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# Inflammation Subtypes and Translating Inflammation-Related Genetic Findings in Schizophrenia and Related Psychoses: A Perspective on Pathways for Treatment Stratification and Novel Therapies

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**Abstract:** Dysregulation of immunological and inflammatory processes is frequently observed in psychotic disorders. Numerous studies have examined the complex components of innate and adaptive immune processes in schizophrenia and related psychoses. Elevated inflammation in these conditions is related to neurobiological phenotypes and associated with both genetics and environmental exposures. Recent studies have utilized multivariate cytokine approaches to identify what appears to be a subset of individuals with elevated inflammation. The degree to which these findings represent a general process of dysregulated inflammation or whether there are more refined subtypes remains unclear. Brain-imaging studies have attempted to establish the link between peripheral inflammation and gray matter disruption, white matter abnormalities, and neuropsychological phenotypes. However, the interplay between peripheral inflammation and neuroinflammation, as well as the consequences of this interplay, in the context of psychosis remains unclear and requires further investigation. This Perspectives article reviews the following elements of immune dysregulation and its clinical and therapeutic implications: (1) evidence supporting inflammation and immune dysregulation in schizophrenia and related psychoses; (2) recent advances in approaches to characterizing subgroups of patients with elevated inflammation; (3) relationships between peripheral inflammation and brain-imaging indicators of neuroinflammation; (4) convergence of large-scale genetic findings and peripheral inflammation findings; and (5) therapeutic implications: anti-inflammation interventions leveraging genetic findings for drug discovery and repurposing. We offer perspectives and examples of how multiomics technologies may be useful for constructing and studying immunogenetic signatures. Advancing research in this area will facilitate biomarker discovery, disease subtyping, and the development of etiological treatments for immune dysregulation in psychosis.

**Keywords:** anti-inflammatory, cytokines, genetics, genome-wide association studies, inflammation, psychotic disorders, schizophrenia

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Peripheral markers of dysregulated inflammation and related immunological pathways are present in psychotic disorders.<sup>1,2</sup> This presence, alongside high antipsychotic discontinuation rates<sup>3</sup> and a decrease in novel antipsychotic drug development efforts by industry,<sup>4</sup> has prompted a surge of studies investigating anti-inflammation and immune modulation interventions. Several drugs with anti-inflammatory properties have demonstrated potential efficacy in psychosis but show variability in treatment response, with accumulating evidence that some patients may benefit more than others.<sup>5</sup> One promising avenue toward advancing precision medicine approaches for these interventions is targeting their use in persons known to have higher inflammation. Doing so, however, is not as straightforward as it may initially seem. While many peripheral markers of inflammation are elevated in persons with psychotic disorders, their specificity is unclear, as their responses to particular drugs may be influenced by numerous innate or environmental factors. Recent studies have moved

beyond examining individual cytokines to using groups of inflammatory markers to identify persons with higher and lower inflammation subtypes. Inflammation studies to date have not clarified whether a general inflammatory process affects a subgroup of patients with psychosis or whether more-refined subtypes of inflammation are present. Furthermore, how peripheral inflammatory measures are related to neuroinflammatory disease mechanisms remains an area of ongoing investigation. Separately, disease-risk genetic studies of psychotic disorders have identified associations linked to inflammation or immune dysregulation pathways. Yet, how these genetic contributions are connected to objectively measured pro-inflammatory markers in the periphery or central nervous system (CNS) and how they can be leveraged for the targeted use of existing therapies or for drug development remain to be clarified. This Perspectives article reviews the current knowledge of inflammation dysregulation in psychosis, strategies and opportunities for identifying subgroups of patients, and how inflammation-related findings from genome-wide association studies (GWAS) may inform treatment stratification and the identification of novel therapies for schizophrenia and related psychoses.

### EVIDENCE SUPPORTING INFLAMMATION AND IMMUNE DYSREGULATION IN SCHIZOPHRENIA AND RELATED PSYCHOSES

Immune dysregulation in persons with schizophrenia and related psychotic disorders has been investigated in related contexts that may arguably require separate consideration when thinking about implications for treatment. These include (1) disease-risk implications and (2) abnormal immune response in those with established illness.

#### Disease-Risk Implications

An etiologic cytokine theory of psychosis proposes that in predisposed individuals, exposure to certain infections, stress, trauma, or other environmental insults during fetal or early life subsequently interferes with normal brain development, mediated through blood-brain barrier (BBB) disruption (Figure 1).<sup>6–9</sup> The resulting imbalance of cytokines or microglial activation has direct effects on brain structure/function, behavior, and the risk for psychopathology later on.<sup>10–12</sup> Infectious agents such as the influenza virus, herpes simplex virus–1/2, cytomegalovirus, and toxoplasma gondii are examples of infectious risk factors for psychosis,<sup>13–16</sup> which may “prime” the immune system, leading to atypical responses to later environmental exposures.<sup>11,17</sup> State versus trait relationships represent related considerations—that is, how inflammation may result from internally or externally mediated factors related to acute illness versus immune systems that may be chronically dysregulated as part of disease. Large disease-risk GWAS have identified multiple loci linked to the development of disease.<sup>18</sup> While some of these genetic findings are linked to immune system genes, how these or other associated genes are related to outcomes from the aforementioned environmental exposures remains to be clarified.

