

# Inflammation and brain structure in schizophrenia and other neuropsychiatric disorders

PIMS collaboration

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# Inflammation and Brain Structure in Schizophrenia and Other Neuropsychiatric Disorders

## A Mendelian Randomization Study

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 Supplemental content

**IMPORTANCE** Previous in vitro and postmortem research suggests that inflammation may lead to structural brain changes via activation of microglia and/or astrocytic dysfunction in a range of neuropsychiatric disorders.

**OBJECTIVE** To investigate the relationship between inflammation and changes in brain structures in vivo and to explore a transcriptome-driven functional basis with relevance to mental illness.

**DESIGN, SETTING, AND PARTICIPANTS** This study used multistage linked analyses, including mendelian randomization (MR), gene expression correlation, and connectivity analyses. A total of 20 688 participants in the UK Biobank, which includes clinical, genomic, and neuroimaging data, and 6 postmortem brains from neurotypical individuals in the Allen Human Brain Atlas (AHBA), including RNA microarray data. Data were extracted in February 2021 and analyzed between March and October 2021.

**EXPOSURES** Genetic variants regulating levels and activity of circulating interleukin 1 (IL-1), IL-2, IL-6, C-reactive protein (CRP), and brain-derived neurotrophic factor (BDNF) were used as exposures in MR analyses.

**MAIN OUTCOMES AND MEASURES** Brain imaging measures, including gray matter volume (GMV) and cortical thickness (CT), were used as outcomes. Associations were considered significant at a multiple testing-corrected threshold of  $P < 1.1 \times 10^{-4}$ . Differential gene expression in AHBA data was modeled in brain regions mapped to areas significant in MR analyses; genes were tested for biological and disease overrepresentation in annotation databases and for connectivity in protein-protein interaction networks.

**RESULTS** Of 20 688 participants in the UK Biobank sample, 10 828 (52.3%) were female, and the mean (SD) age was 55.5 (7.5) years. In the UK Biobank sample, genetically predicted levels of IL-6 were associated with GMV in the middle temporal cortex (z score, 5.76;  $P = 8.39 \times 10^{-9}$ ), inferior temporal (z score, 3.38;  $P = 7.20 \times 10^{-5}$ ), fusiform (z score, 4.70;  $P = 2.60 \times 10^{-7}$ ), and frontal (z score, -3.59;  $P = 3.30 \times 10^{-5}$ ) cortex together with CT in the superior frontal region (z score, -5.11;  $P = 3.22 \times 10^{-7}$ ). No significant associations were found for IL-1, IL-2, CRP, or BDNF after correction for multiple comparison. In the AHBA sample, 5 of 6 participants (83%) were male, and the mean (SD) age was 42.5 (13.4) years. Brain-wide coexpression analysis showed a highly interconnected network of genes preferentially expressed in the middle temporal gyrus (MTG), which further formed a highly connected protein-protein interaction network with IL-6 (enrichment test of expected vs observed network given the prevalence and degree of interactions in the STRING database: 43 nodes/30 edges observed vs 8 edges expected; mean node degree, 1.4; genome-wide significance,  $P = 4.54 \times 10^{-9}$ ). MTG differentially expressed genes that were functionally enriched for biological processes in schizophrenia, autism spectrum disorder, and epilepsy.

**CONCLUSIONS AND RELEVANCE** In this study, genetically determined IL-6 was associated with brain structure and potentially affects areas implicated in developmental neuropsychiatric disorders, including schizophrenia and autism.

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Numerous avenues of inquiry suggest a relationship between immune dysfunction and psychiatric disorders, including schizophrenia, autism spectrum disorders, and depression.<sup>1</sup> There is robust evidence for increased circulating concentrations of proinflammatory cytokines before the onset of illness,<sup>2</sup> and epidemiological studies have shown that exposure to a variety of infections during prenatal life and childhood are associated with increased risk of schizophrenia and autism spectrum disorder.<sup>3-5</sup> Recent analyses using mendelian randomization (MR) suggest potential causality between inflammatory cytokines and schizophrenia and depression.<sup>6</sup> This background supports theories of maternal immune activation of early inflammatory processes and a 2-hit model with subsequent environmental factors triggering nonresolving inflammation and the precipitation of psychiatric disorders.<sup>7-10</sup>

Patients with mental disorders show a range of differences in structural brain measures compared with healthy controls, but the cause of these differences remains uncertain.<sup>2</sup> Interleukin 6 (IL-6) and its receptor IL-6R could be of particular interest as it is able to cross the blood-brain barrier and increase its permeability, drawing in further local inflammatory actors,<sup>11</sup> and may be related to treatment resistance and poor functional outcomes.<sup>12,13</sup> Inflammation is implicated in structural brain changes underlying neuropsychiatric disorders via microglia and astrocytic function with disordered synaptic pruning and subsequent effect on gray matter volume (GMV).<sup>14</sup> Immune glial dysfunction may differentially influence risk of mental health disorders; for example, radioligands for translocator protein, a marker of microglial activation, is reduced in medication-naïve patients with psychosis but increased in patients with depression.<sup>2</sup> Mental health disorders are highly comorbid, suggesting a potentially common inflammatory mediated mechanistic pathway for a subgroup of patients.<sup>15-18</sup>

