One size does not fit all: trans-diagnostic immune signatures for personalized treatment of psychoses

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Immune dysregulation has been widely implicated in the pathophysiology of schizophrenia and related psychoses, as well as in depression and other psychiatric disorders.[1-3] Meta-analyses consistently show elevated levels of pro-inflammatory cytokines in the blood and cerebrospinal fluid of patients during a first episode and before drug treatment. Longitudinal studies suggest that inflammation in childhood/adolescence precedes the onset of psychoses and depression in adulthood. Large Mendelian randomization studies, which use genetic variants that regulate the levels/activity of a biomarker, have provided compelling evidence that inflammation, in particular interleukin-6, is unlikely a consequence of residual confounding or reverse causation and may be causally related to both psychoses and depression. The reasons for the apparent trans-diagnostic effect of inflammation are still obscure, but it is possible that inflammation is a biological mechanism for symptoms commonly shared across psychiatric disorders.

Approximately one-third of patients do not respond to conventional monoamine drug treatment, and a similar proportion has signs of inflammation in the blood that predict poor treatment response. Targeting the immune system may thus be promising for innovative treatment strategies. However, an important paradoxical finding is that large clinical trials have generally failed to show the benefit of adjunctive anti-inflammatory treatments. Notably, a recent study reported that minocycline, an antibiotic that inhibits the inflammation of microglia (resident immune cells in the brain), was as ineffective as adjunctive therapy for schizophrenia.[4]

A potential explanation for the null findings is that previous trials were focused on categorical diagnosis and the ''one size fits all'' approach to treating heterogeneous syndromes. Since inflammation is likely to occur only in a subset of patients, conventional frameworks are too reductionist to transcend traditional diagnostic boundaries and characterize heterogeneous and trans-diagnostic symptom profiles. Innovative approaches, such as the Research Domain Criteria and the Hierarchical Taxonomy of Psychopathology, propose a shift from single disease entities towards trans-diagnostic dimensions of symptoms and multifactorial constructs that map within and across many disorders.[5] Recent research[6] raises the possibility that features occurring in several psychiatric disorders share a common inflammatory substrate unrelated to diagnosis. Emerging investigation[3] has begun to apply symptom-based approaches and Mendelian randomization to test the specificity and causality of associations, unveiling specific symptoms underpinned by trans-diagnostic inflammatory mechanisms, particularly anhedonia, somatic/neurovegetative symptoms (fatigue, appetite/sleep disturbance), and cognitive impairment. Such advanced approaches may provide significant insight into immune pathogenesis and inform more homogeneous sample selection for future clinical trials.

Identifying biomarkers that transcend current diagnostic limits to translate the complex neurobiology of trans-diagnostic symptoms/domains will be challenging but holds the potential to move psychiatry forward to successful personalized treatment.[6] For example, low counts of blood T regulatory cells (a subpopulation of lymphocytes that maintain immune homeostasis) correlate with more negative and cognitive symptoms in some patients with psychoses[2]. Future trials aiming to boost Tregs in blood should target patients with primary negative/cognitive symptoms and consider deep immuno-phenotyping of peripheral blood immune cells combined with conventional cytokine assays and multimodal neuroimaging integrated into a symptom-network.[2,6] Biomarker-based machine learning is beginning to disentangle disease heterogeneity, identify comorbid trans-diagnostic symptoms, and reliably classify patients based on complex immunological features that could affect treatment decisions but may be hidden within conventional categorical diagnoses.[7] These will be key to identifying trans-diagnostic immune signatures and patients with signs of immune dysregulation (who are more likely to benefit from adjunctive anti-inflammatory treatments) for inclusion in future personalized trials.

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