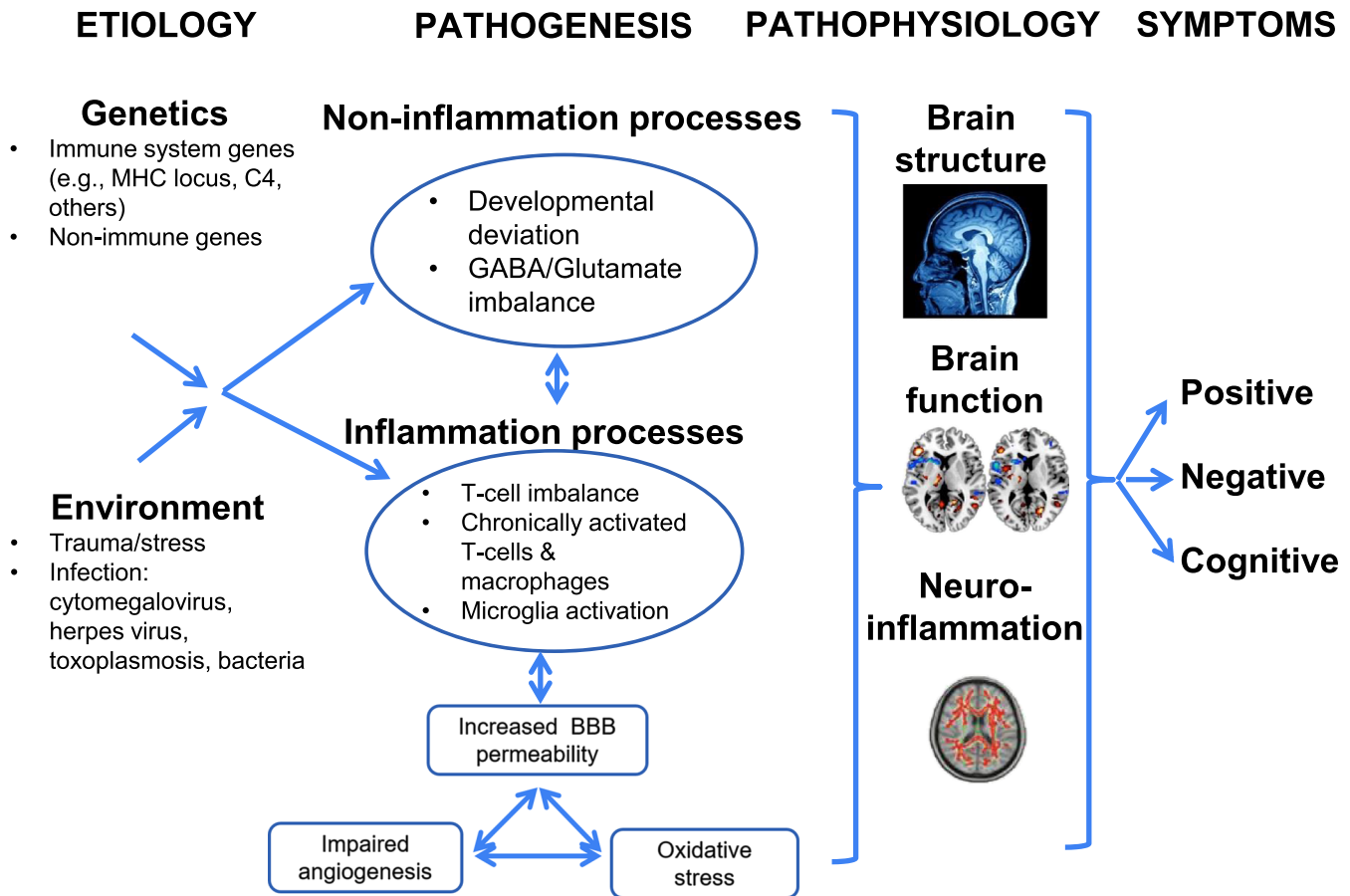
### Abnormal Immune Response in Persons with Established Disease

Abnormal immune responses in psychosis can be grouped into three categories: (1) chronically activated macrophages/T cells, (2) T helper (Th1 and Th2) cell imbalance, and (3) microglial activation. Chronically activated macrophages and Th1/Th2 cells release inflammatory cytokines that increase leukocyte transmigration across the BBB. These processes activate microglia, which further triggers the release of inflammatory cytokines in the brain. These cytokines bind to specific receptors on neurons<sup>19</sup> and adversely affect neurotransmitters, synaptic plasticity, and cortisol concentrations—which subsequently affect mood, cognition, and behavior.<sup>20,21</sup> These inflammatory alterations do not act independently and are intimately linked to changes in other pathways observable in plasma proteins, including oxidative stress, impaired angiogenesis, and increased BBB permeability.<sup>22</sup> These pathways all have strong evidence for disruption in psychosis and for relationships with inflammation. Disruption in any or all of these pathways can result in neuronal degeneration, white matter abnormalities, and decreased neurogenesis, with proposed consequences including a hypoglutamatergic state and impaired N-methyl-D-aspartate signaling that are hallmark neurotransmitter abnormalities in psychosis.<sup>23</sup>

#### Peripheral Measures of Inflammation in Psychosis

Historically, studies have measured and examined how individual cytokines known to be related to inflammatory processes are related to particular diagnostic categories and related phenotypes. Individual relationships of these markers with schizophrenia and bipolar disorders in chronic states, as well as pre/post treatment, have been examined in over 34 cytokine studies,<sup>2</sup> 26 C-reactive protein (CRP) studies,<sup>24</sup> and 15 vascular endothelial growth factor A (VEGFA) studies.<sup>25</sup> These analyses conclude that there are reproducible plasma/serum markers of increased inflammation—in particular, interleukin 1 beta (IL-1 $\beta$ ), IL-1 receptor antagonist (IL-1RA), serum soluble IL-2 receptor (sIL-2R), IL-4, IL-6, IL-8, IL-10, IL-12, CRP, VEGFA, interferon-gamma (IFN $\gamma$ ), transforming growth factor beta (TGF $\beta$ ), and tumor necrosis factor alpha (TNF $\alpha$ )—some of which (e.g., IL-1RA, sIL-2R, IL-6, VEGFA, and CRP) decrease after antipsychotic treatment. Some of the commonly investigated cytokine measures are summarized in Table 1. When interpreting the results of individual studies, it is important to consider the extent to which other factors affecting peripheral cytokines were accounted for in specific analyses. Age, sex, ancestry, smoking, body mass index, childhood trauma, batch effects (of multiplexed assessments), sample-storage time, timing of blood draw, medical comorbidities, current medications, and current illness severity are example variables that should be but are not always included in studies and may be sources of discrepancy.<sup>27,28</sup>

While cytokine alterations in psychosis have been consistently observed, diagnostic specificity remains to be established. Increased peripheral inflammation has also been characterized



**Figure 1. Conceptual model of immune dysregulation in psychosis.** Converging evidence suggests that genetic and environmental factors increase peripheral inflammation that adversely affects the brain and clinical outcomes. BBB, blood-brain barrier; MHC, major histocompatibility complex.