There are relatively few studies exploring the association between IL-6 and related markers and structural brain changes in patient samples *in vivo*. In patients with depression and inflammation, GMV alterations have been reported in the temporal, orbitofrontal and inferiofrontal, and cingulate regions.<sup>19,20</sup> In psychosis, GMV loss and cortical thinning have been related to elevation of immune-proteomic markers in temporal, prefrontal, and cingulate areas.<sup>21</sup> Studies to date are often based on relatively small samples, patient populations with long-term disease, are cross-sectional in nature, or confounded by medication and environmental factors. To our knowledge, MR, which is able to control for environmental confounds, has not previously been used to investigate this association.<sup>22</sup> Transcriptomic profiling of brain regions neuropsychiatric populations have attempted to link inflammatory and neuropsychiatric gene function, with mixed results also potentially related to confounds.<sup>23,24</sup>

A clearer understanding of the association between immune dysfunction and brain structure, with evidence of potential causal inference and relevance to mental health disorders, would be a significant advance and allow a deeper understanding of early causal pathways, offering the potential for more refined targeting of novel treatments.<sup>25</sup> We aimed to

## Key Points

**Question** Is there evidence for a potential relationship between inflammation and brain structure, and is this relevant for schizophrenia and other neuropsychiatric disorders?

**Findings** In this mendelian randomization study including 20 688 participants in the UK Biobank, genetically predicted levels of interleukin 6 were associated with gray matter volume and cortical thickness primarily in the middle temporal gyrus and superior frontal region. The middle temporal gyrus overexpressed a number of genes relevant to interleukin 6 pathway proteins and neuropsychiatric disorder ontologies, including schizophrenia and autism spectrum disorder.

**Meaning** This study found that inflammation may be associated with brain structure and may be an early predeterminant of neuropsychiatric conditions, which has important implications for identification of risk and novel treatments.

test for evidence of potential causality in the association between inflammatory cytokines and brain structure using MR, with genetically predicted levels of cytokine activity as proxies for exposure. Subsequently, we interrogated gene expression in immune-related brain regions and tested the relevance of gene expression patterns in neuropsychiatric disorders.

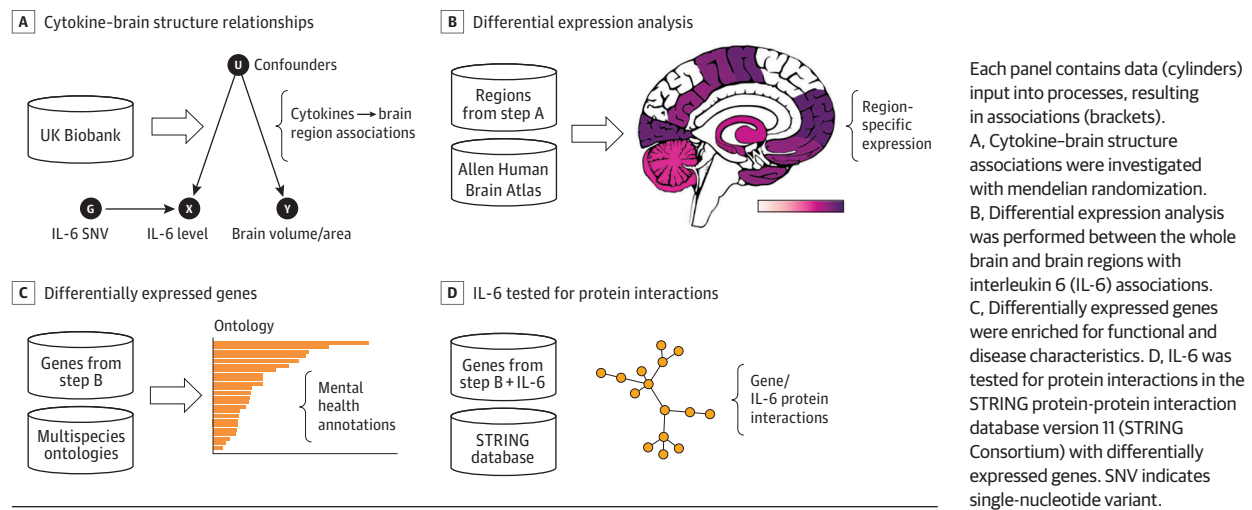
We hypothesized that genetically predicted increased IL-6 and IL-6R activity would be associated with reduced gray matter volume and cortical thickness (CT) in areas highly relevant to neuropsychiatric disorders, including schizophrenia, autism spectrum disorder, and depression. We further expected genes overexpressed in identified regions to participate in biological processes relevant to neuropsychiatric disorders as explored in human biomedical databases and rodent models.

## Methods

Methods are summarized in **Figure 1** and the eMethods in **Supplement 1**, which include the Strengthening of Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) checklist. Briefly, first, we used MR to test associations of genetic predictors of levels of a range of cytokines and acute phase proteins with variation in GMV and CT. We then investigated which genes were differentially expressed in brain regions significantly indicated in MR analyses. Region-specific gene sets were functionally investigated to assess how transcriptional activity in these brain regions may manifest as neuropsychiatric function, and genes functionally interacting with the IL-6 or IL-6R pathway characterized in relation to neuropsychiatric disorders. All participants provided written informed consent. UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee. The present analyses were conducted under UK Biobank application number 26999.

