Gene Expression Associated with Human Brain Activations in Facial Expression Recognition

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Abstract

Previous studies identified some genetic loci of emotion, but few focused on human emotion-related gene expression. In this study, the facial expression recognition (FER) task-based high-resolution fMRI data of 203 subjects in the Human Connectome Project (HCP) and expression data of the six healthy human postmortem brain tissues in Allen Human Brain Atlas (AHBA) were used to conduct a transcriptome-neuroimaging spatial association analysis. Finally, 153 genes were identified to be significantly associated with FER-related brain activations. Enrichment analyses revealed that FER-related genes are mainly expressed in the brain, especially neurons, and might be related to cell junction organization, synaptic functions, and nervous system development regulation, indicating that FER was a complex polygenetic biological process involving multiple pathways. Moreover, these genes exhibited higher enrichment for psychiatric diseases with heavy emotion impairments. This study provided new insight into understanding the FER-related biological mechanisms and might be helpful to explore treatment methods for emotion-related psychiatric disorders.

1. Introduction

Emotion is of great importance in most aspects of human social behavior and cognitive activities (Niedenthal & Brauer, 2012; Pessoa, 2008). Facial expression recognition (FER) is a crucial feature of emotional expressions and is instrumental for our mental health. Facial expressions are created with the morphological changes of the face and reflect internal emotions, needs, and action tendencies of a person, such as frowning, widening eyes, and tightening lips (Ekman, 1992). The ability of FER helps us infer emotions displayed by others and then respond appropriately to such social and emotional information (Lopes, Salovey, Cote, & Beers, 2005). FER impairments are associated with many psychiatric diseases such as attention deficit and hyperactivity disorder (ADHD) (Shaw, Stringaris, Nigg, & Leibenluft, 2014), autism spectrum disorder (ASD) (Harms, Martin, & Wallace, 2010), bipolar disorder (BP) (Lima, Peckham, & Johnson, 2018), major depression disorder (MDD) (Bourke, Douglas, & Porter, 2010), and schizophrenia (SCZ) (Kring & Elis, 2013). For example, several studies investigated that recognizing facial expressions in others could be difficult in individuals with depression (Dalili, Penton-Voak, Harmer, & Munafo, 2015; Groves et al., 2018; Kohler, Hoffman, Eastman, Healey, & Moberg, 2011). Understanding the neurotic mechanism of FER has been becoming an important research topic in neuroscience.

Many neuroimaging studies focused on FER-related brain activations using task-based fMRI (Fusar-Poli et al., 2009; Phan, Wager, Taylor, & Liberzon, 2002; Vytal & Hamann, 2010), and blood oxygen level-dependent (BOLD) signal changes were detected in the amygdala, insula, anterior cingulate cortex, hippocampus, and lateral prefrontal cortex during performing the FER tasks (Barch et al., 2013; Kragel et al., 2018; Nummenmaa et al., 2012). Especially, consistently increased activation was found in the amygdala during fear experiments (Glascher, Tuscher, Weiller, & Buchel, 2004; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002; Phan et al., 2002; Whalen et al., 2001). These neuroimaging findings were helpful for understanding the neuronal mechanisms of FER.

It has been known that emotional processes are moderately heritable (40-60%) (Bouchard & Loehlin, 2001; Robinson et al., 2015). Previous candidate gene studies revealed some genetic loci associated with emotion processing such as the variants in the following genes: oxytocin receptor (*OXTR*) (Skuse et al., 2014), neuropeptide Y (*NPY*) (Mickey et al., 2011; Zhou et al., 2008), catechol-O-methyltransferase (*COMT*) (Enoch, Xu, Ferro, Harris, & Goldman, 2003; Kolassa, Kolassa, Ertl, Papassotiropoulos, & De Quervain, 2010; Weiss et al., 2007), glucocorticoid receptor-regulating co-chaperone of stress proteins (*FKBP5*) (Binder et al., 2008; Binder et al., 2004), pituitary adenylate cyclase-activating polypeptide receptor (*ADCYAP1R1*) (Ressler et al., 2011), and serotonin transporter (*SLC6A4*) (Bevilacqua & Goldman, 2011; Hariri, Mattay, et al., 2002; Raab, Kirsch, & Mier, 2016). Meanwhile, genome-wide association studies (GWASs) have also revealed several variants associated with emotion processing (Coleman et al., 2017; Lancaster, Ihssen, Brindley, & Linden, 2017; Shimanoe et al., 2019; Wingo et al., 2017). For example, *FBXO45*, a gene encoding F-Box Protein 45 was significantly associated with emotional expression (Lancaster et al., 2017). A previous GWAS identified a significant single-nucleotide polymorphism rs322931 associated with positive emotional experiences (Wingo et al., 2017), and another literature found the effect of rs322931 on emotion processing by a similar picture-viewing task (Lancaster et al., 2017).

