Transcriptional and Cellular Signatures of Morphometric Similarity Remodeling in Major Depressive Disorder

Wei Liao (✉ weiliao.wl@gmail.com)

University of Electronic Science and Technology of China <https://orcid.org/0000-0001-7406-7193>

Jiao Li

MOE Key Laboratory for Neuroinformation, University of Electronic Science and Technology of China

Jakob Seidlitz

National Institute of Mental Health <https://orcid.org/0000-0002-8164-7476>

John Suckling

University of Cambridge

Feiyang Fan

University of Electronic Science and Technology of China

Gongjun Ji

The First Affiliated Hospital of Anhui Medical University

Yao Meng

University of Electronic Science and Technology of China

Siqi Yang

University of Electronic Science and Technology of China

Kai Wang

Department of Neurology, the First Affiliated Hospital of Anhui Medical University

Huafu Chen

University of Electronic Science and Technology of China

Article

Keywords: Allen Human Brain Atlas, Depression, Gene enrichment, Morphometric similarity, MRI, Transcriptome

Posted Date: October 2nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-82307/v1>

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Version of Record: A version of this preprint was published on March 12th, 2021. See the published version at <https://doi.org/10.1038/s41467-021-21943-5>.

1 **Transcriptional and Cellular Signatures of Morphometric Similarity**
2 **Remodeling in Major Depressive Disorder**

3 Running title: Transcriptional and Cellular Profiles of MDD

4 **Jiao Li^{1,2}, Jakob Seidlitz^{3,4}, John Suckling⁵, Feiyang Fan^{1,2}, Gong-Jun Ji⁶, Yao Meng^{1,2},**
5 **Siqi Yang^{1,2}, Kai Wang⁶, Huaifu Chen^{1,2}✉, Wei Liao^{1,2}✉**

6
7 ¹ The Clinical Hospital of Chengdu Brain Science Institute, School of Life Science and
8 Technology, University of Electronic Science and Technology of China, Chengdu
9 610054, P.R. China.

10 ² MOE Key Lab for Neuroinformation, High-Field Magnetic Resonance Brain Imaging
11 Key Laboratory of Sichuan Province, University of Electronic Science and Technology
12 of China, Chengdu 610054, P.R. China.

13 ³ Children's Hospital of Philadelphia, Department of Child and Adolescent Psychiatry
14 and Behavioral Science, Philadelphia, PA USA.

15 ⁴ University of Pennsylvania, Department of Psychiatry, Philadelphia, PA USA.

16 ⁵ University of Cambridge, Department of Psychiatry, Cambridge CB2 0SZ, UK.

17 ⁶ Department of Medical Psychology, Chaohu Clinical Medical College, Anhui Medical
18 University, Hefei, China.

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20 ✉ Corresponding authors:

21 Huaifu Chen (chenhf@uestc.edu.cn), and Wei Liao (weiliao.wl@gmail.com). The
22 Clinical Hospital of Chengdu Brain Science Institute, MOE Key Laboratory for
23 Neuroinformation, University of Electronic Science and Technology of China, Chengdu
24 610054, P.R. China. Fax: +86-28-61831273. Tel: +86-28-61831273.

25

26 Title character count: 106

27 Word count of abstract: 150

28 Word count of main text: 4897

29 Number of references: 70

30 Number of Table(s): 0

31 Number of Figure(s): 7

32 Supporting Material (s): 1

ABSTRACT

Little is known about how major depressive disorder (MDD)-related anatomical endophenotypes are driven by transcriptomic profiles. Here, we examined a link between brain-wide gene expression and morphometric similarity (MS) remodeling in two MDD samples. MDD exhibited replicable abnormal MS patterns compared to healthy controls. Using spatially-comprehensive cortical gene expression data, we further identified two types of transcriptional signatures of MS remodeling: i) gene specificity, in which closely linked transcriptionally upregulated genes from postmortem samples in MDD, but not in other brain disorders, were spatially correlated with MDD MS remodeling; and ii) ontological enrichment, which identified reliable neurobiologically-relevant ontology terms and pathways previously described in MDD. Finally, we assigned transcriptional signatures to cell-types, which specified microglia and neurons as contributing most to the transcriptomic relationship of MS remodeling in MDD. Collectively, combined gene transcripts and connectome topology provided insight into how microscale genetic molecular mechanisms cause mesoscale morphometric abnormalities in MDD.

Keywords: Allen Human Brain Atlas; Depression; Gene enrichment; Morphometric similarity; MRI; Transcriptome.

INTRODUCTION

Major depressive disorder (MDD) is a prevalent worldwide psychiatric disease that often first occurs in adolescence ¹. Despite significant efforts, our current understanding of its pathophysiology is unclear with inconsistent brain architectural changes ² and the variable effects of treatment ³. Although neuroimaging studies show some focal structural alterations ⁴, functionally MDD is increasingly recognized as a disorder involving brain “disconnectivity” ⁵.