Genetic data and neuroimaging-derived phenotypes (outcomes) were taken from the UK Biobank.<sup>26</sup> We investigated genetic predictors of 5 available exposures associated with risk

Figure 1. Study Workflow



of neuropsychiatric disorders in MR analyses<sup>6</sup> (IL-1,<sup>27</sup> IL-2<sup>28</sup>, IL-6,<sup>29</sup> C-reactive protein [CRP<sup>30</sup>], and brain-derived neurotrophic factor [BDNF<sup>31</sup>]) to examine specificity of findings for the IL-6 and IL-6R pathway. For each inflammatory biomarker, we selected genetic variants in a relevant coding gene region previously shown to be conditionally associated with the inflammatory biomarker and moderately correlated ( $r^2 < 0.6$ ) (eMethods in Supplement 1). We considered 1436 outcomes derived from T1-weighted magnetic resonance imaging (MRI) from 20 688 individuals in the imaging subset of the UK Biobank study, described previously.<sup>32,33</sup>

We performed 2-sample MR analyses using the inverse-variance weighted method, including estimated genetic correlations from a reference population, using genetic associations with the inflammatory biomarkers obtained from the literature (eMethods and eTable 2 in Supplement 1), and genetic associations with the outcomes from UK Biobank correcting for physical, genetic, and technical covariates. To present results for diverse traits on a common scale, estimates are divided by their standard errors and reported as  $z$  scores, where a positive  $z$  score represents genetically predicted levels of the biomarker that were positively associated with the brain imaging measure. The number of independent hypotheses tested was estimated by principal component analysis, which indicated that 95% of the variation in the outcome data was explained by 442 principal components. Associations were therefore considered significant at a multiple testing-corrected threshold of  $P < 1.1 \times 10^{-4}$  ( $.05/442$ ) from 2-tailed inverse variance-weighted MR (eMethods in Supplement 1).

From the UK Biobank, the regional imaging measures were CT and brain volume extracted from available parcellation atlases. Brain imaging results from MR analysis were imported into the MarsBaR toolbox<sup>29</sup> to aid visualization and identify those brain regions of interest (ROIs) in SPM (Wellcome Centre for Human Neuroimaging) that were statistically significantly associated with genetically predicted levels of biomarkers (eMethods in Supplement 1).

We analyzed gene expression from data in the Allen Human Brain Atlas (AHBA),<sup>34</sup> which annotates 1839 segmented regions in its atlas, and a combination of measurements segmented in the mammalian Allen Brain Atlas (ABA). Where available, we conducted experiments to compare whole-brain expression to gene expression in brain ROIs indicated in MR results, as not all brain regions have corresponding probes in the microarray experiments. In a data-driven approach, differential expression analysis was performed between expression in each indicated brain region and whole-brain expression levels. Overexpressed genes were examined for enrichment in the Gene Ontology's biological process domain,<sup>35</sup> disease ontology,<sup>36</sup> and mammalian phenotype ontology.<sup>37</sup> Genes differentially expressed in significant regions were tested for protein interactions with IL-6 in STRING version 11 (STRING Consortium).<sup>38</sup>

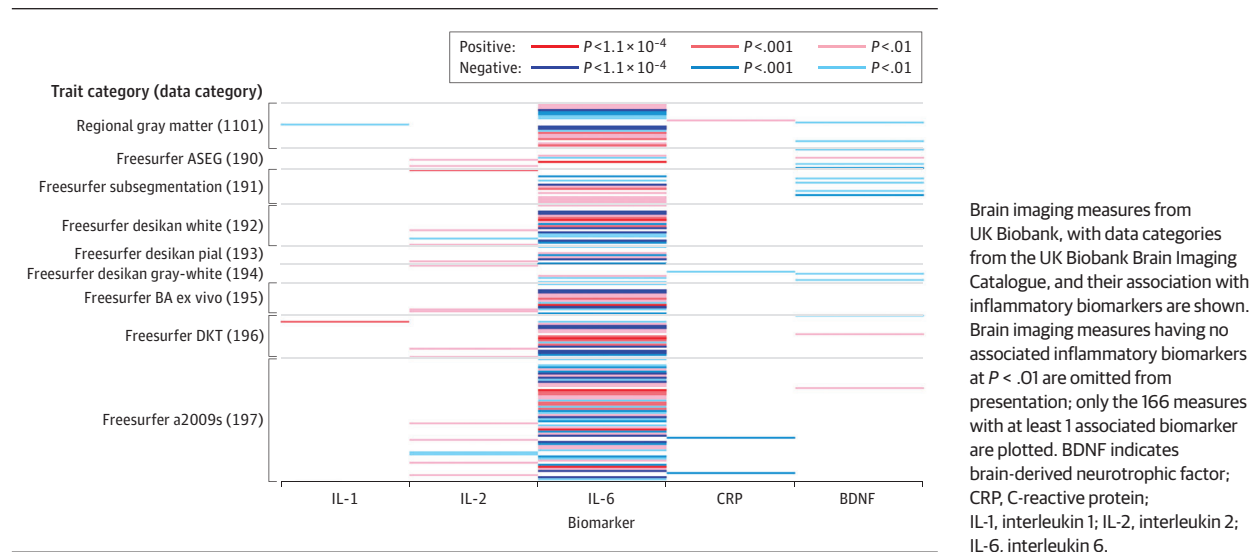
## Results

Of 20 688 participants in the UK Biobank sample, 10 828 (52.3%) were female, and the mean (SD) age was 55.5 (7.5) years. In the AHBA sample, 5 of 6 participants (83%) were male, and the mean (SD) age was 42.5 (13.4) years. A full sample description can be found in eTable 1 in Supplement 1.