across other psychiatric diagnoses.<sup>29–31</sup> A common observation is that some pro-inflammatory markers (e.g., IL-6, TNF $\alpha$ , IL-1 $\beta$ , and CRP) appear to be increased across disorders. It is possible, though still uncertain, that cytokine signatures may be dimensional features across psychiatric disorders. A recent systematic review of 43 meta-analyses evaluated the reproducibility and specificity of findings for 44 inflammatory biomarkers across eight psychiatric disorders, including schizophrenia, autism spectrum disorder, major depressive disorder, bipolar disorder, posttraumatic stress disorder, obsessive-compulsive disorder, suicide, and sleeping disorders.<sup>27</sup> These authors examined the degree to which case-control differences were observed in the same direction across studies. Their analysis conducted post hoc power calculations for each study and determined that inconsistencies were commonly observed because of underpowered studies (e.g., 26% of studies). Across studies that were adequately powered, significant alterations in inflammation-related factors in psychiatric cases (versus controls) showed 84% consistency across disorders and 100% consistency in schizophrenia and bipolar disorder studies. A total of 30 inflammatory markers were found to be associated with at least one disorder, and 11 of these markers had significant alterations across a minimum of three, but

not consistently across all, disorders. Cluster analysis across study findings suggested similar patterns of changes in multiple inflammatory markers shared between two disorders with clinical and genetic similarity (e.g., schizophrenia and bipolar disorder vs. posttraumatic stress disorder and sleeping disorders). Thus, dysregulated inflammatory processes exist across disorders with some similarities. Consideration of multiple markers of inflammation and their patterns of association across studies suggests that genetics may influence these relationships, with the implication that studies within illness domains (e.g., psychosis) remain important.

#### RECENT ADVANCES IN APPROACHES TO CHARACTERIZING SUBGROUPS OF PATIENTS WITH ELEVATED INFLAMMATION

Numerous studies have used inflammation-profiling approaches to examine differences in many peripheral cytokines between psychiatric patients and controls. However, relatively few studies have attempted to identify subgroups within patients to further parse out heterogeneity within those with psychotic disorders. In fact, a question remains whether a “subgroup” of patients actually do have higher inflammation loading as opposed to a general elevation in these measures. A

<b>Table 1</b>			
<b>Commonly Studied Cytokines, Vascular Markers, and Related Measures of Inflammation in Psychosis</b>			
Protein designation	Name	Category	Description and function <sup>a</sup>
CRP	C-reactive protein	General marker of inflammation	Acute-phase protein and peripheral marker of acute inflammation Produced in response to pro-inflammatory cytokines (IL-1 and IL-6) and lipopolysaccharides
FLT1	Vascular endothelial growth factor receptor-1	Vascular	Cell-surface receptor for vascular endothelial growth factors Involved in the development of embryonic vasculature, angiogenesis regulation, cell survival, cell migration, macrophage function, and chemotaxis
IFN $\gamma$	Interferon gamma	Pro-inflammatory cytokine	Produced by lymphocytes and is a potent activator of macrophages
IL-1 $\beta$	Interleukin 1 beta	Pro-inflammatory cytokine	Induces prostaglandin synthesis, neutrophil influx and activation, T-cell activation and cytokine production, B-cell activation and antibody production, and fibroblast proliferation
IL-6	Interleukin 6	Pro-inflammatory cytokine	Activation leads to the regulation of the immune response, acute-phase reactions Plays an essential role in differentiating B cells
IL-8	Interleukin 8	Pro-inflammatory cytokine	Chemotactic factor that attracts neutrophils, basophils, and T cells involved in neutrophil activation It is released from several cell types in response to inflammatory stimuli
IL-10	Interleukin 10	Anti-inflammatory cytokine	Regulatory cytokine that has profound anti-inflammatory functions, limiting excessive tissue disruption caused by inflammation Limits macrophage and monocyte release of pro-inflammatory cytokines
IL-18	Interleukin 18	Pro-inflammatory cytokine	Pro-inflammatory cytokine that promotes the production of IFN $\gamma$ from T and NK cells Enhances cytotoxic activity and proliferation of CD8+ T and NK cells and stimulates the production of IL13 and other cytokines
TNF $\alpha$	Tumor necrosis factor alpha	Pro-inflammatory cytokine	Pro-inflammatory and apoptosis-inducing cytokine secreted by macrophages
TNF $\beta$	Tumor necrosis factor beta	Pro-inflammatory cytokine	Pro-inflammatory and cytotoxic cytokine produced by lymphocytes
VEGFA	Vascular endothelial growth factor A	Vascular	Growth factor that induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces permeabilization of blood vessels
VEGFD	Vascular endothelial growth factor D	Vascular	Growth factor active in angiogenesis, lymphangiogenesis and endothelial cell growth, stimulating their proliferation and migration and also has effects on the permeability of blood vessels

<sup>a</sup>Adapted from information accessed at <https://www.uniprot.org/><sup>26</sup> and reproduced here under Creative Commons Attribution (CC BY 4.0) License, <https://creativecommons.org/licenses/by/4.0/>.

recent meta-analysis of measures of central tendency, distributions, and variability ratios of individual peripheral cytokines or other markers of inflammation in antipsychotic-naïve first-episode patients concluded that this represents an overall shift in the unimodal distributions in cases versus controls as opposed to a subgroup.<sup>28</sup> Based on a premise that inflammatory processes and immunological pathways involve the collective effects of multiple components, additional recent

research highlights the value of considering the multivariate effects of cytokines and related measures of inflammation when testing hypotheses regarding subgroups of patients.