Investigating the MDD brain structural connectomes has primarily relied on two approaches: identifying the white-matter networks by diffusion-weighted imaging (DWI) tractography, and structural covariance networks of correlations of morphological measures ⁶⁻⁹. DWI tractography remains challenging, especially in estimating the connectivity strength of long-distance projections ¹⁰. Structural covariance analysis relies for its accuracy on a large sample sizes, and generally this technique cannot be used for individual analysis. Its biological interpretation also remains controversial ¹¹.

Novel morphometric similarity (MS) analysis has recently been a major step forward in revealing mesoscale cortical organization ¹². MS networks combine morphometric features from multiple modalities to map the similarities among cortical regions. Methodologically, MS networks can be constructed for individuals and have closer associations with a cytoarchitectonic classes, distinguished by cortical lamination

patterns, compared with DWI tractography. In addition, Seidlitz *et al.* has reported three biological associations of MS networks¹². First, strongly connected cortical areas often belong to the same cytoarchitectonic class, supported by histological evidence from nonhuman primates^{13, 14}. Second, strongly connected cortical areas have high levels of co-expressed genes. Finally, clinical abnormalities of the MS network in patients with schizophrenia are highly associated with brain expression of schizophrenia-related genes¹⁵, and uncover transcriptomic and cellular profiles of regional brain vulnerability to neurogenetic disorders¹⁶. Although MS networks are a reliable and robust method, their use for uncovering morphometric differences in MDD remains untried.

Genetic factors play important roles in brain connectomes^{17, 18}, and brain-wide gene expression atlases bridge the gap between connectomes and transcriptomes¹⁹. The Allen Human Brain Atlas (AHBA) microarray dataset has been used to identify transcriptomes associated with human neuroimaging^{20, 21} with multi-modal evidence suggesting a link between conserved gene expression and functionally relevant circuitry²²⁻²⁵. Moreover, combining neuroimaging and gene transcripts has provided insight into how disease-related alterations at the microscale architecture drive macroscale brain abnormalities in various mental disorders^{15, 16, 26-28}.

In this study, we investigated MDD-related morphometric disconnections and their relationships with transcriptomic profiles in discovery and replication independent

samples. We tested four key hypotheses: i) that MS remodeling in MDD is associated with anatomically patterned gene expressions, using the AHBA; ii) that the resultant gene enrichments were specifically associated with genes that were differentially expressed in postmortem samples of MDD patients; iii) that enrichment pathways in gene transcripts most strongly coupled to MS remodeling were generalized in replication samples; and iv) that specific cell types are responsible for transcriptional signatures related to MS remodeling in MDD.

RESULTS

Experimental design

This study combined multi-modal neuroimaging and transcriptomics data to determine links between gene expression and MS remodeling in patients with MDD ([Figure 1](#)). We created two independent samples: a *discovery* sample containing, after image quality control, 217 patients with MDD and 205 healthy controls (HC) and a *replication* sample consisting of 42 patients with MDD and 35 HC ([Table S1](#)). There was no difference in image quality, age and sex between patients and HC for both discovery and replication samples ([Supplemental Result 1 and Fig. S1](#)).

Morphometric similarity remodeling in MDD

We first calculated the MS connection weights (a 308×308 matrix) from inter-regional Pearson's correlation of seven features derived from MRI and DWI images acquired from each participant [12, 15, 16](#). We then calculated the regional MS values as the sum

of connection weights between a particular region, defined by the Desikan-Killiany (D-K) atlas^{12, 15, 29}, and all other regions. Within-group averaged summed weights created an anatomical distribution of positive and negative MS connections in HC (Figure 2A) that were consistent with a previous report by Morgan *et al.*¹⁵ yielding a correlation of mean regional values, $r_{(306)} = 0.91$, $p_{\text{spin}} < 0.0001$ (Supplemental Result 2 and Fig. S2), which was significant after correction for multiple comparisons by spatial permutation testing (spin-test, https://github.com/frantisekvasa/rotate_parcellation)³⁰.

In the discovery sample, summing regional MS weights across all regions for each participant, the MDD patients did not differ from HC ($p = 0.38$; Supplemental Result 3 and Fig. S3). Decomposed into regions, MDD participants exhibited decreased MS weights in the left superior frontal, and increased MS weights in the left orbitofrontal, isthmus cingulate cortex, and the right occipital cortices, when compared with HC (all $p_{\text{FDR}} < 0.05$; Figure 2B; Supplemental Result 4 and Table S2). The identically derived cross-sectional MDD-HC *t*-map from replication sample was significantly spatially related to the discovery sample ($r_{(306)} = 0.43$, $p_{\text{spin}} = 0.0002$; Fig. S4A&B).

The specificity of the observed MS differences to MDD was tested by comparison of correlations of the case-control *t*-map in the discovery sample and that derived from a similar analysis of schizophrenia (SCZ), $r_{(306)} = 0.26$, $p_{\text{spin}} = 0.09$ (Fig. S4C)¹⁵, epilepsy, $r_{(306)} = 0.10$, $p_{\text{spin}} = 0.17$, (unpublished data; Fig. S4C), and sex differences using the HC data, $r_{(306)} = 0.26$, $p_{\text{spin}} = 0.09$, (Fig. S4C). We also demonstrated that the spatial

correlation of t -maps between discovery and replication samples was significantly larger than these comparisons: SCZ, Steiger's z value = 3.14, p = 0.001; epilepsy, Steiger's z value = 4.02, p < 0.001; sex, Steiger's z value = 3.34, p < 0.001.