### Association of Biomarkers With Brain Structure

Associations of genetically predicted values of the 5 investigated biomarkers with the brain imaging measures are displayed as a heat map in Figure 2. In total, genetically predicted IL-6 levels were associated with 33 brain imaging measures of GMV or CT after correction for multiple testing ( $P < 1.1 \times 10^{-4}$ ). No genetically predicted levels of other exposures (IL1, IL2, CRP, or BDNF) were associated with brain imaging measures after correction for multiple testing; at an association of interest (uncorrected  $P < .001$ ), 65, 1, 1, 2, and 2 brain imaging measures were associated with genetically

**Figure 2. Heat Map of Associations Between Genetically Predicted Inflammatory Biomarkers and Brain Imaging Measures**



predicted IL-6, IL-1, IL-2, CRP, and BDNF, respectively. A list of traits associated with genetically predicted IL-6 at an uncorrected significance threshold is provided in eTables 3 and 5 in Supplement 1. Additional heat map visualizations of associations between brain imaging measures and inflammatory biomarkers are provided in eTables 4 and 6 and eFigures 1 to 9 in Supplement 1. Results remained unchanged when excluding 216 participants who reported a neuropsychiatric diagnosis and on adjustment for whole-brain volume (eTables 1, 5, and 6 in Supplement 1).

### Mapping of Brain Structure Associated With IL-6

Genetically predicted IL-6 activity was associated with 33 spatially overlapping MRI measures. When mapped into SPM space,<sup>39</sup> these generated brain ROIs of GMV in the middle temporal gyrus, temporooccipital part (right:  $z$  score, 5.76;  $P = 8.39 \times 10^{-9}$ ), and the temporal fusiform cortex, posterior division (right:  $z$  score, 4.70;  $P = 2.60 \times 10^{-7}$ ; left:  $z$  score, 4.20;  $P = 2.67 \times 10^{-6}$ ), as well as of CT in the frontal superior (left:  $z$  score, -5.11;  $P = 3.22 \times 10^{-7}$ ) were significant. The middle temporal gyrus (MTG), fusiform gyrus (FuG), and superior frontal gyrus demonstrated the strongest associations with genetically predicted IL-6 (eMethods and eTable 16 in Supplement 1; Figure 3).

### Differential Gene Expression in Brain Regions Associated With IL-6

We conducted experiments to compare whole-brain expression to the brain ROIs: MTG, ITG, fusiform gyrus, and a combination of measurements segmented in the mammalian ABA (cerebellar vermis [VeI\_IV] lobules I-II, III, and IV). The  $z$  score-normalized expression of probes uniquely mapped to each ROI indicated relatively stable expression in the MTG and ITG compared with cerebellar regions (VeI I to V) and the putamen (Figure 4A). Differentially expressed genes in the MTG (false discovery rate-corrected  $P < .05$ ; log-fold change  $> 2$ ) are shown in Figure 4B. While many genes were overexpressed in the MTG

compared with the whole brain (mean [SD] log-fold change, 2.47 [0.40]; max log-fold change, 3.59; mean [SD]  $\beta$ , 13.41 [4.37]), none were significantly underexpressed. Differential expression analyses are further described in eTables 7 to 14 and eFigures 10 to 16 in Supplement 1.

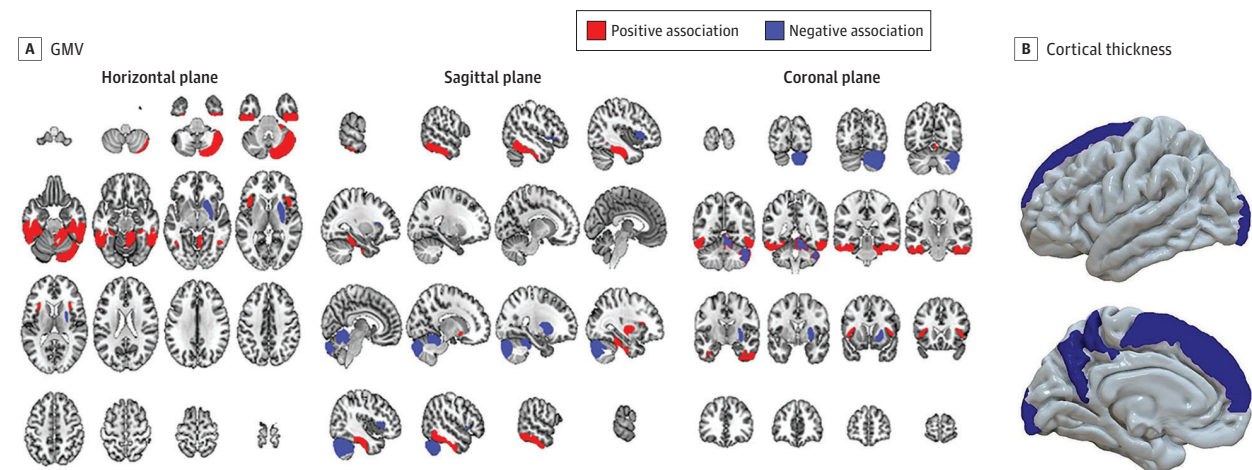
### Interaction Between IL-6 and Proteins Differentially Expressed in the MTG