Although many studies investigated the heritability of emotion, and both candidate genes and GWAS studies revealed genetic loci associated with emotion processing, the biological mechanisms of those emotion-related genes are still unclear. Those studies usually provide limited insight into the transcriptional mechanism of emotion processing. Gene expression assay is a direct measure of a gene's biological functions; assessing the association between emotion processing and gene expression may help understand the neuronal mechanisms of emotion processing. However, few gene expression studies have been performed to explore the neuronal mechanisms associated with emotion processing. Therefore, it is necessary to investigate underlying gene expressions which modulate emotion processing.

Across-individual transcription-neuroimaging association analysis is an excellent method that could be applied to investigate the association between brain functions and gene expression. In this study, The emotion task fMRI data in Human Connectome Project (HCP) was used to detect FER-related brain activation. HCP is a public resource that includes high-resolution task-based fMRI data of healthy adults (Smith et al., 2013) and provides a reliable emotion recognition-related brain activation map (Barch et al., 2013; Hariri, Tessitore, et al., 2002). Gene expression data were extracted from a public dataset, Allen Human Brain Atlas (AHBA) (M. J. Hawrylycz et al., 2012). AHBA provides high-resolution coverage mRNA transcriptome in more than 20000 genes profiled in 3702 samples in different brain regions of six healthy human postmortem brain tissues. The samples could be mapped into Montreal Neurological Institute (MNI) space, allowing researchers to link gene expression with human neuroimaging data. Recent studies using a spatial pattern of gene expression maps provided by AHBA yielded new insights into transcriptional mechanisms of many cognitive activities and psychiatric disorders (Liu, Tian, Li, Li, & Zhuo, 2019; Ritchie, Pantazatos, & French, 2018; Xie et al., 2020).

In the present study, the across spatial association was performed between the AHBA data set and group-level FER activation map of 203 healthy young adults in the HCP. A set of genes were identified as FER-related genes. Then, enrichment analyses of these genes about gene ontology, cell types, tissues, and diseases were performed. Moreover, protein-protein interaction (PPI) networks were conducted to gain an in-depth understanding of the molecular mechanism of emotion recognition. Finally, hub genes were derived through PPI network analysis.

2. Methods

2.1. Subjects

MRI Data in our study were from an open-source database, WU-Minn Human Connectome Project Data-500 Subjects (HCP_500) (Smith et al., 2013). Four hundred and sixty-four subjects were scanned during performing six cognitive tasks (emotion, language, social, working memory, gambling, and relational tasks) in the HCP-500. After excluding 46 left-handedness subjects, 418 subjects from 203 families were retained. Then, one subject was chosen from each family with gender balance. Finally, 203 right-handed healthy young adults (101 males and 102 females; age: 29.11 ± 3.50 years, range: 22-36 years) were included in our study. All subjects were screened for a history of neurodevelopmental, neuropsychiatric disorders, and genetic disorders. Written informed consents were provided by all subjects. The HCP study was ethically approved by the Washington University Institutional Review Board (IRB). The detailed inclusion and exclusion criteria were listed elsewhere (Glasser et al., 2013).

2.2. FER task

The detailed HCP emotion task procedure was described in the previous literature (Hariri, Tessitore, et al., 2002). In brief, the subjects were asked to choose the correct face or shape on the bottom of the screen, which matches the figure on the top of the screen. The facial expression figures showed on the screen were angry or fearful. The subjects pressed the button with their dominant hand to respond during imaging. Two runs contain three face blocks and three shape blocks in each session. Six trials of the same task with a stimulus of 2000 ms and an inter-trial interval of 1000 ms were in each block. Including a 3000 ms task cue (“shape” or “face”), each block lasted 21 seconds.