Next, to identify locations of case-control differences, we divided the cortex using two prior atlases ([Supplemental Result 5](#)): the Yeo 7 functional networks parcellation ([Fig. S5A](#))³¹, and the von Economo cytoarchitectonic parcellation ([Fig. S5B](#))³². Cross-sectionally, MDD patients exhibited increased MS in the Yeo visual network (p_{FDR} = 0.001) and decreased MS in the default mode network (p = 0.048, uncorrected); [Supplemental Table S3 and Fig. S5C](#). For the von Economo parcels, MDD patients had decreased MS in the association cortex (p = 0.044, uncorrected) and increased MS in secondary sensory areas (p_{FDR} = 0.003); [Supplemental Table S4 and Fig. S5D](#).

The case-control t -map was significantly spatially correlated with the mean control regional MS: $r_{(306)} = -0.71$, p < 0.0001 ([Figure 2C](#)), indicating that more connected regions tend to show largest case-control differences^{15, 16}. Negative regional t -values and positive mean MS represents decoupling in MDD patients relative to HC and was found in 34% of regions, whereas 41% of regions had positive t -values and negative mean MS representing dedifferentiation in MDD patients relative to HC.

Assessing the relationship between MS case-control differences and symptoms, we found that the mean MS across six brain regions where MS was significantly greater

in MDD patients relative to HCs was positively correlated with Hamilton Depression Rating Scale (HAMD) scores ($r_{(306)} = 0.136$, $p = 0.046$, uncorrected), and the MS values in the superior frontal cortex where MS was significantly less in MDD patients relative to HCs was marginally negatively correlated with HAMD scores (mean global MS: $r_{(306)} = -0.132$, $p = 0.052$; mean decreased MS: $r_{(306)} = -0.117$, $p = 0.086$) (*Supplemental Result 6 and Table S5*). An exploratory correlation analysis was also performed across all D-K regions. We found that dorsal lateral prefrontal cortex exhibited a significant negative correlation with HAMD scores, whereas occipital cortices, middle/posterior cingulate cortex, and precentral cortex had positive correlations with HAMD scores (*Fig. 6A*). For HAMA scores, right dorsal lateral prefrontal cortex was negatively correlated, whereas left visual cortex and right temporal cortex were positively correlated (*Fig. 6B*).

Cortical gene expression related to regional MS differences

We used the Allen Human Brain Atlas (AHBA) (<http://human.brain-map.org>), a whole-brain transcriptomic dataset, to obtain brain gene expressions (*Supplemental Result 7.1*). Because the AHBA dataset includes two right hemisphere data points alone (*Table S6*), only the left hemisphere was considered in our analysis³³. As a result, a matrix (152 regions $\times$ 10,027 gene expression levels) of transcriptional level values was obtained (*Supplemental Result 7.2*). We then used Partial least squares (PLS) regression³⁴ to determine differences between regional MS in the left hemisphere (*Figure 3A*) and gene expressions (10,027 genes). The first component, PLS1, (*Figure*

3B) explained 36% of the variance (permutation test, $p_{perm} < 0.0001$), and the PLS1-weighted gene expression map was spatially correlated with the case-control t -map ($r_{(150)} = 0.60$, $p < 0.0001$; Figure 3C).

We ranked the normalized weights of PLS1 based on univariate one-sample Z tests in the discovery sample. We found 1,747 PLS1+ ($Z > 5$) and 1,237 PLS1- ($Z < -5$) (all $p_{FDR} < 0.005$; Figure 3D) positively (or negatively) weighted gene expressions were over-expressed (or under-expressed) as increased (or decreased) regional MS differences. In total, 2,984 genes constituted the regional MS difference gene list in MDD patients. Subsequently, we found that 2,150 PLS1+ ($Z > 5$) genes, and 1,503 PLS- ($Z < -5$) genes were significantly overexpressed in cortical regions of replication sample, consisting of 3,653 regional MS gene list differences. The gene lists in the discovery and replication samples were highly overlapped: odds ratio (OR) = 109.5, $p < 0.0001$.

To further determine relationships between prior MDD-related gene expressions and regional MS differences, we identified 12 MDD-related genes (obtained using the overlaps between 24 MDD-related genes and 10,027 background genes) from in-situ hybridization data in adult human brain studies (help.brain-map.org/display/humanbrain/Documentation). Nine MDD-related genes exhibited significant correlations with regional MS differences (all $p_{FDR} < 0.05$; Figure 3E), including five negative correlations (i.e., *CNR1*, *HTR1A*, *PDE1A*, *SST*, and *TAC1*) and four positive correlations (i.e., *ARRA2A*, *CHRM2*, *CUX2*, and *HTR5A*).

