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Synaptic dysfunction in schizophrenia: A neurophysiological and computational modelling approach.

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Introduction

Synaptic dysfunction has emerged as a central theme in the pathophysiology of schizophrenia, a complex and debilitating psychiatric disorder characterized by symptoms such as hallucinations, delusions, disorganized thinking, and cognitive impairments. Mounting evidence suggests that abnormalities at the synaptic level—particularly involving excitatory glutamatergic and inhibitory GABAergic neurotransmission—contribute to the disorganization of neural circuits observed in schizophrenia. Post-mortem studies have revealed reduced dendritic spine density in the prefrontal cortex of individuals with schizophrenia, indicating potential disruptions in synaptic connectivity and plasticity. Furthermore, genetic studies have implicated a range of synaptic proteins, such as neuregulin-1, DISC1, and synaptophysin, which are vital for synaptic formation and maintenance, suggesting that schizophrenia may arise from a neurodevelopmental trajectory influenced by early-life synaptic disruptions [1].

Neurophysiological investigations, particularly those using EEG and MEG, have identified abnormalities in event-related potentials (ERPs) and oscillatory brain activity in patients with schizophrenia. One of the most consistent findings is the reduction in mismatch negativity (MMN), an auditory ERP component reflecting early sensory prediction and synaptic plasticity, especially involving NMDA receptor function. NMDA receptor hypofunction has been proposed as a leading mechanism underlying the cognitive and perceptual disturbances of schizophrenia. This hypothesis is supported by pharmacological studies showing that NMDA antagonists, such as ketamine and phencyclidine, can induce schizophrenia-like symptoms in healthy individuals. Additionally, alterations in gamma-band oscillations—linked to fast-spiking parvalbumin-expressing interneurons—suggest deficits in synchronous neuronal firing critical for working memory and attention. These neurophysiological signatures provide valuable insights into the dysfunctional synaptic processes that underlie cognitive deficits in schizophrenia [2].

Computational modeling offers a powerful complementary approach to unravel the mechanistic basis of synaptic dysfunction in schizophrenia. By simulating large-scale brain networks, researchers can explore how synaptic alterations affect functional connectivity and cognitive performance. Biophysically detailed models have shown that reduced NMDA conductance at pyramidal cell synapses leads to impaired working memory and

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aberrant network dynamics resembling those observed in patients. Moreover, models incorporating altered excitation-inhibition balance can reproduce key electrophysiological abnormalities, such as reduced gamma synchrony and impaired phase-locking of neuronal populations. These models not only validate empirical findings but also enable predictions about how specific molecular or synaptic changes can cascade into large-scale network disruptions. Importantly, computational approaches allow for the testing of pharmacological interventions in silico, accelerating the development of targeted treatments [3].

Translational research that integrates neurophysiological data with computational modeling has begun to bridge the gap between molecular dysfunction and clinical phenotype in schizophrenia. For instance, studies combining EEG measures with dynamic causal modeling (DCM) have demonstrated reduced synaptic gain in cortical circuits, implicating a failure in synaptic efficacy rather than a total loss of synapses. DCM enables inference about hidden neuronal states and synaptic parameters from observed EEG or fMRI data, making it possible to test hypotheses about the role of specific neurotransmitter systems. Similarly, machine learning techniques applied to large-scale datasets can identify biomarkers of synaptic dysfunction predictive of disease onset or progression. These advances hold promise for the development of precision medicine approaches in schizophrenia, where treatment is guided by individualized neural signatures rather than broad symptom categories [4].

Despite significant progress, several challenges remain in elucidating the full extent of synaptic dysfunction in schizophrenia. First, the heterogeneity of the disorder complicates efforts to identify universal synaptic deficits. Some individuals may exhibit predominant NMDA receptor dysfunction, while others may have deficits in GABAergic transmission or synaptic pruning mechanisms. Second, while computational models offer detailed predictions, they often rely on simplifying assumptions that may not fully capture the complexity of human neural systems. Additionally, integrating findings across scales—from genes to behavior—requires multi-modal data and sophisticated analytical frameworks. Lastly, current treatments remain largely symptom-based, with limited efficacy for cognitive impairments. A deeper understanding of synaptic dysfunction could pave the way for novel interventions targeting early synaptic alterations, potentially altering the course of the illness before chronic symptoms become entrenched [5].

Conclusion

Synaptic dysfunction stands at the core of contemporary models of schizophrenia, offering a unifying framework that links molecular abnormalities, neurophysiological disruptions, and clinical symptoms. Through the convergence of empirical research and computational modeling, we are beginning to decipher how specific synaptic alterations—particularly involving NMDA receptor hypofunction and excitation-inhibition imbalances—give rise to the disordered thought processes and cognitive deficits characteristic of the disease. While challenges persist, especially in translating these findings into effective treatments, the integration of neurophysiological techniques with computational frameworks offers a promising path forward. Future efforts should focus on refining these models, expanding longitudinal studies, and developing targeted therapeutic interventions that address the synaptic roots of schizophrenia.

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