To date, studies of peripheral plasma/serum/blood proteins and transcripts (i.e., mRNA) have examined inflammatory subgrouping approaches to aggregate groups of markers together to characterize different aspects of psychosis. Selected examples across disease course (i.e., high risk, first-episode

psychosis, chronic illness) that incorporated methodological approaches to validate or establish the reliability of their findings are reviewed here. The North American Prodrome Longitudinal Study (NAPLS) used such an approach to determine whether 185 plasma measures of inflammation, oxidative stress, hormones, and metabolism distinguished persons who were at high risk for psychosis and eventually converted to a psychosis diagnosis versus those who did not and also controls.<sup>32,33</sup> Using a “greedy algorithm” approach to build analyte profiles distinguishing the three groups, they identified an index of 15 analytes that achieved this goal. This metric included eight cytokines (IL-1 $\beta$ , growth hormone, KIT ligand, IL-7, IL-8, resistin, and chemokine ligand 8) along with other measures of BBB and HPA-axis function. The OPTiMiSE study is by far the largest investigation to date of these relationships in patients with first-episode psychosis. These researchers examined 325 patients before and after treatment, and conducted unsupervised clustering to define clinical subtypes.<sup>34</sup> They examined clinical subtypes with 38 cytokines or infectious exposure (e.g., cytomegalovirus, herpes simplex virus, and toxoplasmosis) with response to antipsychotic treatment, and found that lower levels of IL-15, higher C-X-C motif chemokine ligand (CXCL) 12, and previous exposure to cytomegalovirus were associated with nonremission in one of their clinically defined patient subgroups. Enrico and colleagues<sup>35</sup> utilized machine-learning approaches to classify 160 persons with first-episode psychosis, 70 with chronic psychosis (schizophrenia, bipolar disorder with psychosis, or major depressive disorder with psychotic features), and 132 controls based on 56 transcripts of immune-related genes. Using 33 of the mRNA transcripts and supervised machine learning, they demonstrated an ability to discriminate persons with first-episode psychosis, chronic psychosis, and controls with an accuracy of >80%, and a subgroup of drug-free first-episode patients and controls by >90%. Highlighting the importance of previously mentioned challenges related to confounders (e.g., age, sex, body mass index, and smoking status), the accuracy of their classifications increased when considering these factors in their analyses.

Two recent examples illustrate the potential of subgrouping approaches to categorize higher and lower inflammation status in persons with chronic illness and how these may relate to a range of disease phenotypes (e.g., symptoms, cognition, and imaging). Boerrigter and colleagues<sup>36</sup> examined eight inflammatory cytokines in the plasma, and white blood cells (gene expression) of 97 patients with schizophrenia and 87 healthy controls. Using a two-step clustering approach, they identified higher (~48% of patients) and lower inflammation strata defined by gene expression measures of IL-1 $\beta$ , IL-6, IL-8, and IL-18, with higher inflammation more common in patients than controls. Additional findings from this group were consistent, showing ~40% of individuals with psychosis had high inflammation signatures based on similar cytokine clustering and that this clustering was associated with worse verbal fluency.<sup>1</sup> Recently, our study team examined 140 patients with

chronic psychotic illnesses (schizophrenia spectrum,  $n = 79$ ; bipolar disorder with psychosis,  $n = 61$ ) and 60 healthy controls. We examined 15 cytokines (IL-1 $\beta$ , IL-6, IL-8, IL-10, IL-12/IL-23p40, CRP, complement 4A [C4A], TNF $\alpha$ , TNF $\beta$ , IFN $\gamma$ , VEGFA, VEGFC, VEGFD, TGF $\beta$ 1, and soluble fms-like kinase [a splice variant of the VEGF receptor]) in relation to psychosis and related phenotypes. The specific goals were to compare cytokines between cases and controls, describe relationships between clinical and immune phenotypes, and identify potential subgroups. An exploratory factor analysis was conducted on cytokine measures across patients and controls to identify a shared-factor model while controlling for covariates (e.g., storage days, hemolysis score, age, sex, and ancestry) and determining the effects of other potential confounding factors, such as medications and other concomitant illnesses. Our study identified significantly elevated levels of CRP, TNF $\alpha$ , IL-6, and VEGFA in patients with psychotic disorders compared to healthy controls (adj- $p < .05$ ), consistent with prior findings in the field. Our factor analysis resulted in a five-factor model. The primary Factor 1 had significant loading for CRP, IFN $\gamma$ , IL-1 $\beta$ , IL-8, IL-10, TNF $\alpha$ , and VEGFA, indicating the activation of an inflammatory-vascular cascade in patients compared to controls. Scores on this factor distinguished healthy controls from patients as a whole and from patients with schizophrenia or bipolar disorder with psychosis.<sup>37</sup> Cluster analysis of Factor 1 scores yielded a two-cluster solution, defining subgroups with relatively higher (36% of patients) and lower inflammatory cytokine levels. The inflammatory subgroup of probands did not have any enrichment of diagnosis and were matched on age, sex, ancestry, medications (both psychotropic and non-psychotropic medications), and cardiometabolic disorders.

#### RELATIONSHIPS BETWEEN PERIPHERAL INFLAMMATION AND BRAIN IMAGING INDICATORS OF NEUROINFLAMMATION

Relationships between peripheral and central inflammation remain active areas of investigation. The extent to which environmental exposures and resulting inflammation or immune dysregulation affect the brain, or inflammation originating in the CNS can be linked to cytokine measures in the blood, is a challenge to disentangle. Within the brain, whether the origin is from within the CNS or periphery, our prevailing understanding is that microglial, innate, or adaptive immune response activation mediates an inflammatory response in the brain to upregulate cytokines. Increased BBB permeability due to inherent deficits in brain microvascular endothelial cell dysfunction or inflammation-mediated damage is linked to both peripheral and CNS inflammation.<sup>22</sup> Inflammatory processes in the brain may result in astroglial loss that progresses to further neuronal injury, which, if chronic, may affect neuron development and pruning.<sup>38</sup> Brain imaging in living persons and postmortem analyses of inflammatory markers have provided the field with objective measures of pathophysiological immune dysregulation in psychotic disorders.

### Gray Matter Disruption in Inflammation

Much of our understanding of brain anatomy in high inflammation subgroups come from postmortem studies, whereas these types of investigations represent recent developments in living persons. With respect to postmortem studies, significant contributions to our understanding of the consequences of neuroinflammation have resulted from studies defining and replicating a four-cytokine signature (e.g., IL-6, IL-8, IL-1 $\beta$ , and SERPINA3) used to assign higher or lower inflammation status.<sup>39–45</sup> These studies have demonstrated how molecular indicators of neuroinflammation can distinguish cases and controls, and are related to altered expression of nuclear receptors, amino acid metabolites, and astrocyte integrity, and to reduced cortical gray matter volume.

