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## EXPLORING THE INTERFACE BETWEEN NEUROSCIENCE AND PSYCHOPATHOLOGY: THE ROLE OF SYNAPTIC CONNECTIONS IN SCHIZOPHRENIA

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**Abstract:** INTRODUCTION: Schizophrenia is a complex neuropsychiatric condition characterized by symptoms such as delusions, hallucinations and cognitive deficits, influenced by genetic, epigenetic and environmental factors. Research focuses on synaptic plasticity and brain connections, suggesting that dysfunctions in communication between brain regions and anomalies in the extracellular matrix are crucial to the disease. METHODOLOGY: This systematic review investigates the role of synaptic connections in schizophrenia, following the PRISMA guidelines and including studies from peer-reviewed journals over the last 13 years in Portuguese, English and Spanish. Ninety-three studies were identified, of which 17 were included after strict inclusion and exclusion criteria, with qualitative and quantitative analyses. RESULTS: Current literature shows that schizophrenia is associated with synaptic and neuronal connectivity abnormalities, with genetic, epigenetic and environmental factors influencing synaptic plasticity. Research highlights the importance of the density of perineuronal networks, the function of NMDA receptors and the role of neuroinflammation in the synaptic dysfunction observed in schizophrenia. CONCLUSION: The intersection between neuroscience and psychopathology in schizophrenia reveals synaptic and neural connectivity dysfunctions that contribute to the symptoms of the disease, highlighting the importance of the integrity of synaptic connections for cognitive function. Continued research is essential to develop new therapies and identify biomarkers that can improve clinical outcomes and predict disease progression.

**Keywords:** Psychopathology, Neuroscience, Synaptic Connections and Schizophrenia.

## INTRODUCTION

Schizophrenia is a complex neuropsychiatric condition that affects millions of people worldwide, characterized by a variety of symptoms, including delusions, hallucinations and cognitive deficits. The understanding of schizophrenia has advanced significantly in recent decades, especially with the emergence of research exploring the interface between neuroscience and psychopathology. One of the central focuses of this research is the role of synaptic connections and synaptic plasticity in the pathogenesis of schizophrenia. The disconnection hypothesis suggests that ineffective communication between different brain regions, particularly between the prefrontal cortex and the parietal cortex, may be a critical factor in the manifestation of the cognitive deficits observed in the disease. Furthermore, anomalies in the extracellular matrix and in the expression of synaptic proteins have been associated with alterations in neuronal connectivity, suggesting that synaptic integrity is fundamental to normal brain function and that its dysfunction may contribute to the symptoms of schizophrenia.<sup>2,8</sup>

Recent studies have shown that synaptic plasticity, which is the ability of synapses to strengthen or weaken over time, is altered in individuals with schizophrenia. These changes can be attributed to genetic, epigenetic and environmental factors that influence neural development and the formation of synaptic circuits. Research into the expression of genes associated with schizophrenia, such as neurexin-1 and dysbindin-1, reveals that these genes play crucial roles in the formation and maintenance of synapses, and their mutations can result in impaired synaptic connectivity. In addition, the presence of perineuronal networks, which surround neurons and are essential for synaptic stability, has been implicated in the pathology of schizophrenia, with evidence that their density is reduced in

brain regions affected by the disease.<sup>8,15,16</sup>

## METHODOLOGY

This systematic review on the role of synaptic connections in schizophrenia has been prepared in accordance with the guidelines of the Principal Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). The aim is to identify the challenges related to this condition and their implications. The inclusion criteria for the studies to be reviewed include: (1) studies addressing the role of synaptic connections in schizophrenia; (2) articles published in peer-reviewed journals in the last 13 years; and (3) publications in Portuguese, English or Spanish, ensuring broad comprehension and accessibility. On the other hand, the exclusion criteria include: (1) articles that do not directly address the topic of synaptic connections in schizophrenia, ensuring the relevance of the analysis; (2) qualitative or quantitative studies that do not answer the guiding questions; (3) academic documents not published in journals; and (4) duplicate articles, in order to avoid redundancies in the analysis. The systematic literature search was carried out in the PubMed electronic databases and used standardized descriptors and a combination of keywords, including “Psychopathology”, “Neuroscience”, “Synaptic Connections” and “Schizophrenia”, adjusting the strategy as necessary for each database. The search was carried out in Portuguese, English and Spanish. In total, 93 results were identified, of which 17 were included in the review (figure 1) after a rigorous process of inclusion and exclusion. The analysis of the data collected included both qualitative and quantitative syntheses, depending on the nature of the studies included.

For studies with homogeneous results, a meta-analysis was carried out, allowing the data to be statistically combined. For those with heterogeneous results, a narrative synthe-

sis was chosen, highlighting the main trends and patterns observed in the literature. In addition, the implications of the results for clinical practice and future research in the field of neurology were discussed, with special attention to the management of schizophrenia.

