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Biological Psychiatry

Commentary

Linking Infections to Mental Disorders via Genetics

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The link between infections and mental disorders has been investigated since the 1880s. In 1887, through observing his own patients, Julius Wagner-Jauregg, Nobel Laureate and a leading psychiatrist, published a paper concluding that fever could cure psychoses and discussed infecting patients to induce fever as a therapeutic intervention (1). Epidemics and pandemics throughout history suggest that infections could trigger various mental disorders and influence the course of mental health and infectious disorders. During the influenza epidemic in 1890, Emil Kraepelin, a key founder of modern psychiatric classification, described 11 patients who presented with psychiatric symptoms ranging from depressed mood, cognitive deterioration, involuntary movements, paranoia, hallucinations, and delirium (2). During the Spanish flu in 1918, Karl A. Menninger linked influenza with neuropsychiatry through observations in 100 patients with influenza (3). The COVID-19 pandemic has also revealed a link between COVID-19 infection and mental disorders. A cohort-based study of adults with COVID-19 infections demonstrated that those with schizophrenia (SCZ) had a 2.5-fold increased risk for mortality, even after controlling for cardiovascular disease, diabetes, smoking, obesity, age, sex, and race (4). On the other hand, among patients with no previous psychiatric history, a diagnosis of COVID-19 was associated with increased incidence of a first psychiatric diagnosis in the following 14 to 90 days compared with 6 other health events; this risk was independent of known physical health risk factors for COVID-19 (5). These studies highlighted the link between mental disorders and the immune system and supported Kraepelin, who rightly postulated that the immunological defense and adaptation system should be made a major focus in psychiatric research.

Current epidemiological and clinical data correlate between early-life immune dysfunction and an increased risk of physical and mental problems later in life. For example, higher rates of SCZ have been reported among individuals exposed to infections in early life (6), and children with streptococcal infections are shown to have an increased risk of obsessive-compulsive disorder during adulthood (7). Recently, a nationwide study in Denmark strengthened the notion that infections in childhood could lead to the development of mental illness later (8). Despite the growing evidence of associations between infection and an increased risk of mental health outcomes, several questions remain unanswered. For instance, it is unknown whether the association between infection and mental disorders is common or specific to some mental disorders, and the direction of causality remains unclear. There are several proposed mechanisms whereby infection may be linked to mental disorders. The first mechanism is direct neurotoxicity, in which infective agents can cross the blood-brain barrier through active and/or passive transport, directly influencing the brain and central nervous system. This theory was backed by the results from the Danish study showing that the risks of mental disorders increased with and depended on the amount and severity of the infections (8). The second mechanism is disturbed gut microbiota. Anti-infective agents may influence the microbiome of the gut, disturbing microflora and altering the brain via the vagus nerve, resulting in alterations in the blood-brain barrier and subsequently increasing the risk of mental disorders. The third mechanism is common risk factors, such that common environmental risk factors such as stress might lead to an increased likelihood of both infections and mental disorders. The link between infections and mental disorders might also reflect common genes that drive an increased genetic susceptibility for both.

In the current issue of *Biological Psychiatry*, Shorter *et al.* (9) disentangled the association between mental disorders and infectious diseases through the lens of the common risk factors hypothesis. Through cross-disorder genetic analysis of results from large-scale genome-wide association studies (GWASs), they characterized the underlying shared genetics (i.e., pleiotropy) between mental disorders and infectious diseases.

Shorter *et al.* (9) used a case-control population based on iPSYCH 2012 dataset involving 6 case groups—major depressive disorder, bipolar disorder, autism spectrum disorder, anorexia, attention-deficit/hyperactivity disorder, and SCZ—and control subjects that included individuals without a diagnosis of the corresponding mental disorder from a randomly chosen cohort population. First, the authors confirmed the link between the infectious diseases and the risk of developing a mental disorder. To this end, they interrogated the effect of infection on the risk of a mental disorder given the sex, year of birth, and genetics (the first 10 genetic principal components) and found a significant risk for all mental disorders except anorexia regardless of the order of manifestation of the first recorded infection and the diagnosis of the mental disorder (hazard ratios ranging from 1.25 to 1.56; $p \leq 2.11 \times 10^{-9}$). The confirmed link was characterized via bivariate linkage disequilibrium score regression analysis, with the resulting genetic correlation scores (r_g) indicating significant shared genetic overlaps between risk of infection and posttraumatic stress disorder, major depressive disorder, attention-deficit/hyperactivity disorder, bipolar disorder, and SCZ (r_g ranging from 0.16 to 0.88; $p \leq 5 \times 10^{-4}$). Complementary to these results, Nudel *et al.* (10) found strong links between the occurrence of infection and presence of at