2.3. MRI data acquisition, preprocessing, and statistical analysis

The MRI data were collected using a customized Siemens 3.0 T Connectome Skyra scanner with a standard 32-channel Siemens receive head coil at Washington University in St. Louis. The HCP data preprocessing methods are detailed elsewhere (Barch et al., 2013; Glasser et al., 2013). The parameters in MRI data acquisition and preprocessing steps shown in Supplementary materials.

A general linear model (GLM) was used to identify FER-related brain activation. Face versus shape contrast was used in the first-level analysis. Then, the 203 subjects were randomly divided into 102

subjects in one group and 101 subjects in another group. This step was repeated five times, and a total of ten groups were formed. A group-level activation map for each group was obtained using a voxel-wise one-sample *t*-test in Statistical Parametric Mapping 12 (SPM12; https://www.fil.ion.ucl.ac.uk/spm/). The familywise (FWE) rate method with $P < 0.05$ and the minimum cluster size of 100 voxels were used to conduct multiple comparison corrections.

We hypothesized that FER-related genes would be distinct from the genes correlated with other cognitive functions to some extent. Therefore, other cognitive tasks in the HCP dataset, including language, social, working memory, gambling, and relational tasks, were also analyzed using the same method as the emotion task to confirm this hypothesis. The statistical contrast used in other tasks: reward versus punish in the gambling task, story versus math in the language task, relational versus match in the relational task, social versus random in the social task, and two back versus 0 back in the working memory task.

2.4 Gene expression data processes

In this study, we leveraged gene expression data of six donated human postmortem brain tissues from the AHBA open-source dataset (http://human.brain-map.org) (M. J. Hawrylycz et al., 2012). According to a published pipeline, the gene expression data were processed (Arnatkeviciute, Fulcher, & Fornito, 2019). Detailed processing steps are shown in Supplementary materials. In this study, only 1782 samples in six left brain hemispheres were used because only two donors included samples of the right hemisphere. These processing procedures generated a 1782 samples × 10185 genes transcription matrix.

2.5. Identification of the FER-related genes

The FER-related brain activation of each sample was represented by the mean *t*-score extracted from the group-level emotion activation map with a 4-mm radius sphere centered at this sample's MNI coordinates. Spearman correlation analyses were performed between brain activations and the expression levels of each given gene across 1782 samples. Multiple comparisons (10185 genes) were corrected using the Bonferroni method with a threshold of $P < 0.05$. The same correlation analysis was conducted in all ten groups. To ensure the results' reliability, only genes that exhibited significant correlation in the same direction (i.e., positive or negative) in the ten groups were identified as final FER-related genes and used for further analyses. The same correlation analysis was conducted between the gene expression and the other cognitive task-related brain activations.

2.6. Gene Set Enrichment Analysis (GSEA) of the FER-related genes

Functional enrichment analysis of Gene Ontology (GO) was performed to analyze the FER-related genes' biological functions. The GO enrichment contains biological processes (BP), molecular function (MF), and cellular components (CC). The enrichment analysis was performed using an open online tool g: Profiler (Raudvere et al., 2019) (https://biit.cs.ut.ee/gprofiler) with a threshold of $P < 0.05$ (Bonferroni corrected).

2.7. Tissue-Specific Expression Analysis and Cell Type Enrichment Analysis

Tissue-specific expression analysis was performed using an online tool TSEA (http://genetics.wustl.edu/jdlab/tsea/), to detect in which type of tissue the FER-related genes were predominantly expressed. To characterize differential expressions of FER-related genes in major cell types, an online cell type-specific expression analysis (CSEA) tool (http://genetics.wustl.edu/jdlab/csea-tool-2/) (Dougherty, Schmidt, Nakajima, & Heintz, 2010; Xu, Wells, O'Brien, Nehorai, & Dougherty, 2014) was used to identify the cell types in which FER-related genes specially expressed. The multiple comparison corrections method is the Benjamini-Hochberg FDR method ($P < 0.05$). The smaller specificity index probability (pSI = 0.05, 0.01, 0.001, and 0.0001) represented a gene that was more likely expressed in a given tissue or cell type relative to other tissues or cell types.