Specificity of genes to MDD remodeling

From the gene list of regional MS differences, we found that 34 genes overlapped between the weighted gene expression of PLS1- ($Z < -5$) and the significant upregulated genes in MDD reported by Gandal *et al.* ³⁵. There was a significant association of the PLS1- weights and differential gene expressions (DGE): $R^2_{(32)} = 0.23$, $p_{\text{FDR}} = 0.005$ (Figure 4). PLS1- weighted gene expressions were not significantly correlated with upregulated DGE in SCZ, bipolar disorder (BD), alcoholism, and inflammatory bowel disease (IBD), but were associated with DGE in autism spectrum disorder (ASD) ($R^2_{(151)} = 0.08$, $p_{\text{FDR}} = 0.0005$) ³⁶. There were no significant results in other correlation analyses.

Enrichment pathways of MS remodeling

We aligned the gene ontology (GO) biological processes and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways with the PLS1- gene list using Metascape (<https://metascape.org/gp/index.html#/main/step1>). After correcting for enrichment terms ($p_{\text{FDR}} < 0.05$) and discarding discrete enrichment clusters, there were 10 significant GO biological processes including “synaptic signaling”, “regulated exocytosis”, and “regulation of ion transport”, and three KEGG pathways, including “retrograde endocannabinoid signaling”, “neuroactive ligand-receptor interaction”, and “Rap1 signaling pathway” (Figure 5).

The PLS1+ genes were enriched for GO biological processes ([Supplemental Result 7.3](#)), such as “signal release”, and “synaptic vesicle priming”, but not for KEGG pathways ([Fig. S7 and Table S7](#)). Genes that were downregulated postmortem in MDD patients were not correlated with weighted gene expressions of PLS1+.

Validation against gene expression from MS remodeling

To validate the gene ranks, we performed multi-gene-list meta-analysis ³⁷ between the PLS1– gene list and genes that were significantly associated with the MDD phenotype from recent genome-wide meta-analysis studies (GWAS) ^{38, 39}. We found that enrichment pathways of the PLS1– gene list contained 6 of 7 pathways of genes from GWAS studies. The enrichment pathways included “cognition”, “Ras protein signal transduction”, “regulation of ion transport”, “synaptic signaling”, “synapse organization”, and “cell-cell adhesion via plasma-membrane adhesion molecules” ([Supplemental Result 7.4 and Fig. S8](#)). These results indicate that functional roles of PLS1– genes were not only consistent with previous studies, but also provide additional complementary functional information.

Generalization of transcriptional enrichments of MS remodeling

To investigate the generalization of transcriptional enrichments of MS remodeling, a multi-gene-list meta-analysis was performed ³⁷. We first identified the overlapped enrichment pathways between discovery and replication samples where there was a significant overlap of PLS1– genes: $OR = 174.6, p < 0.0001$ ([Figure 6A](#)). After correcting

for enrichment pathways, several ontological terms survived (Figure 6B), which were the same as those from discovery enrichment analyses, including “synaptic signaling”, and “Rap1 signaling pathway”. The overlapping ontology terms between discovery and replication samples concentrated on “synaptic signaling”, “Glutamatergic synapse”, “Rap1 signaling pathway”, “behavior”, “regulated exocytosis”, “negative regulation of phosphate metabolic process”, and “response to metal ion” (Figure 6C). For visualization, uncorrected overlapping ontology terms are shown in Fig. S9. Significantly overlapping ontology terms support the generalized relationship between gene expression and the MS differences in MDD.

Transcriptional signatures for canonical cell types

To further refine our analysis, and considering cellular diversity in the brain, we took an indirect approach to sort PLS1– genes according to different cell types. We used gene sets for seven canonical cell classes¹⁶ to identify cell types enriched for MS alterations in our analysis. We first visualized the distribution of gene expression in each cell type (Figure 7A). Genes related to astrocytes and excitatory neurons highly overlapped with the PLS1– gene list (Figure 7B). Notably, consistent with previous single cell sequencing in MDD, we found that the cell type of gene expression showed a similar cell type of excitatory neurons⁴⁰. Confirming our strategy, enrichment analysis using cell type specific genes revealed that MS differences in MDD patients were significantly enriched for biological processes associated with inflammation in microglial and neuronal cells (Figure 7C). MS differences identified in neuronal cells

were enriched for GO terms including “serotonergic synapse”, “synapse organization” and “chemical synaptic transmission”. Together, our approach identified MS differences-related gene expression to unique cell types, allowing us to pinpoint specific cell types known to be associated with MDD pathology.

DISCUSSION

Using structural MRI to define replicable maps of MDD patient-related differences in anatomical organization, we found that this cortical pattern of MDD effects was significantly associated with normative gene expression gradients enriched for MDD-related genes. Specifically, the MS differences-related gene transcripts (PLS1–): i) were enriched for *prior*-defined MDD-related genes, and exhibited almost the same ontological terms as those genes identified from GWAS studies; ii) were specifically associated with genes that were significantly upregulated in prior postmortem material from MDD; and iii) were ontologically enriched for synapse-related terms that were generalized in the replication sample. In addition, we also mapped MDD-related genes to biological processes associated with microglial and neuronal cells. These findings reveal MS network phenotypes in MDD, and bridge the gap between transcriptome and neuroimaging promoting an integrative understanding of MDD.