Subsequent enrichment with the STRING protein-protein interaction database (Figure 4C) revealed a highly interconnected network of genes preferentially expressed in the MTG, suggesting these genes act in concert on the protein as well as transcript level (43 nodes/30 edges observed vs 8 edges expected; mean node degree, 1.4; genome-wide significance,  $P = 4.54 \times 10^{-9}$ ). IL-6 itself was not found to be differentially expressed in the MTG. However, several differentially expressed genes form an interaction network with IL-6. Among these are neuropeptide Y (NPY), met proto-oncogene (MET), cholecystokinin (CCK), muscular LMNA-interacting protein (MLIP), and heat shock protein family B (small) member 3 (HSPB3).

### Associations Between MTG-Enriched Genes and Neuropsychiatric Disorders

Genes differentially expressed in each identified ROI were enriched for overrepresentation in the disease ontology (Figure 5A) and the biological process domain of the gene ontology (Figure 5B; eTable 15 in Supplement 1). The MTG contained a highly enriched set of genes involved in neuropsychiatric disorders, specifically schizophrenia (OR, 2.44; 95% CI, 1.87-3.16;  $z$  score, 7.10;  $P = 5.7 \times 10^{-7}$ ), psychotic disorder (OR, 2.43; 95% CI, 1.86-3.15;  $z$  score, 7.06;  $P = 6.5 \times 10^{-7}$ ), autism spectrum disorder (OR, 3.70; 95% CI, 2.42-5.50;  $z$  score, 7.01;  $P = 1.1 \times 10^{-5}$ ), cognitive disorder (OR, 2.37; 95% CI, 1.86-2.99;  $z$  score, 7.56;  $P = 2.8 \times 10^{-8}$ ), and epilepsy (OR, 4.66; 95% CI, 3.17-6.71;  $z$  score, 9.27;  $P = 3.2 \times 10^{-10}$ ). Enriched biological processes in the AHBA results relate to nervous system

**Figure 3. Brain Imaging Measures Associated With Genetically Predicted Levels of Interleukin 6 and Interleukin 6 Receptor Through Mendelian Randomization**



A, Genetic association of interleukin 6 and its receptor with gray matter volume (GMV) (Harvard-Oxford cortical and subcortical atlas and probabilistic mendelian randomization atlas of the human cerebellum): middle temporal gyrus, temporooccipital part (right: z score, 5.76;  $P = 8.40 \times 10^{-9}$ ), and temporal fusiform cortex, posterior division (right: z score, 4.70;  $P = 2.60 \times 10^{-7}$ ; left: z score, 4.20;  $P = 2.67 \times 10^{-6}$ ), at a multiple testing-corrected threshold of  $P < 1.1 \times 10^{-4}$ . Additional measures with  $P < .001$  include the inferior temporal gyrus, posterior divisions (right: z score, 3.38;  $P = 7.20 \times 10^{-5}$ ; left: z score, 3.73;  $P = 1.90 \times 10^{-5}$ ), frontal operculum cortex (right: z score, -3.59;  $P = 3.30 \times 10^{-5}$ ), putamen (right: z score, -3.78;  $P = 1.60 \times 10^{-5}$ ), and regions I to IV of the cerebellum vermis (right: z score,

-3.64;  $P = 2.70 \times 10^{-5}$ ). B, Cortical thickness (Destrieux cortical atlas): frontal superior (left: z score, -5.11;  $P = 3.22 \times 10^{-7}$ ). Additional measures with  $P < .001$  include the G-precuneus (left: z score, -3.59;  $P = 3.30 \times 10^{-5}$ ), pole-occipital (left: z score, -3.61;  $P = 3.10 \times 10^{-5}$ ), S-parieto-occipital (left: z score, -3.34;  $P = 8.40 \times 10^{-5}$ ), and S-pericallosal (right: z score, 3.32;  $P = 9.00 \times 10^{-5}$ ). Estimates are reported as z scores, where a positive z score represents that genetically predicted levels of the biomarker were positively associated with the brain imaging measure. Red color denotes a positive association and blue color denotes a negative association. See the eDiscussion in Supplement 1 for further details.

development and synaptic transmission, while phenotypes from orthologous mouse models (Figure 5C) exhibit abnormal brain, cognition, anxiety, and affective traits.

## Discussion

Using mendelian randomization in a large population data set, we explored potential causal associations between inflammation and brain structure. In keeping with our hypothesis, this study found that genetically predicted IL-6, but not other inflammatory markers, was significantly associated with GMV and CT. We found the strongest associations with GMV in the MTG and fusiform gyrus and with CT in the superior frontal gyrus. Using the AHBA, we also demonstrated that the MTG significantly overexpressed a highly interconnected number of genes in an interaction network with IL-6 together with a set of overexpressed genes for epilepsy, cognitive disorder, schizophrenia, psychotic disorder, and autism spectrum disorder. These results suggest that function within the innate immune system, and particularly IL-6-related pathways, are essential for normal brain development and that elevation of IL-6 may affect development of brain structure in areas highly implicated in mental health disorders, particularly those with a neurodevelopmental pathway.

