Commentary

Probing the Brain White Matter in Psychotic Disorders Using Neuroimaging

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Psychotic disorders are severe psychiatric conditions which are characterised by losses, namely the loss of touch with reality during which the patient may often experience auditory hallucinations, persecutory delusions, and which are often accompanied by a crippling loss of awareness about the need for treatment and ensuing social disability.[1] The paradigmatic example of a psychotic disorder is schizophrenia which occurs in 1% of the population and the patient often suffers from a loss of ability to plan, work and not infrequently, a loss of interpersonal relationships in the longer term.[2] According to the World Health Organisation (WHO), schizophrenia lists amongst the top 10 leading causes of years lost to disability worldwide,[3] and is one of the medical conditions with the highest disability weights.[4] Due to the huge burden of illness for both patients and carers, there is a pressing need to better understand its underlying neurobiology so as to inform and hopefully reform treatment of these incapacitating conditions.

In the study of the pathophysiology of any complex neurobehavioural disorder including psychotic disorders, one seeks to look for unifying hypotheses which take into account 3 cardinal aspects, namely the context of continuing evidence, core neurobiology based on current investigations, as well as clinical relevance to the patient's experience.[5] In this regard, one such hypothesis posits that white matter brain changes underlie psychotic disorders and its clinical manifestations, and which can be studied with current neuroimaging modalities including structural magnetic resonance imaging (MRI) and diffusion tensor imaging.[6] In terms of the continuity of evidence, there is mounting evidence to suggest that brain white matter anomalies underlie psychotic conditions from neuropathological, genetic and neuroimaging studies. Earlier neuropathological studies found reductions in the quantity as well as altered spatial distributions of cortical oligodendrocytes in patients with schizophrenia when compared with controls.[7,8] One of the earliest genetic studies found differential expression of myelination-related genes suggesting a disruption of oligodendrocyte function germane to white matter brain changes.[9] This was further supported by subsequent studies highlighting dysregulation of white matter genes in psychotic patients versus healthy controls.[10,11] Later in vivo neuroimaging studies of schizophrenia have reported reductions of specific white matter brain volumes involving the frontal, temporal and parietal cortical regions.[12]

In terms of core neurobiology, there are several patterns that have been noted. In early onset schizophrenia, disruptions of white matter integrity were found in the cortical, subcortical brain regions and white matter associative and commissural tracts, suggesting that changes of cortical-subcortical white matter integrity were found at an early stage of the disorder.[13] In more chronic schizophrenia, differences in the area and volume of the commissural white matter tract, corpus callosum, were greatest in patients whose condition was longstanding relative to patients with a first episode and controls.[14] These findings emphasise the need to understand the wider brain network as well as progressive white matter changes over the illness course. Another area of interest regarding core neurobiology relates to sustained efforts to examine relationships between genetic biomarkers and intermediate phenotypes such as brain white matter changes. The proliferation of recent genome-wide association studies (GWAS) for the last few years encapsulates the vigour in trying to map out heritable biomarkers which may allow better detection of illness and delineation of disease mechanims.[15] Past GWAS have pointed to genetic signals related to neuronal communication, signaling, and neuroplasticity underlying schizophrenia.[16] A recent landmark study involving 150,000 subjects, 300 collaborators and spanning 30 countries uncovered more than 80 novel genetic loci which have not been previously identified and which are related to body systems including the immune system and gut brain axis.[17] This and other collaborative strategies in medicine would augur well for the future as resources are pooled together by different international groups to generate more generalisable findings in the united quest to advance our understanding of disease mechanisms which can later point

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towards potential treatment targets. Based on such genetic signals from GWAS, we have studied their genotype-intermediate phenotype relationships related to brain white changes in schizophrenia. We found that genome-wide supported susceptibility genes such as *ZNF804A*, *NRGN* and *CACNA1C* affect cortico-limbic white matter network,[18] thalamocortical morphology,[19] as well as extensive cortical white matter integrity,[20] respectively, in our local patients with schizophrenia.

Regarding daily clinical relevance, there are ongoing efforts to elucidate brain white matter changes underlying psychotic phenomenology. Hubl et al[21] found specific greater fractional anisotropy (FA) in the temporoparietal section of the arcuate fasciculus and anterior corpus callosum which are related to auditory hallucinations, suggesting ongoing neurodevelopmental or neuroplastic changes involving white matter tracts. We found that the distressing control-override passivity phenomena was associated with white matter integrity changes involving the frontal cortex, cingulate gyrus and subcortical structures such as thalamus and striatum.[22] For positive psychotic symptoms, the white matter integrity of fornix in proximity with the medial temporal lobe correlated negatively with the severity of these clinical manifestations as measured using the Positive and Negative Syndrome Scale (PANSS).[23] Furthermore, greater left FA lateralisation in the temporal segment of the arcuate fasciculus was associated with more severe positive psychotic symptoms supporting the notion of aberrant fronto-temporal connectivity underlying schizophrenia psychopathology.[24] It is hoped that a better understanding of these white matter changes may further support the development of new promyelinative therapies including biological interventions such as brain-derived neurotrophic factor mimetic peptides, growth factor release promoters, glutamatergic antagonists[25,26] and even psychosocial interventions with the prospect of influencing white matter neuroplasticity.[27] Peering ahead, there is even greater need to better integrate the multiple research platforms including neuroimaging, genomics, systems biology models, and clinical correlations in order to test different unifying hypotheses to get us closer to clarification of pathogenetic mechanisms underlying psychotic disorders.

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