MS remodeling in MDD

Rather than using single anatomical and morphometric features, such as cortical thickness, curvature, and volume, MS networks combine information across multiple

cortical features ^{12, 15, 16, 28, 41}. MDD shares common brain alterations with other psychiatric and neurological disorders ⁴², as well as having diagnostic-specific features. Transdiagnostic patterns of gray matter loss are located in the anterior insula and dorsal anterior cingulate cortex ⁴³; whereas transdiagnostic patterns of anatomical connectome are related to highly-connected hubs ⁴⁴. However, diagnosis-specific effects volumetric changes are found only in MDD and SCZ ⁴³. Our reliable MS alterations showed a general convergence of affected regions with other psychiatric disorders in regions including the medial prefrontal cortex, and isthmus cingulate.

MDD-risk genes related to MS remodeling

MDD-related MS differences may be due to a host of factors such as genetic, molecular, and neuronal alterations. Recently, human imaging genetics has emerged as a powerful strategy for understanding the molecular basis of brain connectome organization ^{15, 19, 26, 27}. Using the multivariate PLS method, we found cortical patterns of weighted gene expression that were significantly co-localized with MS differences, and further identified significantly weighted genes in the first PLS component that may play roles in the pathogenesis of MDD.

MDD-related gene analysis suggested that a substantial part (9/12) was related to MS differences. The discovered gene *SST* codes for a neuromodulatory peptide expressed in a subtype of GABA neurons that inhibits the dendritic compartment of excitatory pyramidal neurons ⁴⁵. Reduced *SST* gene expression has frequently been observed

postmortem in brains of MDD patients ^{46, 47}. *SST* was the third strongest negatively correlated gene, with *TAC1* showing a stronger inverse association, which is a gene earlier noted to be involved in MDD and related to depression-like behaviors ⁴⁸⁻⁵¹. Similarly for *SST*, *TAC1* is also a gene related to neuron excitation and behavioral responses ⁵¹. The underlying pathogenetic mechanism of both positively versus negatively correlated genes presently remains unclear. A potential explanation may lie in the distinct types of cortical interneurons between genes marked by neuropeptides (e.g., *SST* and *TAC1*) and genes related to biological processes, such as genes involved in protein coding ⁵².

The PLS1– gene list was specifically associated with genes that were significantly upregulated in postmortem MDD patients. Large-scale GWAS has identified the shared significant genetic commonalities across major psychiatric disorders ^{53, 54}, and MDD shows positive genetic correlations with most other psychiatric disorders ^{54, 55}. However, negatively weighted gene expression profiles in this study did not show significant correlations with genes differentially expressed in postmortem case-control studies of SCZ, BD, alcoholism, and IBD, indicating that the MDD-related genes identified by PLS on MS are likely specific to MDD. In contrast, consistent with potential disorder-specific associations, PLS1– showed a significantly positive correlation with differential gene expression in ASD suggestive of potential converging pathophysiological mechanisms in these two disorders ⁵³, which will require future studies to validate this proposition in the context of neuroimaging-transcriptomics.

339 Additionally, there were significantly more upregulated genes in the list of negatively
340 weighted genes with MS differences, indicating that genes with increased brain
341 postmortem transcription in MDD were overexpressed in cortical areas with lower
342 levels of MS difference. An important future direction involves quantifying the degree
343 to which genetic influences risk for MDD may be directly mediated by their effects on
344 MS.

346 **Weighted gene expressions enriched for functional annotations**

347 PLS1– identified a gene expression profile with high expression in the frontal and
348 temporal cortices. The subset of 1,237 negatively weighted genes comprised a dense,
349 topologically clustered interaction network that was enriched for several GO biological
350 processes and KEGG pathways. The highly overlapping PLS1– genes were associated
351 with the same ontological terms in both discovery and replication samples, suggesting
352 a generalization of transcriptional signatures of MS remodeling.

354 The identified KEGG pathways (i.e., “retrograde endocannabinoid signaling”, and
355 “neuroactive ligand-receptor interaction”) have been reported to modulate a wide
356 variety of synaptic neurotransmissions or neural functions, including cognition, motor
357 control, and pain ^{56, 57}. Abnormalities or dysregulations of these pathways have been
358 implicated in MDD ⁵⁸. Moreover, the endocannabinoid signaling system is a potential
359 antidepressant candidate ⁵⁹ as it may help reverse the acute and chronic stress
360 response, and produce antidepressant physiological changes. The endocannabinoid

signaling system deserves additional study as a potential target for therapeutic intervention ^{56, 60}.

Our identified GO biological processes were related to responses to stimuli and synaptic transmission, indicating that members of negatively weighted genes had diverse molecular functions ⁵⁷. In particular, the discovered pathway “synaptic signaling”, which influences synaptic maturation and stability ⁶¹, and which was one of the replicable pathways between discovery and replication samples, showing a high Metascape value out of all other pathways. Loss of synapses has been reported to produce depressive behavior in rodent models ⁶². The cluster of interactive proteins related to “G protein-coupled receptors” (GPCRs) signaling pathways mediate most cellular responses to hormones and neurotransmitters ⁶³. As suggested for the “synaptic signaling” pathway, GPCRs signaling pathways are implicated in the pathophysiology and pharmacology of MDD. These findings highlight GPCRs as potential therapeutic targets for MDD, which warrant follow-up analyses.