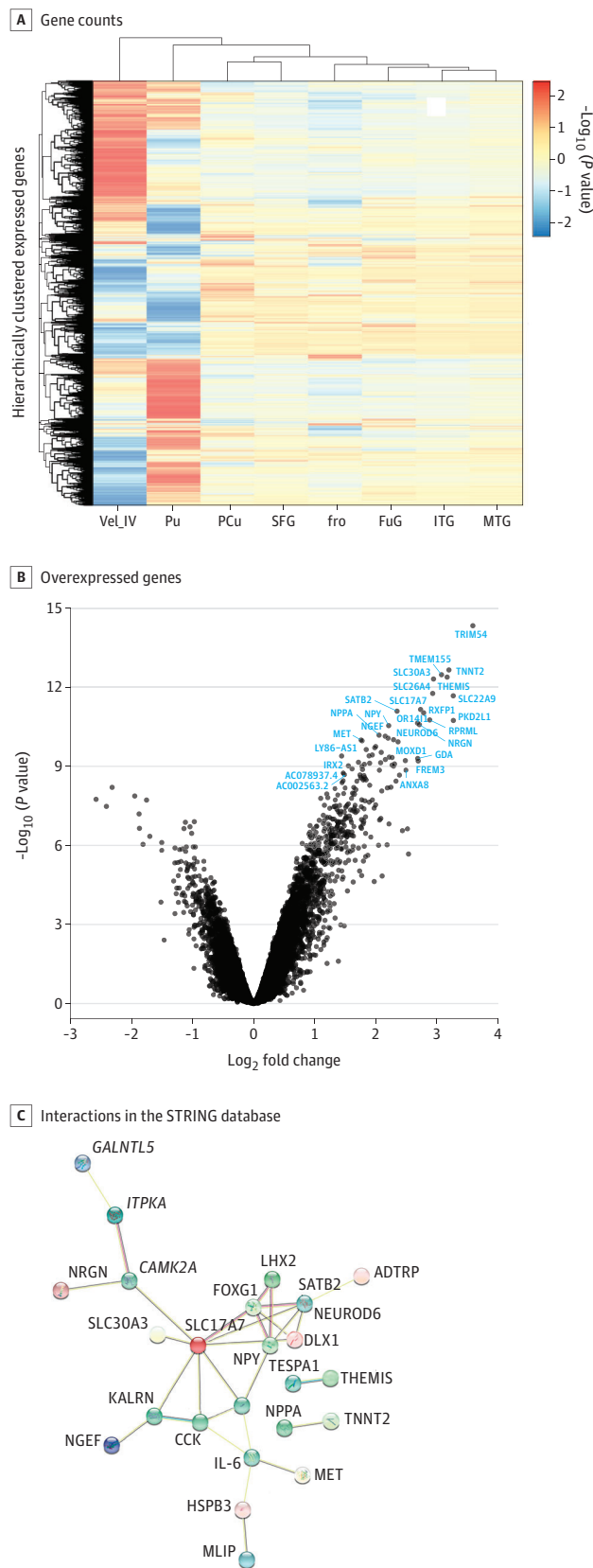
It should be noted that IL-6 genetic variants used as instruments in MR are associated with increased circulating IL-6 levels but decreased IL-6 classic signaling owing to reduced

expression of membrane-bound IL-6R.<sup>40</sup> Thus, caution is needed when considering the directionality of association between IL-6 levels and change in brain volumes. However, dysregulation of the inflammatory response can trigger a cascade that affects neuronal development and subsequent downstream behavioral phenotypes.<sup>41</sup> Our results are suggestive of elevation of IL-6 levels and reduction in GMV, with the largest associations within the MTG, a key area of language, semantic memory processing, and sensory integration implicated in a number of neuropsychiatric disorders.<sup>42,43</sup> These findings extend recent evidence of association between inflammation and brain structure in schizophrenia and depression<sup>22,44-46</sup> and address uncertainties of smaller samples and confounding.

As a whole, genes differentially expressed in the MTG share unexpectedly frequent occurrences in schizophrenia (Figure 5A) as well as autism spectrum disorder, cognitive dysfunction, and epilepsy, suggesting a role for these genes across comorbid and highly heritable illnesses. Suggested mechanisms from our results include neuropeptide and chemical synaptic transmission disruption (Figure 5B) and neurogenesis/developmental processes. The homologs of differentially expressed genes preferentially affect abnormal synaptic transmission and predicate anxiety, emotion, learning, conditioning, and memory behavior—all hallmarks of phenotypically related neuropsychiatric disorders (Figure 5C).

