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BJPsych Editorial

Towards a unified theory of the aetiology of schizophrenia

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Summary

We emphasise the existence of two distinct neurophysiological subtypes in schizophrenia, characterised by different sites of initial grey matter loss. We review evidence for potential neuromolecular mechanisms underlying these subtypes, proposing a biologically based disease classification approach to unify macro- and micro-scale neural abnormalities of schizophrenia.

Keywords

Schizophrenia; aetiology; biotype; neuromolecular mechanism; hippocampus.

Schizophrenia is a complex and heterogeneous mental disorder with a rich history of evolving pathophysiological explanations. One such long-standing hypothesis is the synaptic hypothesis, which posits that aberrations in synaptic function play a pivotal role in the aetiology of schizophrenia. Building on this groundwork, Keshavan et al revisited the synaptic hypothesis in 1994, proposing an intricate interplay of excessive cortical pruning and insufficient subcortical pruning (version II). More recently, Howes et al described a multi-hit model in which genetic and environmental risk factors increase the susceptibility to excessive synapse elimination.[1] Synaptic loss disrupts the balance of cortical excitation–inhibition, contributing to cognitive deficits and negative symptoms. Aberrant synaptic pruning also leads to disrupted projections to striatal regions, affecting the dopamine system and thereby giving rise to psychosis (version III).[1] The synaptic hypothesis (version III) can be further supplemented from two perspectives. First, it needs to elucidate the specific brain regions associated with initial synaptic loss in schizophrenia. Second, the hypothesis should account for the heterogeneity of the disease in terms of clinical symptoms, disease progressions and treatment responses. This suggests that different neurobiological pathways may exist in subgroups of patients. Identification of brain regions in which grey matter loss is initiated could help us look for effective target sites for intervention, which is particularly needed to alleviate cognitive deficits and negative symptoms. Parsing disease heterogeneity using biologically based subtyping will ultimately enable us to devise individualised prevention and treatment strategies.

Here, we present a perspective that underscores distinct sites of pathophysiological origins in two subtypes of schizophrenia. In a recent study, we utilised a novel machine learning algorithm called Subtype and Stage Inference (SuStaIn) to identify subgroups of patients with similar grey matter loss trajectories using brain volume information derived from magnetic resonance imaging (MRI).[2] This approach models the sequence of grey matter loss across brain regions in each subtype and allows for classification of patients based on their brain atrophy trajectories. Our application of SuStaIn reveals that grey matter loss in schizophrenia can be best characterised by two distinct trajectories: a cortical-predominant progression that begins in Broca's area and the fronto-insular cortex (subtype 1) and a subcortical-predominant progression that begins in the hippocampus (subtype 2). The two subtypes exhibit obvious differences in brain anatomical pathology: cortical volume is more extensively reduced in subtype 1, whereas subcortical volume reduction is more pronounced in subtype 2. As brain atrophy progresses, individuals exhibited worse negative symptoms in subtype 1. In addition, we provided preliminary support for the prognostic potential of schizophrenia subtypes. Treatment data showed that the 3 months of antipsychotic medications had more improvement in positive symptoms in subtype 1 compared to subtype 2. In addition, the outcomes of transcranial magnetic stimulation (TMS) as an adjunct to antipsychotics were better for these patients characterised with less loss of grey matter (Fig. 1).[2]

To delve deeper into the neuromolecular mechanisms underlying the two subtypes, it is imperative to link our results with the known dysfunction in the dopamine and glutamate systems in schizophrenia.[3] The different neurochemical abnormalities may have potential implications for treatment outcomes. Below we review pertinent studies on the pathology of the two subtypes in schizophrenia.

Prefrontal pathology in schizophrenia

In subtype 1, the initial occurrence of grey matter loss is notably observed in Broca's area and the fronto-insular cortex,[2] which is consistent with our previous results showing that dysconnectivity in first-episode schizophrenia predominantly centres around Broca's area, and this dysconnectivity correlates with the pathway polygenic risk score (PRS) of language-related genes. Anatomically, the dorsolateral prefrontal cortex projects to the caudate and rostral putamen (associative striatum) and receives feedback connections via the thalamus. This pathway represents one of the classic cortico–basal ganglia pathways that have been implicated in the pathophysiology of schizophrenia.

Neuroimaging studies provided preliminary evidence of prefrontal cortex involvement in striatal dopaminergic dysfunction in schizophrenia. Specifically, these studies reported a negative correlation between frontal cortical volume or activation and striatal dopamine levels measured using positron emission tomography (PET). Pharmacological studies injecting low-dose amphetamine (a dopamine agonist) into healthy volunteers found an increase in striatal dopamine release, and that dopamine level correlated with prefrontal cortex morphology. Animal studies also suggested that dopamine depletion in the prefrontal cortex leads to dopamine elevation in the nucleus accumbens in the midbrain and striatum. These collective observations point to a close relationship between striatal dopaminergic dysfunction and prefrontal cortex abnormalities in schizophrenia.