Structural imaging in living patients reveals peripheral inflammation relationships with brain anatomy, but it also provides an opportunity to clarify the complex connections with the brain. In younger persons at high risk for developing psychosis, a summed measure of cytokine levels (e.g., summed IL-2 + IFN $\gamma$  + TNF $\alpha$ ) was negatively associated with prefrontal cortical thickness (i.e., greater cytokine scores are associated with lower thickness), particularly in individuals at risk for, and who eventually developed, psychotic disorders.<sup>46</sup> Other findings have demonstrated that increased inflammatory subtypes as determined by four cytokine markers (IL-1 $\beta$ , IL-18, IL-8, and IL-2) were related to decreased Broca's area volume in schizophrenia.<sup>1</sup> Kindler and colleagues<sup>41</sup> identified correlations between dorsolateral prefrontal cortex volumes and altered kynurenine (l-tryptophan metabolite) metabolism in high, but not low, inflammatory subgroups also defined by IL-1 $\beta$ , IL-18, IL-8, and IL-2. This is an example in living subjects of how inflammation burden may predispose patients to neurotransmitter dysregulation. Our group recently examined regional gray matter thickness and subcortical volumes based on prior studies proposing links to inflammation.<sup>47</sup> We found the following in our study sample: (1) three regions of shared vulnerability within psychosis–high inflammation (defined by factor and cluster analyses of CRP, IFN $\gamma$ , IL-1 $\beta$ , IL-8, IL-10, TNF $\alpha$ , and VEGFA) and psychosis–low inflammation groups compared to the control–low inflammation group (similar to prior studies, lower volumes in probands in right rostral middle frontal, bilateral medial orbitofrontal, and left inferior temporal cortex); (2) greater thickness and volume for the proband–high inflammation group versus the proband–low inflammation group in several brain regions; and (3) profound thinning observed in the psychosis–low inflammation group compared to the control–low inflammation group. Our findings suggested that the presence of a low-grade inflammatory signature may be associated with “pseudothickening,” whereas the absence of low-grade inflammation is related to the expected thinning observed in psychotic disorders.

As noted across the studies above, there are differences in relationships between pro-inflammatory markers and structural brain volume or thickness measures, with both positive and negative correlations identified. Yet, inflammation

associations with worse cognitive performance remain consistent across studies.<sup>1,47</sup> These findings suggest that the interactions between peripheral inflammation and brain structure alterations may represent a dynamic process. A possible interpretation for our observations of greater volumes in the hippocampus, amygdala, putamen, and left thalamus in the psychosis–high inflammation group compared to the psychosis–low inflammation group, as well as for the observed thickening in the psychosis–high inflammation group, is that peripheral inflammation is mediating swelling via altered BBB permeability and the resulting vasodilation in structures with closer proximity to the BBB. Longitudinal studies are required to adequately test hypotheses about whether increases in inflammation-mediated volume or thickness precede eventual decreases related to cell death or atrophy—or whether, perhaps, certain combinations of cytokines or related markers of inflammation (e.g., angiogenic markers such as VEGF) mediate vasodilation that may affect imaging findings. While the answers may not be immediately clear, the convergence of different imaging modalities may provide further insights.

### White Matter Abnormalities in Relation to Peripheral Inflammation

Neuroinflammation in psychosis is associated with white matter pathology generally characterized by axonal degeneration, myelin breakdown, reduced density of astroglia and oligodendroglia in selected areas, and increased white matter neuronal density.<sup>48</sup> Free-water (FW) imaging is an *in vivo*, diffusion-weighted, magnetic resonance imaging (dMRI) technique that extends diffusion tensor imaging (DTI) to quantify extracellular water that may be increased as a result of neuroinflammation via microglial activation, microvessel permeability, or vasodilatation.<sup>49,50</sup> Investigation of white matter measures of fractional anisotropy and diffusivity were recently investigated in 47 patients with schizophrenia and 49 healthy controls in relation to IL-10, a regulatory cytokine that functions to maintain pro-inflammatory and anti-inflammatory balance.<sup>51</sup> Elevated IL-10 in plasma was observed in patients and was correlated with lower fractional anisotropy and diffusivity measures in tracts with subcortical connections in patients but not controls, indicating disrupted microstructural white matter integrity in relation to this peripheral measure of inflammation. Disrupted white matter integrity may be related to neuroinflammatory processes linked to cytokine dysregulation and measurable by DTI as well as FW.<sup>52,53</sup> A recent, large study by Di Biase and colleagues<sup>50</sup> of 199 persons with psychosis and 109 controls underscores the importance of examining both DTI and FW. Their investigations of DTI and FW demonstrated that higher levels of IL-6 and TNF $\alpha$  were associated with higher FW levels in white matter but not with fractional anisotropy, and that these changes were widespread in patients with schizophrenia but not in controls.<sup>50</sup> Relationships between multivariate categorizations and these imaging measures have not yet been established.

### Convergence of Large-Scale Genetic Findings and Peripheral Inflammation Findings

As sample sizes for analyses increase over time, schizophrenia disease-risk GWAS have gained better power to determine the contributions of many genes across the genome. In 2014, the Psychiatric Genomics Consortium published results for wave 2 of the schizophrenia study, which included 36,989 cases and 113,075 controls.<sup>18</sup> Nearly twice that sample size is anticipated for the third wave. In the primary analyses of that study, the major histocompatibility complex (MHC) locus on chromosome 6 was removed due to repetitive sequences. Separate analyses evaluated associations to 7751 polymorphisms across the extended MHC locus (chromosome 6: 25–34 Mb), C4 structural alleles, and human leukocyte antigen polymorphisms to examine haplotype relationships.<sup>54</sup> Previous reviews and post hoc analyses of these findings have discussed implications for the immunogenetic architectures of schizophrenia and a possible relationship with autoimmune diseases.<sup>55–57</sup>

A recent overview of existing findings regarding immune implications from schizophrenia GWAS highlighted 39 schizophrenia immune gene candidates outside of the MHC region. These include 6 individual immune genes overly expressed in human brain tissues and linked to schizophrenia susceptibility,<sup>55</sup> 28 schizophrenia risk genes highly expressed in B and T lymphocytes,<sup>56</sup> and 11 genes with dual roles in the immune and inflammation systems and in schizophrenia susceptibility that encode proteins known to be drug targets.<sup>58</sup> Protein-protein interaction and functional enrichment analyses suggested extensive co-expression and functional interactions among the 39 schizophrenia immune gene candidates and overrepresentation of multiple immune and inflammatory pathways/processes.<sup>55</sup> The potential genetic mechanisms of immune and inflammation processes in schizophrenia pathogenesis likely involve the coaction and interplay of multiple immune genes that contribute to regulation/dysregulation of innate and adaptive immune system mechanisms in the context of psychosis.