For validation, an additional enrichment analysis helped us specify the gene ranks related to MS remodeling. Consistent with GWAS in MDD, the same ontology terms, especially synapse-related terms, support the reliability and sensitivity of genes identified by PLS in this study ^{38, 39}. In addition, the multi-gene-list result exhibits several other enrichment pathways which are found in genes related to MS

remodeling, but not in genes of GWAS, and thus the genes obtained by PLS might provide additional enrichment information for MDD.

Cellular characterization of the MDD-related genes

We showed that cellular organization of the human brain provides a biological mechanism that can translate genes of MDD-related brain alterations into MDD-related alterations of specific cell types. The density and form of cells abnormalities (in astrocytes, microglia, or oligodendrocytes) plays an important role in psychiatric disorders, including ASD, BD, MDD and SCZ ⁵⁵. Alterations in cortical thickness for major psychiatric disorders have been related to gene expression specific to astrocytes (except for BD) and microglia (except for obsessive-compulsive disorder) ⁵⁵. Astrocytes were the greatest proportion in gene ranks obtained by PLS on MS remodeling in MDD, and have also been considered as a promising target for mood disorder interventions ⁶⁴. The dysfunction of astrocytes influences synaptic activity, and astrocytes can modulate neuronal circuits and behavior. Furthermore, we identified that the most enriched pathway was related to microglia, aligning with prior reports ⁶⁵. Microglia play crucial roles in the regulation of ongoing structural and functional processes, from individual synapses to neural circuits and behavior ⁶⁶. The disturbances of microglia activation could influence immune functioning of the brain, synaptic plasticity and mood under physiologically strained conditions. Finally, we found the dysregulation of gene expression in MDD was related to excitatory and inhibitory neurons, which was consistent with the single-nucleus transcriptomics study in MDD ⁴⁰. In recent

years, the target cell types in MDD pathophysiology have expanded from excitatory neurons to inhibitory interneurons ⁶⁷. The identified MDD-related cell types verified the validity of the gene ranks obtained from MS differences and enabled us to explore the biology of human disorders using data from postmortem human brain tissue.

Methodological considerations

Several methodological issues have to be considered. The AHBA gene data were measured postmortem in six subjects without psychiatric diagnoses, which limited examination of transcriptome–neuroimaging association across groups and possibly placed individual effects out of scope. In addition, the AHBA only included data for the right hemisphere for two subjects. Thus, the relationship between genes and MS remodeling in MDD does not represent the condition of the entire brain.

Conclusions

Our study links MS network phenotypes to gene expression levels, supporting the idea that synapse-related terms are implicated in the pathophysiology and pharmacology of MDD. We further showed that abnormalities of microglial and neuronal cells may cause MS remodeling leading to depressive symptoms. Crucially, despite not requiring access to any postmortem brain tissue from patients, we can screen the MS-remodeling related brain-wide gene expression and cell types to capture molecularly validated anatomical differences in psychiatric patients.

MATERIALS AND METHODS

Samples

The discovery sample included patients with MDD (n = 242) and age- and sex-matched healthy controls (HC, n = 231). Patients were recruited from the First Affiliated Hospital of Chongqing Medical University and diagnosed using the Structural Clinical Interview for DSM-V. Depression severity was assessed by the 17-item Hamilton Depression Rating Scale (HAMD). MDD patients were excluded if they: i) were < 18 years or > 65 years; ii) had HAMD < 8; iii) had major neurological or other psychiatric disorders; and iv) had magnetic resonance imaging (MRI) abnormalities, or had any metal or electronic implants. HCs were recruited with the following eligibility criteria: i) no mood disorder or neurological disorders, and ii) no history of psychiatric illness among their first-degree relatives. The replication sample included patients with MDD and age- and sex-matched HC ([Supplemental Material 1](#)).

The study was approved by the Ethics Committee of Southwest University and First Affiliated Hospital of Chongqing Medical University. All study protocols were performed according to the Helsinki Declaration of 1975 and approved by the local institutional review board. Written informed consent was obtained from all participants.

Multi-neuroimaging data acquisition and preprocessing

All MDD patients and HC underwent structural and DWI scanning (*Supplemental Material 2*). The three-dimensional T1w images were preprocessed on surface-based space using FreeSurfer (v6.0, <http://surfer.nmr.mgh.harvard.edu/>). Briefly, the cortical surface was reconstructed using skull stripping, segmentation of brain tissue, separation of hemispheres and subcortical structures, and construction of the gray/white interfaces and the pial surfaces¹². The DWI images were preprocessed on volumetric space using FSL (v6.0, <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>). Briefly, the DWI images were corrected for the eddy-current-induced distortions and head movements. Diffusion tensor models were then estimated using linear least squares fitting.