## RESULTS

The results of recent studies indicate that schizophrenia is associated with a series of synaptic and neuronal connectivity anomalies. For example, research by Mauney et al. (2013) demonstrated that the density of perineuronal networks in the prefrontal cortex is significantly reduced in individuals with schizophrenia, which may compromise the integrity of synaptic connections and contribute to the cognitive deficits observed. In addition, the analysis by Berretta et al. (2020) revealed that the loss of synapses and the deterioration of associative fiber pathways in the cortex are correlated with decreased cortical activity in schizophrenic patients, suggesting that alterations in synaptic connectivity may be a factor underlying cognitive dysfunction.<sup>2,11</sup>

The research by Chen et al. (2020) also highlighted the importance of epigenetic processes in schizophrenia, suggesting that DNA methylation and other epigenetic modifications can influence synaptic plasticity and neural connectivity throughout development. In addition, studies on the function of NMDA receptors indicate that dysfunction of these receptors may be related to cognitive deficits and synaptic pathology in schizophrenia, corroborating the hypothesis that synaptic disconnection is a central mechanism in the disease.<sup>5,17</sup>

The interaction between genetic and environmental factors also plays a crucial role in schizophrenia. The literature suggests that neuroligins, which are proteins involved in synapse formation, can be affected by environmental factors, resulting in alterations in synaptic connectivity and contributing to the

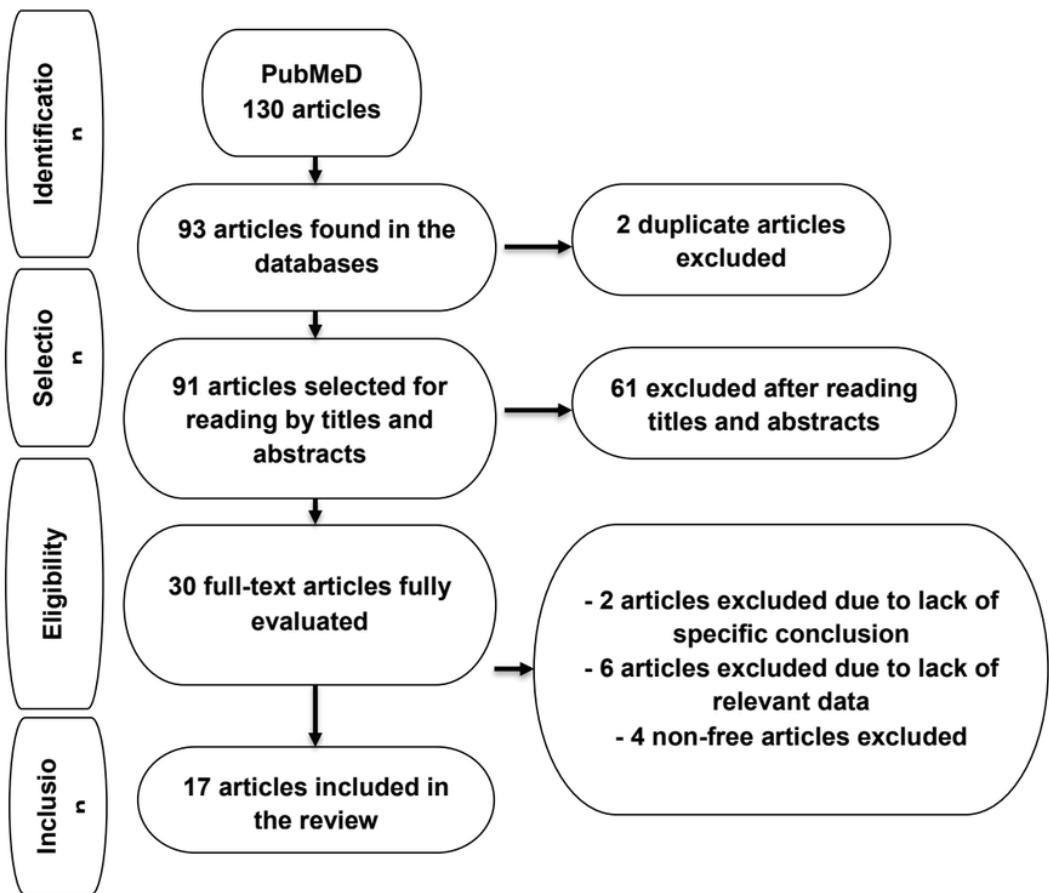


Figure 1. Flowchart of the articles included in this review.