When one considers the totality of findings of peripheral cytokines and results of genetic studies, an intriguing observation is the lack of notable associations of genes encoding or regulating the expression of “usual suspect” peripheral markers repeatedly found to be dysregulated in psychosis, either individually or in combination. The extent to which these peripheral cytokines then represent differing or distinct biological mechanisms and are linked to the sources of inflammatory dysregulation is unclear. Additionally, how these genes and related proteins may be linked to existing drugs or leveraged to drug development efforts is a continued work in progress. To gain insights into the interrelationships between schizophrenia risk genes and commonly dysregulated peripheral measures of inflammation, we generated a functional protein-association network involving previously reported 41 schizophrenia immune gene candidates (39 non-MHC genes + C4A/C4B) and 13 psychosis-relevant inflammatory biomarker candidates (see Supplemental Table 1, <http://links.lww.com/HRP/A179>, for full lists of genes/biomarkers) using STRING v11 (<https://string-db.org>) with

default parameter settings.<sup>59</sup> The functional network (Figure 2A) represents intricate and multilateral co-expression, co-occurrence, and functional interactions within and between peripheral cytokines and immune genes.

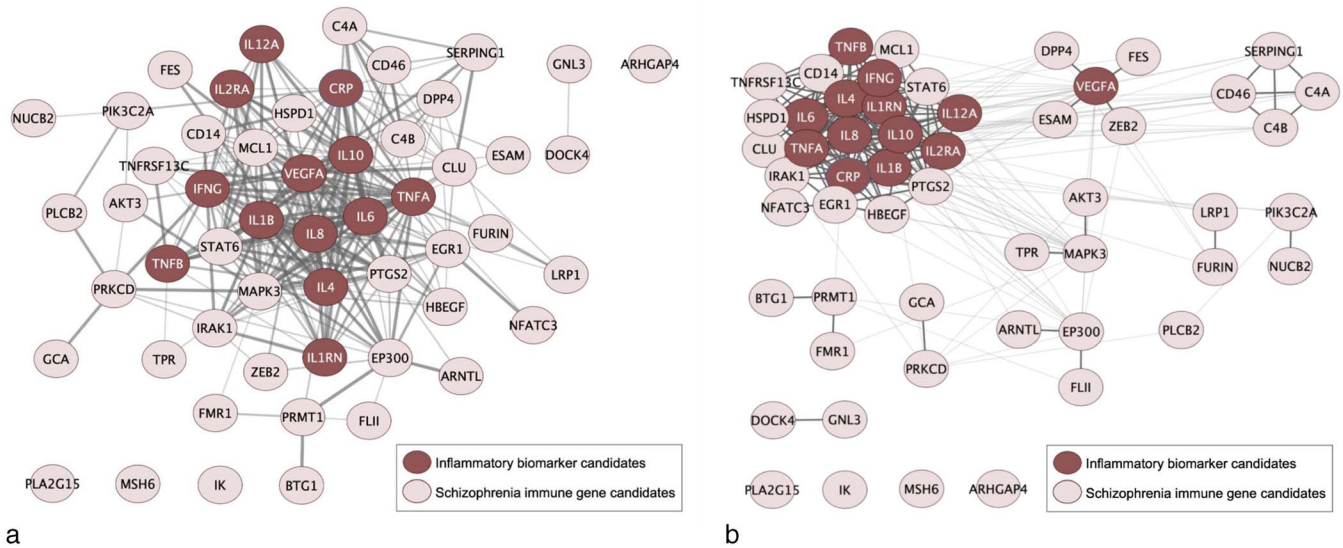
Network analyses provide insights on the interconnectivity between molecules commonly measured in the periphery versus those encoded by genes in disease-risk studies. A lingering question in the field concerns the extent to which inflammation dysregulation in psychosis represents a general inflammatory process or whether distinct pathways of dysregulation have common downstream effects in measurable peripheral markers. Cluster analyses, even in the context of known limitations, may provide some insights for future hypothesis testing. As a conceptual example, we performed an exploratory Markov clustering (MCL) analysis of components of the aforementioned functional association network with clusterMaker<sup>60</sup> and Cytoscape.<sup>61</sup> This analysis included 41 previously published schizophrenia risk genes and 13 psychosis-relevant peripheral inflammatory markers that have been extensively studied. With an inflation parameter of 5, the MCL cluster (Figure 2B) was able to detect distinct communities of pro-inflammatory cytokines, vascular markers, and complement proteins based on the strengths of functional interactions identified from curated data sources.

To better understand the complex immune and inflammatory responses in psychosis, future efforts should focus on system-wide investigations at multiple levels of molecular biology and on signaling pathways involving gene expression and protein interaction. There have been exciting advances in multivariate marker approaches to characterize inflammation and immune dysregulation in psychosis. However, differences in the markers examined across studies necessitate further clarification to harmonize the markers for examination in future mechanistic and clinical studies. Large-scale comprehensive proteomic studies examining the “usual suspect” cytokines along with all other known immune-related markers are now feasible. Multiomics approaches will improve our understanding of the pathophysiology of inflammation and immune dysregulation. Examples include aligning findings from disease-risk genetic studies, epigenetic signatures affected by environmental exposures, and proteomic characterization of inflammation and immune dysregulation. Machine-learning approaches will facilitate analyses of multiple sources of molecular and phenotype data to better understand the molecular mechanisms of immune system regulation/disturbances and the pathogenesis of CNS dysfunction in schizophrenia and related psychoses.