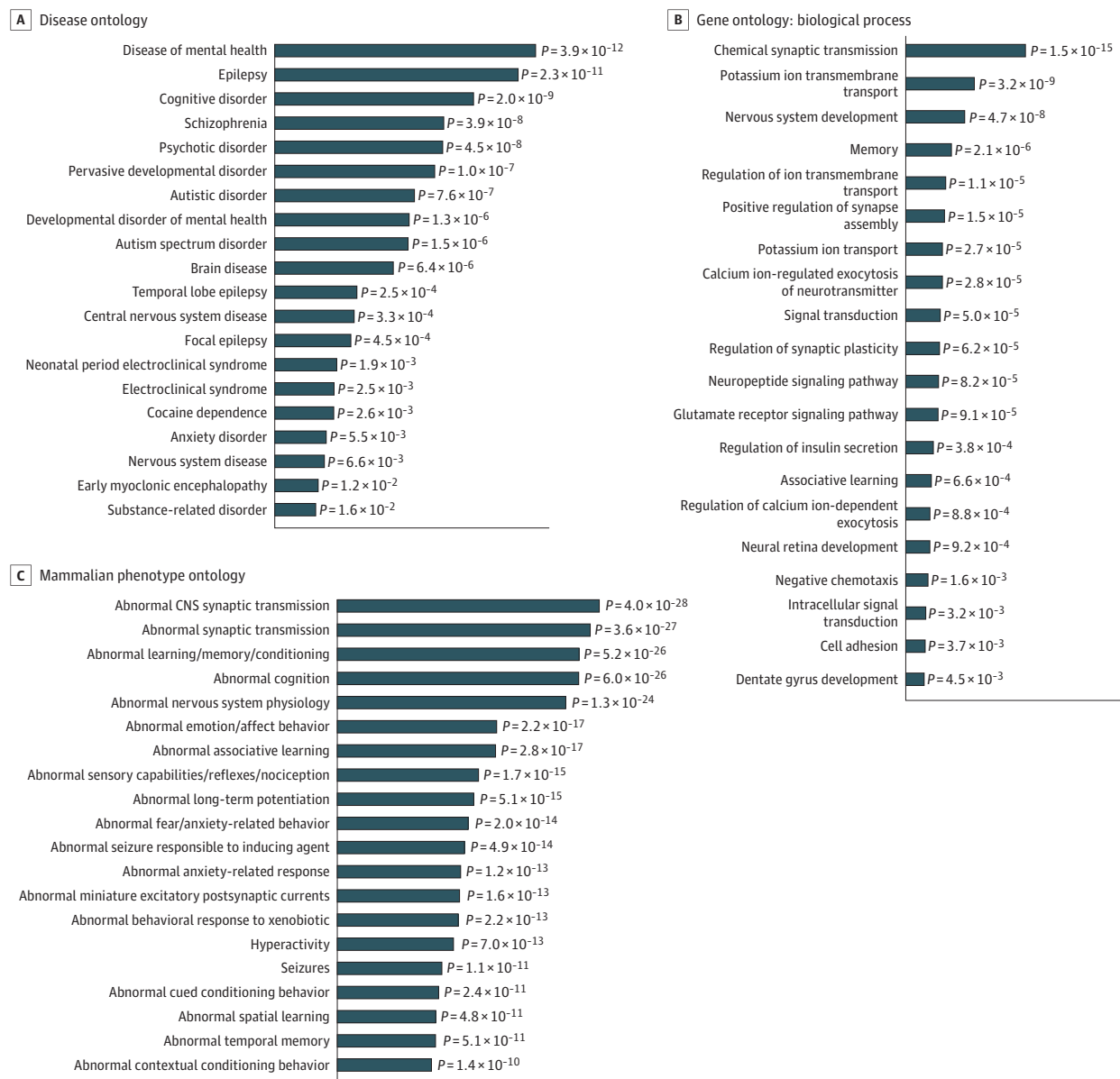
Recently, evidence has emerged for a reduction in GMV, particularly in the temporal lobe in those at risk of poor out-

Figure 4. Genes Differentially Overexpressed in the Middle Temporal Gyrus (MTG) and Interleukin 6



A, z Score normalized mean gene counts in each region of interest show little within-region variation within genes expressed in the MTG compared with other regions, particularly compared with the cerebellar regions, which show pronounced variation compared with the whole brain. Each row represents one gene's expression. B, Compared with the whole brain (mean non-MTG values), 47 genes were highly overexpressed (false discovery rate-corrected  $P < .05$ ; log-fold change  $>2$ ) in the MTG specifically. C, Protein products of these genes plus interleukin 6 were highly enriched for interactions (connectivity  $P = 4.54 \times 10^{-9}$ ) compared with the frequency of interactions in the STRING database, as measured in the sum of unweighted degrees in the network. Edge colors represent different evidence underlying predicted protein-protein interactions in the STRING database. Images within spheres represent known protein structures; node color is aesthetic. fro Indicates operculum; FuG, fusiform gyrus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; PCu, precuneus; Pu, putamen; SFG, superior frontal gyrus; Vel\_IV, cerebellar vermis.

Figure 5. Association of Genes Overexpressed in the Middle Temporal Gyrus (MTG) and Brain Disorders



A and B, Genes significantly overexpressed in the MTG were enriched for psychiatric diseases and neurological biological processes in annotations to the disease ontology and biological process domain of the gene ontology, respectively. C, Their mammalian orthologs were enriched for neurological and behavioral phenotypes present in the Mouse Genome Database. For each

database, hypergeometric tests were performed comparing the frequency of ontology entity annotations for MTG-expressed genes vs genes available in the Allen Human Brain Atlas datasets. All *P* values are false discovery rate-adjusted. The top 20 most highly enriched results for each ontology are shown.

come in psychosis.<sup>42</sup> Our results are in keeping with findings from large cohort analysis; for example, Boedhoe et al<sup>47</sup> identified increased CT in frontal regions in autism spectrum disorder and Jalbrzikowski et al<sup>48</sup> found reduced GMV in the fusiform, temporal, and paracentral regions in patients who converted from clinical high-risk status to psychosis.