Source: the authors.

pathology of schizophrenia. In addition, microglia activation and neuroinflammation have been implicated in synaptic dysfunction, suggesting that brain inflammation may exacerbate the synaptic abnormalities observed in schizophrenia.<sup>13</sup>

## DISCUSSION

The intersection between neuroscience and psychopathology, especially in the context of schizophrenia, has been a field of intense research, with a focus on synaptic connections and their implications for understanding and treating the disease. Schizophrenia is characterized by a series of cognitive deficits and alterations in neural functioning, which can be attributed to dysfunctions in synaptic connections and synaptic plasticity. Current literature suggests that the disconnection between different brain

regions, particularly between the prefrontal cortex and parietal areas, plays a crucial role in the pathophysiology of schizophrenia. This disconnection is often associated with deficits in working memory and contextual processing capacity, which are common features in patients with schizophrenia.<sup>8,10</sup>

One of the most intriguing aspects of schizophrenia is its relationship with the function of NMDA receptors, which are fundamental for synaptic plasticity and the formation of memories. Studies have shown that inhibition of NMDA receptors can lead to cognitive deficits that resemble those observed in schizophrenia, suggesting that NMDA receptor dysfunction may be a mechanism underlying the cognitive deficits observed in the disease. Furthermore, the administration of glycine transporter inhibitors, which act as NMDA receptor co-ago-

nists, has shown potential to restore working memory in animal models, indicating that modulation of synaptic function may be a promising therapeutic strategy.<sup>4,17</sup>

Genetics also plays a significant role in schizophrenia, with polymorphisms in genes such as NRXN1 (neurexin 1) associated with variable responses to antipsychotics. These genes are involved in synaptic connectivity and the formation of neural networks, suggesting that genetic alterations may contribute to the synaptic dysfunction observed in schizophrenia. Research into the expression of extracellular matrix proteins, such as Reelin, has also revealed that anomalies in the extracellular matrix can affect synaptic function and neuronal connectivity, implicating the extracellular matrix as an important factor in the pathology of schizophrenia.<sup>16</sup>

In addition, the presence of perineuronal networks, which involve neurons and are crucial for maintaining synaptic integrity, has been associated with deficits in schizophrenia. Studies indicate that the density of these networks is reduced in regions such as the prefrontal cortex, which can compromise the stability of synaptic connections and contribute to the symptoms of the disease. The loss of dendritic spines, which are primary sites of excitatory synaptic connections, has also been documented in patients with schizophrenia, reinforcing the idea that synaptic pathology is a central component of the disease.<sup>3,9,12</sup>

Synaptic plasticity, which is the ability of synapses to strengthen or weaken over time in response to activity, is another critical aspect in schizophrenia. Alterations in synaptic plasticity can lead to inefficient neural communication, resulting in cognitive and behavioral deficits. The research suggests that pharmacological interventions aimed at restoring synaptic plasticity may be beneficial for patients with schizophrenia, especially those who do not respond well to conventional treatments.<sup>6,7,8,14</sup>

Antipsychotics, which are the basis of schizophrenia treatment, also have complex effects on synaptic architecture and functional connectivity. Studies have shown that these drugs can induce changes in synaptic morphology and plasticity, which can influence treatment response and resistance. Understanding the mechanisms by which antipsychotics affect synaptic connectivity is essential for the development of new therapies that can improve clinical outcomes for patients with schizophrenia.<sup>6,7,15</sup>

In addition, microglia activation and brain inflammation have been implicated in the pathogenesis of schizophrenia, suggesting that the interaction between the immune system and synaptic function may be an important factor in the disease. Microglial activation can lead to apoptosis of dendritic spines, exacerbating synaptic dysfunction and contributing to the negative symptoms and cognitive deficits observed in patients with schizophrenia. This interrelationship between neuroinflammation and synaptic plasticity highlights the need for therapeutic approaches that consider both the neurochemical and immunological aspects of schizophrenia.<sup>7</sup>

Research into schizophrenia continues to evolve, with new discoveries about the importance of synaptic connections and synaptic plasticity in understanding and treating the disease. The identification of biomarkers that can predict the response to treatment and the progression of the disease is a promising area of research. In addition, exploring new therapeutic strategies, such as modulating synaptic function and restoring neural connectivity, may offer new hope for patients struggling with this complex and debilitating condition.<sup>5,13</sup>

## CONCLUSION

In short, the intersection between neuroscience and psychopathology in schizophrenia reveals a complex panorama of synaptic dysfunctions and neural connectivity that contribute to the manifestation of the disease's symptoms. The accumulated evidence suggests that the integrity of synaptic connections is fundamental to cognitive function and that their alterations can result in significant deficits in patients with schizophrenia.

Continued research into the mechanisms underlying synaptic dysfunction, including genetic, epigenetic and environmental factors, is essential for the development of new therapeutic approaches aimed at restoring synaptic connectivity and improving clinical outcomes for patients. In addition, the identification of biomarkers that can predict treatment response and disease progression represents a promising area for future research, with the potential to transform the therapeutic approach to schizophrenia.

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