### THERAPEUTIC IMPLICATIONS: ANTI-INFLAMMATION INTERVENTIONS AND LEVERAGING GENETIC FINDINGS FOR DRUG DISCOVERY AND REPURPOSING

#### Anti-inflammation or Immune-Modulating Interventions

Antipsychotics and antidepressants—in addition to reducing psychotic and depressive symptoms, respectively—may also



**Figure 2. Functional protein-association network of schizophrenia immune gene and inflammatory biomarker candidates.** (A) 41 previously identified schizophrenia immune gene candidates (pink nodes), including 39 non-MHC genes and C4A/C4B, and 13 psychosis-relevant inflammatory biomarkers (maroon nodes) were entered in a protein-protein interaction network analysis using STRING software<sup>59</sup> under default settings with medium confidence (interaction score  $\geq 0.4$ ) for identified interactions. The line thickness denotes the strength of data support for a functional interaction between two molecules. (B) MCL clustering of the function network (panel A) to the inflation parameter of 5.0 was performed with clusterMaker<sup>60</sup> and Cytoscape<sup>61</sup> based on the interaction score. Functional interactions within a cluster and between clusters are indicated by thick and thin lines, respectively. MCL, Markov cluster; MHC, major histocompatibility complex.

affect inflammatory cytokine levels (e.g., IL-1 $\beta$ , IL-4, IL-6, IL-10, IL-12, and TNF $\alpha$ ) in the blood.<sup>2,62</sup> With respect to psychosis, however, it is important to note that anti-inflammatory drug studies to date have been adjunctive to stable doses of antipsychotics in patients and may thus confer an additional benefit to these therapies. Of ~18 anti-inflammatory or immune-modulator agents studied to date, 6 (cyclooxygenase inhibitors, minocycline, neurosteroids, N-acetylcysteine, statins, and estrogens) have replicated beneficial effects, whereas others have produced mixed results.<sup>5,63–65</sup> Within individual studies, there are indications that some groups of patients may preferentially respond. A closer look at the “anti-inflammation” mechanisms of the agents studied, as well as others that one might consider, reveals substantial pharmacological diversity, including selective cyclooxygenase inhibition (e.g., aspirin, and celecoxib), broad “antioxidant” (e.g., N-acetylcysteine), broad immunological/anti-inflammatory properties (e.g., minocycline), monoclonal antibodies (e.g., tocilizumab), neurosteroids, and statins. These drugs may have selective effects on specific cytokines (e.g., TNF $\alpha$ , IL-1 $\beta$ , CRP, and IL-6) or broader mechanisms, including links to vascular function and neurobiological pathways. Most published studies to date characterizing patterns of “inflammation” in psychosis have examined only a relatively focused group of cytokines, with broader connections to other pathways investigated separately or not at all.

Of ~70 randomized, controlled trials to date that have examined adjunctive anti-inflammatory drugs on psychosis symptoms or cognition in schizophrenia,<sup>5,63</sup> 22 publications<sup>64–85</sup> have investigated and reported the influence of the interventions on peripheral measures of inflammation. Eight<sup>65–72</sup> of

these identified changes in these measures corresponding to clinical or cognitive outcome measures of response. Of those eight, only four<sup>65,74,81,83</sup> have performed planned or post hoc analyses stratified by higher/lower inflammation defined by CRP or relationships of baseline markers (e.g., CRP, IL-1 $\beta$ , IL-4, IL-6, IL-10, IL-12, IL-17a, INF $\gamma$ , and TNF $\alpha$ ), with higher inflammation being linked to greater benefit in three of these four studies (tocilizumab, aspirin, and pravastatin).<sup>65,81,83</sup> With only roughly one-third of anti-inflammatory interventions replicating efficacy to date, it is conceivable that treatment effects could have been stronger if they were targeted to participants with elevated markers of inflammation or disruption in related pathways.

### Treatment Implications of Disease-Risk Genetic Findings for Drug Discovery and Repurposing

As previously mentioned, numerous studies have already investigated the clinical impact of drugs with anti-inflammatory or immune-modulating properties for improving psychosis symptoms.<sup>5,63</sup> Furthermore, post hoc analyses of the wave 2 Psychiatric Genomics Consortium schizophrenia study examined links between GWAS findings and currently approved drugs and compounds in registered clinical trials.<sup>58</sup> Among the 341 genes mapped (based on the 108 distinct significant loci associated with schizophrenia risk), Lencz and Malhotra<sup>58</sup> identified 20 genes that code for proteins known to be targets of Food and Drug Administration–approved drugs and an additional 20 genes that have been investigated in clinical trials as treatment targets. Pouget<sup>55</sup> further reviewed the immune implications of each druggable schizophrenia risk gene on Lencz and



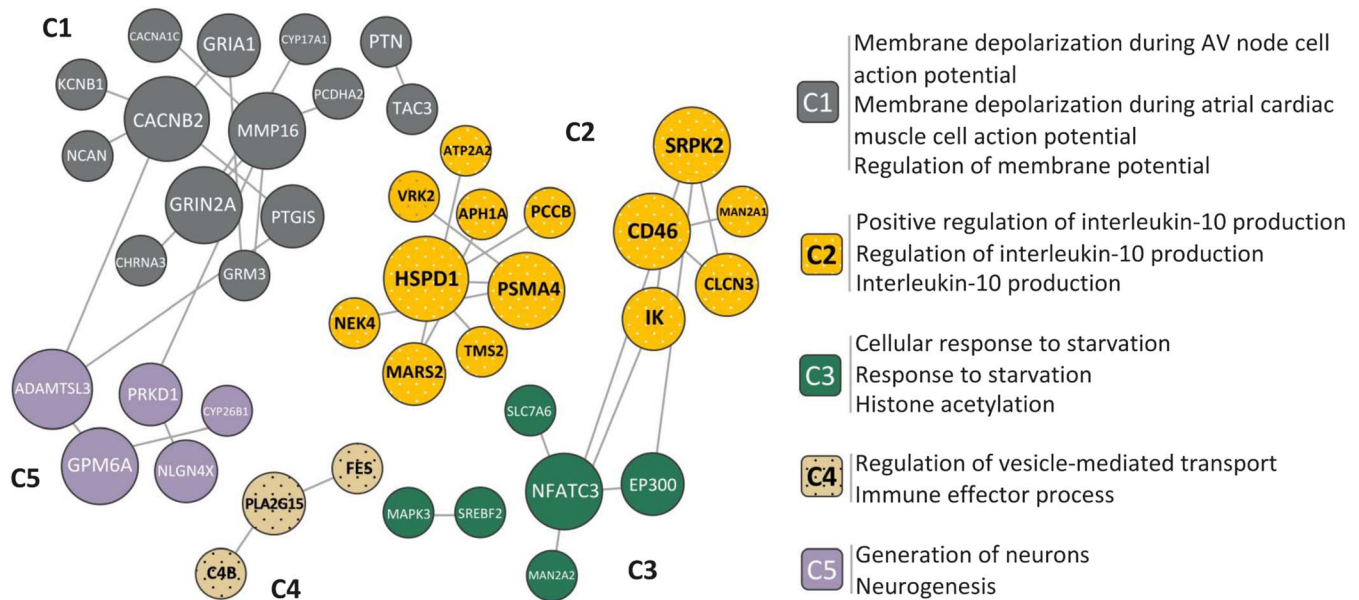
Malhotra’s list and found 11 “druggable” genes involved in immune function. Four of these genes (*DPP4*, *FURIN*, *MAPK3*, and *SERPING1*) encode proteins targeted by approved drugs, and seven (*AKT3*, *C14*, *CLU*, *EGR1*, *HSPD1*, *LRP1*, and *TNFRSF13C*) encode proteins that are potential treatment targets for clinical trials.