Participants were excluded if they had images with poor scan quality (*Supplemental Result 1*). To further check for differences in motion and image quality between groups, the Euler number was calculated for each T1w image⁶⁸.

Construction of MS network

The cortical surfaces were divided into 308 regions derived from the Desikan-Killiany (D-K) atlas^{12, 15, 29}. This D-K atlas was transformed to each participant's surface to obtain an individual surface parcellation which was then interpolated and expanded to the participant's DWI volumes^{12, 15}. For each region, seven features from the MRI and DWI images were extracted¹⁵, including surface area, cortical thickness, gray

matter volume, Gaussian curvature, mean curvature, fractional anisotropy, and mean diffusivity. For each participant, each morphometric feature vector was z-normalized across regions to account for variation in value distributions between the features ^{12, 15}. Pearson's correlation analysis was then performed on the seven features between each paired cortical region, forming a 308 × 308 MS matrix for each participant.

Case-control analysis of the MS network

The regional MS was calculated by using the sum of weighted correlation coefficients between a given region and its correlations to all other regions. To estimate the spatial pattern, regional MS was averaged across all HC participants. To examine the case-control differences, a generalized linear model was used with regional MS values as the dependent variables. Age, sex, and education level were added as covariates. Significance was set at $p < 0.05$ with false-discovery rate (FDR) correction for multiple comparisons across regions.

The above case-control analyses were also used for the replication samples. To test replicability of regional MS differences, a spatial similarity analysis was conducted on t -value maps between discovery and replication samples ^{15, 69}.

Estimation of regional gene expressions

The AHBA dataset bridges the gap between regional MS differences and transcriptomes⁷⁰. Brain-wide gene expressions were measured in six post mortem brains (age = 42.5 ± 13.38 years; male/female = 5/1) with 3,702 spatially distinct samples (*Supplemental Result 7.1 and Table S6*). The AHBA dataset was processed according to Arnatkevic *et al.*³³. Because the AHBA dataset included only two right hemisphere data, only the left hemisphere was considered in our analysis³³. Thus, after six steps of preprocessing (*Supplemental Result 7.2*), a matrix (152 regions × 10,027 gene expression levels) of transcriptional level values was obtained.

Regional MS differences and gene expression

PLS regression³⁴ was used to determine the relationship between regional MS differences (*t*-values from 152 cortical regions in the left hemisphere) and transcriptional activity for all 10,027 genes. Gene expression data were used as predictor variables of regional MS differences in the PLS regression. The first component of the PLS (PLS1) was the linear combination of gene expression values that was most strongly correlated with regional MS differences. Permutation tests (1,000 permutations) were used to test whether the explained variance of PLS1 was significant. Bootstrapping was used to estimate the variability of each gene's PLS1, and the ratio of the weight of each gene to its bootstrap standard error was used to calculate the Z scores and rank the genes according to their contributions to PLS1¹⁵. The set of genes with an FDR of 5%, either positive, PLS1+, or negative, PLS1–, was

the regional MS differences gene list. This procedure was also conducted on the replication sample.

Gene specificity analysis

A list of genes, which were transcriptionally dysregulated in postmortem brain tissue measurements of messenger RNA from case-control studies of MDD, were used to analyze the specificity of the regional MS difference gene list. The list reported by Gandal *et al.* included 1,992 upregulated and 2,093 downregulated ($p < 0.05$) genes in MDD patients³⁵. Pearson's correlation analysis was used to determine relationships between PLS1+ or PLS1– and differential gene expression of up- or down-regulated genes. To validate the specificity, this analysis was also applied for ASD, SCZ, BD, alcoholism, and IBD.

Enrichment analysis

Metascape analysis (<https://metascape.org/gp/index.html#/main/step1>) provides automated meta-analysis tools to understand either common or unique pathways in 40 independent knowledge bases³⁷. The PLS1+ ($Z > 5$) or PLS1– ($Z < -5$) was input into the Metascape website, and the obtained enrichment pathways were thresholded for significance at 5%, corrected by the FDR.

Multi-gene-list meta-analysis

To investigate the generalization of transcriptional enrichments of MS remodeling, a multi-gene-list meta-analysis was performed. First, the enrichment analysis was applied to for replication samples. Then, multi-gene-list meta-analysis ³⁷ between discovery and replication samples were performed using the Metascape website to compare an arbitrary number of gene lists across both gene identities and ontologies. The degree of overlapped genes was measured by the odds ratio (OR).

Assigning MDD-related genes to cell types

Gene sets for each cell type were provided by a previous study ¹⁶. These cell types include microglia, endothelial cells, oligodendrocyte precursors, oligodendrocytes, astrocytes, excitatory and inhibitory neurons obtained from the postmortem cortical samples in human postnatal participants. To assign MDD-related genes obtained by PLS analysis to cell types, we overlapped the gene set of each cell type with the PLS1-rank gene list. Then we calculated an average expression for each cell-class gene set in each of the 152 regions of the AHBA parcellation.

