may exacerbate schizophrenia symptoms [64]. Thus, the choice of antipsychotics needs to be approached with caution.

2.7. Neuroimaging

Structural neuroimaging has greatly advanced the understanding of schizophrenia by detecting abnormal changes in brain structure and neurotransmitter systems (e.g., dopamine, glutamate) [65,66]. Neuroimaging techniques such as MRI, fMRI, PET, and DTI have been used to identify brain abnormalities in the early stages of schizophrenia[67,68,52]. For example, [69] combined structural MRI and PET imaging findings with synaptic measurements to show that brains of schizophrenic patients have reduced levels of protein SV2A, which may imply that they have fewer synaptic connections. [70] used MRI to measure the size and volume of different parts of the brain, finding that children with schizophrenia had lower total grey matter volume. This may be influenced by genetic factors.

Neuroimaging has increasingly been used to explore how schizophrenia affects the brain, thereby improving diagnosis, understand risk, and predict treatment outcomes [71]. [72] used MRI to investigate structural and connective changes in the brain resulting from medication. The study revealed that patients who responded to treatment showed increased activity and connectivity in brain networks involving the prefrontal cortex and striatum. This confirms the role of neuroimaging technology in determining the effectiveness of treatment. In [72] study, however, the sample size was small and different methods were used to measure treatment outcomes, making it difficult to compare results and reach firm conclusions. Changes in the condition of schizophrenia patients may arise from the disorder itself or from the effects of antipsychotic medication [65], which limits their usefulness as clinical diagnosis tools. Another issue is the prohibitive cost and low availability of certain neuroimaging methods, such as PET [66], which constrains their widespread clinical application.

Nevertheless, brain plasticity can be altered. [73] conducted social cognition training (SCT) to improve the way people with schizophrenia understand the interactions of others in class. Research indicates that in the early stages of schizophrenia, the brain may experience a disproportionately large amount of change prematurely, and treatment without timely intervention can severely damage brain structure and function and worsen symptoms [12]. Consequently, early intervention in the prodromal phase of schizophrenia (the period before symptoms appear) is critical to altering the trajectory of the disease.

3. Discussion

Building on the neurodevelopmental hypothesis, this study has examined the role of environmental factors in the psychopathology of schizophrenia, focusing on two approaches: epidemiological and neurological. Each perspective provides evidence for understanding various aspects of the complexity of schizophrenia.

Prenatal exposure to infections (e.g., influenza, toxoplasmosis, and rubella), prenatal malnutrition, and urban living are associated with alterations in fetal brain development that affect short- and long-term brain development. While these prenatal factors do not conclusively predict the development of schizophrenia, they are plausible risk enhancers, particularly when combined with genetic predispositions or environmental stressors. Research also confirms the importance of inherited traits and early-life experiences. While this study has not considered genetic influences on neurodevelopment in schizophrenia in detail, it acknowledges that genetic factors may interact with prenatal environmental risks to increase the risk of developing schizophrenia [47].

Neurodevelopmental theory further confirms that early environment and trauma can cause structural and functional changes in the brain. Childhood trauma can affect the development of brain regions associated with stress and emotion regulation, which may increase the risk of schizophrenia. Early-life trauma in individuals with schizophrenia is linked with a reduction in the total gray matter volume, particularly in the prefrontal cortex, which is involved in decision-making and impulse control. Trauma may also cause shrinkage in the hippocampus, which has an important role in memory

DOI: 10.54254/2753-8818/60/20241404

and stress response. Early-life stress is also associated with increased activity and sensitivity in the dopamine system. This affects how the brain processes stress and regulates emotion, and may contribute to development of psychiatric disorders including schizophrenia.

This study has also considered the effects of neuroplasticity on schizophrenia. Schizophrenia is related to disruptions to this process, which may prevent the brain from adequately adapting to internal and environmental stimuli. Schizophrenia is associated with abnormalities in the glutamatergic neurotransmitter system, which is crucial for neuroplasticity. This suggests that issues with glutamatergic signaling may impair the adaptability and functioning of the brain, which can increase the risk of schizophrenia.

Neuroimaging techniques provide insights into various brain features of individuals with schizophrenia, including changes in brain structure and interactions between brain regions. These techniques can support early intervention by identifying markers that predict schizophrenia risk before symptoms emerge. Neuroimaging can also identify chemical changes in the brain associated with schizophrenia, which may support the development of new treatment approaches.

There are several limitations in previous research. Notably, epidemiological studies generally depend on large populations and may fail to capture individual differences in genetic predisposition, lifestyle, and other personal factors. From a neurodevelopmental perspective, most previous studies are cross-sectional. However cross-sectional studies often do not allow enough time to observe the complete progression of schizophrenia, especially when symptoms manifest in late adolescence or early adulthood. Thus, more long-term follow-up research is needed to fully understand the outcomes.

Additionally, this present literature review is limited in scope, focusing mainly on the impact of environmental factors. It has not considered recent advances in genetics and other non-environmental fields related to neurodevelopment in schizophrenia. Future research should shift focus to longitudinal studies that track participants from prenatal to adulthood, and incorporate more interdisciplinary studies that explore gene-environment interactions.

4. Conclusion

The neurodevelopmental hypothesis emphasises the essential role of early environmental factors in the etiology of schizophrenia. The critical findings from epidemiological and neuroimaging studies highlight the importance of prenatal infections, nutritional deficiencies, urban living, childhood trauma and substance abuse in increasing the risk of this complex mental disorder. These factors can be identified and addressed through early intervention to significantly reduce the risk and severity of schizophrenia. This paper emphasises the need for continued research into the intricate interactions between genetic and environmental factors with the aim of developing more effective preventive measures and treatments.

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