An additional way to gain insights into potential drugs or drug targets for future study is through functional module detection and tissue-specific enrichment analyses. Of 341 genes from the Psychiatric Genomics Consortium schizophrenia GWAS report, 103 were determined to be druggable based on the Drug Gene Interaction Database (DGIdb).<sup>86</sup> We performed an exploratory analysis of functional interactions and module detection among these 103 genes (see Supplemental Table 2, <http://links.lww.com/HRP/A180>, for the gene list) within the CNS by using the HumanBase online toolkit (<https://hb.flatironinstitute.org/>). A total of 70 genes were clustered using the published shared-nearest-neighbor-based community-finding method,<sup>87</sup> and 42 of them revealed significant membership to one of five clusters as shown in Figure 3. Each cluster, containing 3 to 14 genes, was examined for CNS-specific functional enrichment with genes annotated to Gene Ontology Biological Processes (GO:BP) terms, the top of which are presented in Figure 3 along with the network (full results of functional enrichment are summarized in Supplemental Table 3). Two (cluster C2 and cluster C4) out of five clusters involving 17 schizophrenia-associated druggable genes with known CNS function and statistically overrepresented immune-relevant GO:BP terms stand out with strong immune/

inflammation implications. These clusters were represented by nine and three genes, respectively (Supplemental Table 3, <http://links.lww.com/HRP/A181>). The highest-associated GO:BP terms for cluster C2 were related to the regulation of IL-10, which is involved in regulating anti-inflammatory processes. The GO:BP terms associated with cluster C4 components were regulation of vesicle-mediated transport and immune effector process. In addition to these 12 genes being categorized as “druggable,” 8 (*APH1A*, *ATP2A2*, *CLCN3*, *HSPD1*, *NEK4*, *PSMA4*, *TMX2*, and *FES*) were identified as having direct interactions with currently approved or developmental drugs. Findings included some examples such as celcoxib and atorvastatin—which, as previously noted, already have replicated findings suggesting efficacy in schizophrenia and related psychoses. Novel examples included investigational therapies for Alzheimer’s disease (tarenflurbil, begacestat, semagacestat, and avagacestat). As expected, a number of immune-modulating biologics were also included in the findings above. These identified interactions do not necessarily translate to clinical utility but provide elements of both face validity and connections for hypothesis generation for further exploration. These findings may exemplify pathways or provide insights based on known drug mechanisms for future drug development efforts or novel application of existing pharmacological agents.

### CONCLUSIONS

Inflammatory and immune processes are dysregulated in schizophrenia and related psychoses. Elevated measures of



**Figure 3. CNS-specific functional modules for druggable schizophrenia risk genes.** The network is comprised of 42 out of 103 druggable genes assigned to one of five clusters (C1–C5) with significant membership. The network clustering was performed based on shared k-nearest-neighbors and community-finding algorithm.<sup>87</sup> Functional enrichment with genes annotated to Gene Ontology Biological Process (GO:BP) terms was examined across five clusters, with the top overrepresented GO:BP terms within each cluster listed on the right (the mapped gene list and full results of pathway enrichment are available in supplemental materials). C2 and C4 containing a total of 17 genes (with polka dots in figure) and 50 enriched terms had strong immune/inflammation implications associated with central nervous system function.

peripheral and neuroinflammation within patients are associated with brain structure abnormalities and lower performance on cognitive assessments. Studies are now moving beyond univariate analyses of individual inflammatory markers to examine how discrete groups of them may define subgroups of patients with dysregulated pathways. Accumulating data support the existence of at least one subgroup of psychosis represented by alterations in inflammation-related pathways. Studies examining this phenomenon in different ways all converge at a similar proportion, which is ~40% of patients. We still need to clarify the defining components of this dysregulation and to determine whether there is one or more subgroups. This research presents opportunities to inform precision-medicine approaches to improve treatment strategies and identify novel therapies. Brain-imaging studies utilizing structural measures of gray matter as well as white matter DTI or FW provide initial links to CNS pathology that is correlated to peripheral measures of inflammation and cognitive dysfunction. Differences in the types of associations that have been reported (e.g., related increases or decreases in brain structure volume or thickness) indicate that additional studies are needed to clarify these relationships or determine the components of what may be a more dynamic process than originally hypothesized.

Anti-inflammatory interventions for psychosis have revealed promising leads for future study. Opportunities abound to better target these interventions to those with higher indices of inflammation. Information from genetic studies and examining the possible interplay of genetics with peripheral measures of inflammation represent an avenue for additional research. Genes linked to immune dysregulation may converge to common endpoints in the periphery. Groups or networks of these molecules present novel areas for further mechanistic exploration, including new drug development or targeted application of existing therapies to persons most likely to benefit. Upcoming larger-scale genetic studies will undoubtedly provide additional opportunities to clarify these relationships. Additionally, leveraging large studies to converge data spanning peripheral inflammation, illness domains, and detailed clinical, cognitive, neurophysiology, and imaging phenotyping will provide clarity on the complex relationships of immune dysregulation and psychosis pathophysiology.

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