Biological Psychiatry: Celebrating 50 Years

Commentary

Evaluating Associations Between Non-neuronal Autoimmune Disorders and Psychosis

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The relationship between autoimmunity and psychotic illness is complex. Converging evidence for an association between systemic and brain-specific innate and adaptive inflammatory markers with psychotic illness—for example, raised C-reactive peptide and interleukin-6 (1) levels—has provided new targets for clinical trials of therapies. Increasingly, psychiatrists and neurologists are asked to consider possible inflammatory causes for new onset neuropsychiatric symptoms. In patients with autoantibodies to specific neuronal or glial cell surface markers, there may be a causal relationship of inflammation-induced psychosis—for example, if antibodies disrupt synaptic transmission. The archetypal example of this is anti–*N*-methyl-D-aspartate receptor antibody encephalitis, which was initially described in young women who presented with psychosis and who were often admitted to a mental health unit before developing seizures, movement disorders, and autonomic disturbance (2), who have an excellent clinical response to targeted immunotherapies. Following the advances in neuroimmunology over the last decade, patients are frequently screened for antibodies targeting neural or glial antigens, and even then, there are often confusing results. The identification of antibodies to LGI1 and CASPR2 proteins in patients who were previously seropositive on voltage-gated potassium channel complex radioimmunoassays and the delineation of their associated clinical syndromes has helped us to be critical of using positive serology to define disease (3). Therefore, it remains unclear whether patients with psychosis and *N*-methyl-D-aspartate receptor antibodies have a mild form of encephalitis or clinically irrelevant or false positive antibodies, and this is an active area of research.

The relationship between clinically distinct non-neuronal autoimmune (NNAI) diseases and psychotic illness is much less clear. Some systemic disorders, such as systemic lupus erythematosus (SLE), have well-described neurological or psychiatric associations. Most systemic autoimmune disorders, however, are not typically associated with neuropsychiatric symptoms or active central nervous system inflammation, for instance Graves' disease (thyrotoxicosis). Several studies have suggested an association between NNAI diseases and psychosis or schizophrenia, though the reasons for such associations are not understood. In this issue of *Biological Psychiatry*, Cullen *et al.* (4) provide the first meta-analysis of these studies and demonstrate a small overall positive association between NNAI diseases and psychosis or schizophrenia (odds ratio, 1.26 [95% confidence interval, 1.12–1.41]), though with significant variation by diagnosis and a considerably large heterogeneity measured (I^2 = 88.08), which means that the data require caution in interpretation.

For individual NNAI diseases, small, positive correlations were found between psychosis and each of pernicious anemia, pemphigoid, psoriasis, celiac disease, and Graves' disease. Conversely, negative correlations were found with ankylosing spondylitis and rheumatoid arthritis, and no significant association was found with alopecia areata, Crohn's disease, polymyalgia rheumatica, SLE, type 1 diabetes, or ulcerative colitis. The positive associations are between primarily organ-specific autoimmune disorders (i.e., Graves' disease and pernicious anemia) and not multiorgan systemic diseases (e.g., rheumatoid arthritis), and while the classification of autoimmune disorders in this way is not clear cut, the underpinning biology may reveal mechanisms that can explain a proportion of psychotic illness. Epidemiological studies rely on clinical diagnosis data that have not caught up with the emergence of mechanistic definitions of autoimmune disease and variants, for example autoinflammatory diseases (5) and autoinflammatory components of autoimmune diseases, and therefore teasing apart biological mechanisms is a challenge from studies of this type. On examining the temporal relationship between psychosis and NNAI diseases, a positive association between both diagnoses was found, both for NNAI diseases preceding psychosis and vice versa. Genetic variants, exposure and response to infection, the nature and the effects of medications used as therapies in the disorders, and alterations in the gut microbiome are mechanisms that may underpin the effects seen in this study.

The lack of association found between SLE and psychosis in this meta-analysis is surprising but may be due to the nature of the captured data and variability in definitions of neuropsychiatric lupus in the literature. Perhaps enriched clinical cohorts are needed to tease out causality and relationships in complex disorders like SLE—see, for example, Roberts *et al.* (6), who demonstrated evidence of an association between depression and the risk of developing SLE in the longitudinal U.S. Nurses' Health Study cohort. However, we must be wary of confirmation bias, and the data from Cullen *et al.* (4) should be given due weight.

This work raises important questions for understanding the role of autoimmunity in psychotic illness. If inflammation does have a pathogenic role in psychotic illness, then at what stage(s) in life does it have such an effect: does inflammation in fetal brain development increase the risk of subsequent adolescent psychosis, or is aberrant inflammation an important modifier of disease course and therefore amenable to therapeutic intervention later in life? What are the roles of long-term therapies for autoimmune diseases (including corticosteroids), or therapies for psychotic illness in manifesting the

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associations seen? Should we study clinical disease diagnoses or mechanistic pathways? In many instances, pathway analysis is now the most fruitful research, and there are likely to be unifying mechanisms underpinning disparate autoimmune diseases that could be relevant to psychiatric illness, such as an approach that has led to find variants in *TNFSF13B* (which encodes B-cell activating factor) to be relevant to multiple sclerosis and SLE (7). Variants in complement pathways could give rise to shared mechanisms in NNAI diseases and psychotic illness or bystander effects—for example, aberrant synaptic pruning (8).

Does rheumatoid arthritis have an artifactual negative association with psychosis because rheumatoid arthritis is predominantly a disease of older adults, a population perhaps enriched by those protected from psychotic illness, or are there biological mechanisms that could be exploited to help treat psychiatric disease? Malavia *et al.* (9) have recently explored shared mechanistic pathways emerging from an analysis of the pleiotropic genetic associations from genome-wide association studies of schizophrenia and rheumatoid arthritis, e.g. HLA-B, that supports the latter view (9). Benros *et al.* (10) have speculated that the genetic variants here may influence response to infections as a further mechanism.

These lines of work are all still in early stages. No definite shared unifying genetic susceptibility and/or infection trigger has been demonstrated for NNAI diseases and psychosis or schizophrenia to date, and nor should we expect to find one alone. It seems most likely that the associations seen here are multifactorial and that further research, particularly into mechanistic pathways revealed by genetic data, will help develop advances in precision-(immuno)psychiatry.

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