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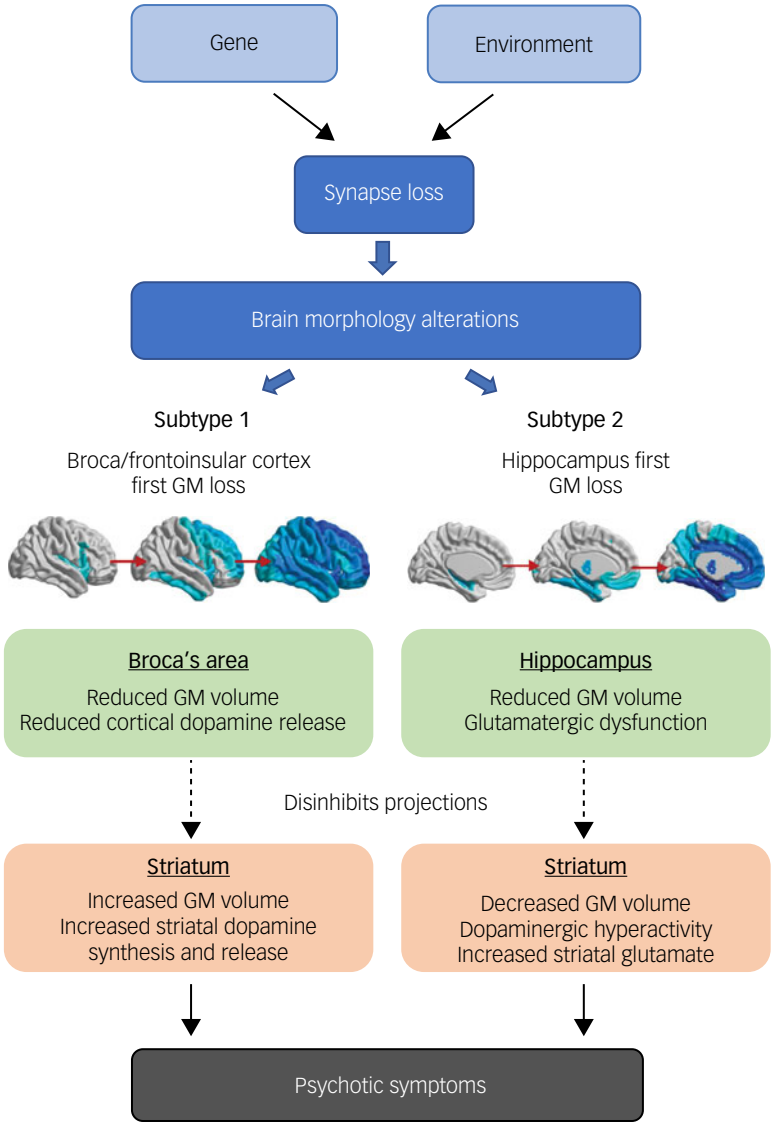

Fig. 1 A unified theory integrating macro- and micro-scale neural abnormalities of schizophrenia. Genetic and environmental risk factors increase the susceptibility to excessive synapse elimination during development. Synaptic loss results in altered structural morphometry, characterised by reduced grey matter (GM) volume, separately initiating at the prefrontal cortex (Broca's area and the fronto-insular region) and hippocampus. The reduced dopamine release in the prefrontal cortex or glutamatergic dysfunction in the hippocampus may result in dysregulated projections to the striatum. The final results include dopaminergic neuron disinhibition and increased glutamate levels in the striatum, which gives rise to a range of psychotic symptoms.

Although the precise mechanism linking striatal dopaminergic dysfunction and prefrontal cortex abnormalities is still unclear, some recent studies suggested that glutamate-mediated excitotoxicity in the medial prefrontal cortex may mediate the influence of the prefrontal cortex on the striatum.[2] In our results, patients of subtype 1 had better improvement in positive symptoms following short-term antipsychotic treatment, suggesting the potential benefits of early intervention for such patients. However, further investigation is warranted to investigate the long-term treatment outcomes for both subtypes.

Hippocampal pathology in schizophrenia

In subtype 2, grey matter loss initiates in the hippocampus,[2] consistent with studies highlighting this abnormality in the early phase of the disease. Studies in high-risk individuals with prodromal symptoms also found abnormalities in the hippocampus and suggested that lower baseline CA1 volume could predict conversion to psychosis up to 2 years later.

A growing body of evidence points towards glutamatergic dysfunction in the hippocampus,[3] potentially underpinning both positive symptoms and cognitive deficits in schizophrenia. Regarding positive symptoms, the hippocampal glutamatergic dysfunction model suggested that hypofunction of glutamate receptors on parvalbumin-expressing gamma-aminobutyric acid (GABA)-ergic interneurons in the hippocampus may disinhibit pyramidal neurons and trigger downstream dopaminergic hyperactivity. Supporting this hypothesis, a study found that CA1 hypermetabolism precedes hippocampal atrophy in high-risk individuals and a similar progression pattern in a ketamine-injected mouse model. This study also suggested that the disinhibition of parvalbumin-expressing GABA neurons in the hippocampus may lead to extracellular glutamate release and drive this pathogenic cascade. Human pharmacological studies replicated the finding that ketamine induces glutamate + glutamine (Glx) increase in the

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hippocampus, with Glx level negatively correlated to a decrease in functional connectivity between the hippocampus and other brain regions including the cingulate and medial prefrontal cortex. Beyond positive symptoms, the impaired excitation–inhibition balance in the hippocampus may contribute to cognitive deficits in schizophrenia, particularly concerning episodic memory and replay-associated ripples.

However, amid these compelling findings and theoretical constructs, some negative findings also warrant attention. For example, a muti-model neuroimaging study failed to find a significant correlation between hippocampal glutamate and striatal dopamine synthesis levels in 51 clinical high-risk individuals and 19 healthy controls. Another study found that hippocampal Glx level is related to the duration of untreated psychosis (DUP): only patients with long DUP (>12 months) showed a higher hippocampal Glx level. These findings underscore the existence of individual variations within the patient group, which may be influenced by illness duration and symptom profiles, resulting in conflicted research findings.

Research and clinical implications

The two neurophysiological subtypes of schizophrenia discussed in this article may further enrich the synaptic hypothesis and offer insights to guide the development of more effective treatment strategies for schizophrenia.

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Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Author contributions

All authors contributed to the conceptualisation, writing and revision of the paper.

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Declaration of interest

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