Genome-wide association studies in schizophrenia and autism spectrum disorder have implicated the major histocompatibility complex on chromosome 6, with key loci that code for specific cell-surface proteins essential within the immune

system.<sup>49</sup> Additional variants on genes coding for inflammatory cytokines have also been implicated in schizophrenia risk.<sup>23</sup> Results presented in our analysis support the potential role of IL-6 with brain structure and potentially related neuropsychiatric disorders.

However, we found no significant associations with CRP, BDNF, IL-1, or IL-2 that survived testing for multiple comparison. Higher levels of CRP have been shown to be associated with risk of psychosis and depression,<sup>50</sup> although depression has a varied relationship with individual inflammatory mark-



ers, while more unified evidence exists in schizophrenia.<sup>6</sup> It is possible that IL-6 has a specific pathway to increased effect on brain structure and poor functional outcome in subgroups transdiagnostically.<sup>51,52</sup> A plausible effect of IL-6 in inducing changes in brain structure may be maternal immune activation during development, although it is possible that the exposure continues and may indeed affect brain structure throughout adulthood.<sup>53,54</sup>

In the adult human brain, we found that IL-6 may form an interacting community with other proteins differentially overexpressed in the MTG, including CCK and NPY, which are also implicated in schizophrenia and other mental illnesses (Figure 4C). CCK is one of the most abundantly expressed neurotransmitters in the brain.<sup>51</sup> In humans, GWAS has found an association of CCK in pathways with increased neurofibrillary tangles and TREM2 protein levels, both previously associated with Alzheimer disease and related tauopathies.<sup>55,56</sup> Despite mixed success as a direct therapeutic aid to ameliorate anxiety and symptoms of schizophrenia via CCK receptor antagonists,<sup>57</sup> CCK knockout mice have increased prepulse inhibition,<sup>58</sup> a key biomarker of the sensory overload characteristic of psychosis,<sup>59</sup> and NPY mouse models of schizophrenia show increased anxiety traits<sup>60</sup> and abnormal susceptibility to induced seizures.<sup>61,62</sup>

MET and HSPB3 are also differentially overexpressed in the MTG. Mouse models reveal developmental neurological roles for MET, including impaired learning and cued conditioning behavior,<sup>63,64</sup> potentially relevant for models of perceptual prior beliefs in psychosis.<sup>65</sup> These proteins potentially interact with IL-6 directly and join IL-6 to a highly connected functional hub of coexpressed genes in the MTG implicated together in neuropsychiatric disorders. MLIP, which interacts with MET is implicated in 13 schizophrenia trios in a 5.59-kilobase deletion.<sup>66</sup> In mice, there have been no reported studies investigating MLIP and mental health inflammation-mediated mechanisms<sup>58</sup>; thus, our findings may support future MET/MLIP knockout behavioral assays.

### Strengths and Limitations

Strengths include a novel multistage investigation, well-characterized single-nucleotide variants, large data set, stringent corrections for multiple comparisons, and detailed unrestricted gene expression analysis from postmortem human data with homologues from mice, allowing potential for back translation. This study also has limitations that need to be acknowledged. First, our sample was of neurotypical participants in both UK Biobank and AHBA. Other potential data, eg, the Stanley Medical Research Institute database,<sup>67</sup> from individuals with mental illness did not have transcriptomics data

from the brain subregions significant in our MR analysis. The UK Biobank includes patients with a schizophrenia diagnosis; however, only 15 had relevant brain imaging data. Excluding individuals with psychiatric conditions did not alter our results (eTables 5 and 6 in Supplement 1). Second, our MR analysis used hemisphere-specific (left or right) MRI-derived phenotypes, whereas the AHBA is largely of the left hemisphere only. This creates the assumption that the gene expression in each hemisphere is correlated and ignores functional and structural asymmetry. The degree to which hemispheric differences and the quality of the AHBA data vary between individuals may mitigate this limitation. Third, it is possible that the genetic variants in our MR analysis could be associated with other pathways that influence brain structure directly (ie, environmentally via infection-induced effect on brain structure or otherwise not via the associated biomarker); however, given the known genetic architecture of the inflammatory biomarkers, this may be unlikely. This study used a conservative approach to inferring causal gene-mediated phenotype-phenotype relationships, ensuring robust findings for further investigation. In the MR analysis, we used characterized single-nucleotide variants with known cis-regulatory effects on levels of each inflammatory cytokine studied. However, as with any MR analysis, we have made several assumptions: in these analyses, we have tested the assumption that our instrumental variables are associated with inflammation directly, with the example of circulating CRP, which is available in the UK Biobank. We assume that instrumental variables are independent of potential confounders and that horizontal pleiotropy is not present. Fourth, the AHBA used only 6 participants, a small sample size in transcriptomics. Fifth, the available data in UK Biobank and AHBA are limited to people of European ancestry, and significant replication when diverse samples become available is essential.

### Conclusions

This mendelian randomization study found that IL-6 was associated with changes in brain structure, with associations strongest in the MTG where several genes are differentially overexpressed compared with the whole brain. These genes form a highly connected network at the protein level and functionally contribute to diseases and phenotypes related to schizophrenia, autism spectrum disorder, and epilepsy. This suggests a genetically mediated, tissue-specific neuroinflammatory cascade relevant to brain structure in neuropsychiatric disorders. These findings can be modeled computationally and should be tested further for mechanistic insights in further preclinical models.

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