ACKNOWLEDGEMENTS

We are grateful to all the participants in this study. We thank International Science Editing (<http://www.internationalscienceediting.com>) for editing this manuscript. This work was supported by the National Key Project of Research and Development of Ministry of Science and Technology (2018AAA0100705), the National Natural Science Foundation of China (61871077, 61533006, and U1808204), and Sichuan Science and Technology Program (2018TJPT0016).

AUTHOR CONTRIBUTIONS

W.L. and H.C. led the project. J.L., W.L. and H.C. were responsible for the study concept and the design of the study. J.L. and W.L. analyzed the discovery data, created the figures and wrote the manuscript. J.S. and J.S. made substantial contributions to the manuscript and provided critical comments. F.F., Y.M., and S.Y. checked the imaging quality and contributed to interpretation of the discovery samples. G-J.J. performed data analysis in replication samples. K.W. contributed to data acquisition and interpretation of replication samples. All authors reviewed and commented on the manuscript.

COMPETING INTERESTS

The authors report no biomedical financial interests or potential conflicts of interest.

DATA AVAILABILITY

Requests for the discovery and replication samples supporting the findings of this paper will be promptly reviewed by the corresponding author (Wei Liao) to verify whether the request is subject to any intellectual properties or confidentiality obligations.

CODE AVAILABILITY

The preprocessing software is freely available (FreeSurfer v6.0, <http://surfer.nmr.mgh.harvard.edu/> and FSL v5.0.9, <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>). The code for MS analysis is openly available at https://github.com/SarahMorgan/Morphometric_Similarity_SZ. The code for gene expression analysis can be found at <https://github.com/BMHLab/AHBProcessing>. Gene enrichments were analyzed at <https://metascape.org/gp/index.html#/main/step1>. The code for spatial permutation testing can be found at https://github.com/frantisekvasa/rotate_parcellation.

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FIGURE LEGENDS

Figure 1. Study overview. (A) Morphometric similarity (MS) analysis. Individual MS matrices were constructed across multimodal magnetic resonance imaging features (e.g., myelination, gray matter, and curvature) to produce a 308 × 308 matrix (depicted by a subdivision of the Desikan-Killiany atlas, D-K 308). Then, case-control differences across regions were computed. **(B) Gene expression profiles.** Gene expression profiles from the Allen Human Brain Atlas in 152 regions (left hemisphere only) were averaged across six postmortem brains. Partial least squares regression was then used to identify imaging-transcriptomic associations. Finally, enrichment analysis was performed on the gene list associated with PLS1.

Figure 2. Case-control differences of regional morphometric similarities. (A) Mean regional morphometric similarity (MS) pattern of healthy controls (HCs). The frontal and temporal lobes exhibited high MS values, whereas the occipital and somatosensory cortices showed low MS values. **(B)** Case-control comparison (t -map) of regional MS in discovery samples (first row, unthresholded). Seven cortical regions showed statistically significant differences (bottom row, $p_{\text{FDR}} < 0.05$). **(C)** A scatterplot of the mean regional MS (x -axis) and case-control t -map (y -axis) (first row). Most cortical regions exhibited de-differentiation (34%) and de-coupling (41%) in MDD patients (bottom row).

Figure 3. Gene expression profiles related to morphometric similarity differences. (A) Regional morphometric similarity (MS) differences in the left hemisphere (unthresholded). (B) A weighted gene expression map of regional PLS1 scores in the left hemisphere (unthresholded). (C) A scatterplot of regional PLS1 scores (a weighted sum of 10,027 gene expression scores) and regional MS differences. (D) Ranked PLS1 loadings. (E) Major depressive disorder (MDD)-related genes from in-situ hybridization in the adult human brain positively (e.g., *CUX2*; Pearson's $r_{(150)} = 0.50$, $p < 0.0001$) and negatively (e.g., *TAC1*; Pearson's $r_{(150)} = -0.53$, $p < 0.0001$) correlated with regional MS differences.

Figure 4. Specificity of gene expression in major depressive disorders. The PLS1-weighted gene expression was significantly associated with upregulated differential gene expression (DGE) postmortem in MDD reported by Gandal *et al.* ($R^2_{(32)} = 0.23$, $p_{FDR} = 0.005$). Associations between PLS1-weights and DGE were also evaluated for other brain disorders: autism spectrum disorder ($R^2_{(151)} = 0.08$, $p_{FDR} = 0.0005$), schizophrenia ($R^2_{(151)} = 0.03$, $p = 0.04$), bipolar disorder ($R^2_{(89)} = 0.03$, $p = 0.09$), alcoholism ($R^2_{(158)} = 0.01$, $p = 0.19$), and inflammatory bowel disease ($R^2_{(378)} = 0.003$, $p = 0.31$).

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Figure 7. Cell type-specific expression to MS differences-related genes. (A) Regional gene expression maps of each cell type from overlapping genes between PLS1– gene list and each cell type-specific genes. **(B)** The number of overlapping genes for each cell type. **(C)** Gene ontology terms enriched for MS differences-related genes for the cell types

Figures

A. Morphometric similarity analysis

B. Gene expression profiles

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Supplementary Files

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