SEE CORRESPONDING ARTICLE ON PAGE 283

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least one psychiatric disorder (odds ratio = 1.72; $p = 2.6 \times 10^{-108}$) based on GWAS results of 65,000 Danish individuals assessed for multiple infections and mental disorders from birth to the end of follow-up. They also identified an r_g of 0.496 between diagnosis of an infection and diagnosis of a mental disorder. Further genetic analyses of the results by both Shorter *et al.* (9) and Nudel *et al.* (10) could provide deeper insights into the genetic association between the two disorders. For example, pairwise or case–case GWAS analysis could inform the causal genetic loci associated with both disorders. Functional characterization of the identified shared genetic loci through gene-based analyses, quantitative trait loci analysis, or functional enrichment analysis may shed light on the underlying biological mechanisms involved in etiology of the two disorders.

Shorter *et al.* (9) also identified the contribution of genetic susceptibility to infections to mental disorder diagnosis using polygenic risk scores (PRSs). Using mediation analysis, they showed that the PRS of infection risk mediates 7% to 14% of its causal effect via infection diagnosis on the risk of mental disorders. The authors also examined if the PRSs for mental disorders moderated the influence of infection risk loci via infection diagnosis and found that infection diagnosis contributes only a 6% to 12% risk for attention-deficit/hyperactivity disorder, autism spectrum disorder, major depressive disorder, or SCZ diagnosis. Lastly, they established that inclusion of information on infection diagnosis and PRS for infection risk did not greatly improve the prediction of risk of mental disorders. In contrast, prediction models with information on parental history of mental illness and PRS for mental illness were better predictors. The minor contribution of infection risk is also supported by study conducted by Nudel *et al.* (10) that reported that the single nucleotide polymorphism heritability of susceptibility to infections among different psychiatric diagnoses samples ranged from ∼2% to 7%. These findings suggest that the environment is a major contributor to the infection susceptibility. As pointed out by Shorter *et al.* (9), this low heritability and substantial contribution by the environment could possibly explain the low predictive ability of infection risk loci on mental disorders risk in their study. To further understand the genetic contribution of infection susceptibility to mental disorder risk, it would be beneficial to use the Mendelian randomization approach, which uses genetic variants as instrumental variables to examine the effects modifiable risk factors for disease, or to employ multiomics association studies to integrate GWASs with other -omics based on a causal chain hypothesis that genotype to phenotype is partially mediated by intermediate molecular processes, such as gene expression, DNA methylation, or protein expression.

In summary, the systematic characterization of the link between infectious disease and mental disorders by Shorter *et al.* (9) reported 3 crucial findings: the presence of common genetic risk factors (pleiotropy) for both disorders as reported by previous studies, a significant albeit small contribution of the genetic loci associated with infection risk for mental disorder risk, and varying association between infection and type of mental disorder. These results support the theory that immune dysregulation is a crucial aspect for the etiology and pathogenesis of mental disorders.

The link between infection, the immune system, and psychiatric disorders is fascinating, and further research is needed to clarify the directionality between these. The timing of infection and/or the onset of psychiatric disorders might be crucial, and this might drive the subsequent health trajectories and determine the directionality. This research strengthens the notion that anti-inflammatory and/or immunomodulating agents might play a key role in the treatment of psychiatric disorders. Unravelling the biological mechanisms and pathways of psychiatric disorders and their co-occurring symptoms will potentially lead to the development of novel biomarkers and facilitate the effective diagnosis, treatment, and management of psychiatric disorders.

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Article Information

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