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Commentary

Towards a unified theory of the aetiology of schizophrenia: commentary, Shergill et al

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Schizophrenia; systems neuroscience; neuroimaging; treatment response.

Response

Diagnostic systems in medicine go through phases of evolution. Historically, medical diagnoses relied heavily on descriptive observations of symptoms and physical manifestations, with less emphasis on underlying mechanistic explanations. However, with the increase in anatomical and physiological understanding of disease processes, the descriptive disease model gradually gave way to a more systematic understanding of disease processes in which physicians correlate the observed symptoms with the underlying physiological abnormalities.

Schizophrenia is a complex disorder characterised by significant heterogeneity in behaviour, psychological function, neural network dysfunction, and synaptic and cellular dysfunction. This raises the question of how to link these processes together at different levels in a coherent whole. Several models have been proposed to link these processes using a systems neuroscience approach.[1] Jiang and colleagues propose a bold unified theory of the aetiology of schizophrenia, primarily based on the application of data-led machine learning approaches to structural neuroimaging data from individuals with schizophrenia.[2]

The development of structural brain imaging techniques and their application to understand the aetiology of schizophrenia achieved prominence in 1976, when the first reports by Eve Johnstone and Tim Crow, using computed tomography brain imaging, showed enlarged ventricles in people with chronic schizophrenia.[3] At the time this was controversial, and a subsequent letter to the Lancet by Denis Hill suggested that schizophrenia is a functional psychosis and that cases with such brain abnormalities are organic psychoses that by definition cannot be schizophrenia; however, the somewhat circular nature of this argument was noted by other commentators.[4] Despite this criticism, the paper was considered a validation of the Kraepelinian view that schizophrenia may have a neurodegenerative component, and triggered a change in research direction that encouraged neuroimaging methods to study psychosis.[4]

Jiang and colleagues have attempted to address the challenges of a unified model by proposing a biologically based disease classification that unifies macro- and micro-scale neural abnormalities while looking longitudinally at disease progression. They build their theory on the basis that differential degrees of regional synaptic loss could be a mechanism underlying subtypes of schizophrenia. Therefore, using structural neuroimaging to examine regions of grey matter loss could potentially index brain regions that may be amenable to differential novel interventions. They also suggest that such regional grey matter loss in schizophrenia would be associated with a behavioural profile characterised by greater cognitive deficits and negative symptoms. They used a novel machine learning algorithm to identify subgroups of people based on longitudinal trajectories of grey matter loss; these were linked to the profile of clinical symptoms and treatment response. Two distinct subtypes were identified: a cortical-predominant progression that begins in Broca's area/frontoinsular cortex (subtype 1) that had more prominent negative symptoms and demonstrated greater improvement in positive symptoms after antipsychotic treatment, and a subcortical predominant progression that begins in the hippocampus (subtype 2). Treatment with transcranial magnetic stimulation (TMS) adjunct to antipsychotics was better for individuals at early stage of both subtypes.

Their theory was supported by data from the broad corpus of imaging literature that highlight the role of fronto-striatal loops and the established correlation between frontal cortical volume loss and increased striatal dopamine levels. Given the lack of efficacy of contemporary dopaminergic blocking antipsychotic medication in a subtype of refractory schizophrenia, the role of glutamate-mediated excitotoxicity in the medial prefrontal cortex was suggested to potentially play a role in mediating the prefronto-striatal connectivity. They suggest that a more prominent glutamatergic dysfunction could be reflected in the schizophrenia subtype 2 characterised by early hippocampal change. Indeed, hippocampal glutamate dysfunction has been associated both with dopaminergic hyperactivity mediated via GABA-ergic interneurons[5] and cognitive deficits observed in schizophrenia. Although this model has the benefit of offering a novel application of machine learning to an easily accessible neuroimaging metric, the relationship to treatment response and the basic science changes observed in schizophrenia appear to be far more speculative. The authors note that there is a body of data that does not support their classification and this may be because of the heterogeneity observed in the illness, notably from sampling differences in illness duration and symptom profiles.

However, given the heterogeneity of the disease, it will be critical to continue our efforts to fractionate the different subtypes of schizophrenia, if we aim to reach our target of developing better personalised treatments. Structural neuroimaging data provide accessible neural network metrics at the focal point of the systems neuroscience paradigm – in between the cellular dysfunction and alterations in behaviour presenting as symptoms – and has the benefit that it can be examined in both clinical and preclinical populations.[6] There is a caveat that grey matter volumetric measurements are far from optimal measures for indexing changes in cellular or synaptic changes in schizophrenia. The changes in grey matter volume are impacted by multiple factors that are potential consequences rather than cause of pathology, including the effect of antipsychotic medication, chronic stress, physical illness and duration of symptoms. The use of treatment response as a stratifying factor offers one of the outcome metrics with better face validity in order to distinguish between different subtypes of schizophrenia. The current systems neuroscience models applied to schizophrenia – exemplified by this paper – invoke abnormalities of the glutamatergic system to address the explanatory gaps in the more mechanistic early dopaminergic models. Examining illness trajectories with multi-modal imaging using treatment response as a classifier may offer the optimal approach towards developing more robust phenotypic subtyping of schizophrenia.[7]

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Data availability

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Author contribution

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Declaration of interest

None.

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