2.8. Protein-Protein Interaction Network

We constructed the PPI network of the FER-related genes using the STRING (Szklarczyk et al., 2019) database version 11.0 (https://string-db.org/), with a medium confidence value of 0.4, and other parameters were set to default. Key nodes in the PPI network were explored by cytoHubba (Chin et al., 2014) in Cytoscape software (version 3.8.0) (Shannon et al., 2003). Among the different topological algorithms provided by CytoHubba, Maximal Clique Centrality (MCC) has been reported to be the best option (Chin et al., 2014). Therefore, the MCC method was used to identify the top five key genes in the PPI network, which were considered hub genes with important biological functions. Enrichment analysis of the PPI network was also conducted to understand the biological functions of FER-related genes using the STRING.

2.9. Enrichment analysis for psychiatric diseases

Enrichment of psychiatric diseases for FER-related genes was conducted to assess the association between the FER-related genes and the psychiatric conditions. Common genetic variants related to psychiatric diseases, including Alzheimer's disease (AD), attention-deficit disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder (BP), major depression disorder (MDD), and schizophrenia (SCZ), were obtained from the Psychiatric Genomics Consortium (Demontis et al., 2019; Grove et al., 2019; Jansen et al., 2019; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Stahl et al., 2019; Wray et al., 2018). MAGMA (de Leeuw, Mooij, Heskes, & Posthuma, 2015) was used to get gene-based *P*-values and *Z* scores. Fisher's exact test ($P < 0.05$, FDR corrected) was performed to carry out the enrichment analysis of each psychiatric disease for the FER-related genes.

3. Results

3.1. Group-level activations in emotion task and other cognitive tasks

FER-related brain activation patterns were similar across ten groups under the face versus shape contrast and were consistent with previous work in HCP (Barch et al., 2013). Positive activation areas mainly included the bilateral amygdala, middle occipital gyrus, middle temporal gyrus, superior frontal gyrus; negative activation was observed in the inferior parietal lobule, postcentral gyrus, and cingulate gyrus (FWE, P < 0.05) (Fig. 1). The ten group-level FER-related activation maps of emotion tasks are shown in Fig. S1. The activation maps of other cognitive tasks (language, social, working memory, gambling, and relational tasks) are shown in Fig. S2.

3.2. Genes associated with FER-related brain activations

With a transcription-neuroimaging association analysis, 301 genes in group one, 327 genes in group two, 384 genes in group three, 244 genes in group four, 316 genes in group five, 331 genes in group six, 456 genes in group seven, 232 genes in group eight, 307 genes in group nine, and 311 genes in group ten were found significantly related to FER-related brain activation ($P < 0.05$, Bonferroni corrected). Among these genes, 153 exhibited significant correlation in the same direction (positive,79 genes; negative, 74 genes) in all the ten groups. The detailed information of FER-related genes in the ten groups was listed in Table S1. The representative scatter plots of the three top genes with significant positive and three top genes with negative correlations in group one were shown in Fig. 2.

3.3. FER-related genes were partly distinct from genes associated with other cognitive tasks

Using the same transcription-neuroimaging association analysis with the emotion task, 205 gambling-related genes, 2037 language-related genes, 289 working memory-related genes, 392 social-related genes, and 35 relational-related genes were identified, respectively ($P < 0.05$, Bonferroni corrected). Among those genes, only three gambling-related genes, 69 language-related genes, 48 working memory-related genes, 40 social-related genes, and two relational-related genes overlapped with FER-related genes (Fig. 2). The detailed information of genes significantly related to other cognition-related brain activation was listed in Table S2. This analysis revealed that genes associated with FER were partly different from other cognitive functions.

3.4. Gene Set Enrichment Analysis (GSEA) of FER-related genes

A list of GO terms related to the FER-related genes were generated with a threshold of $P < 0.05$ (Bonferroni corrected), including biological processes: anterograde trans-synaptic signaling ($P = 1.81 \times 10^{-5}$), chemical synaptic transmission ($P = 1.81 \times 10^{-5}$), nervous system development ($P = 9.43 \times 10^{-4}$), neuron development ($P = 7.48 \times 10^{-3}$), and neuron projection development ($P = 9.69 \times 10^{-3}$); cellular component: cell junction ($P = 5.31 \times 10^{-6}$), synapse ($P = 1.67 \times 10^{-5}$), distal axon (3.85×10^{-4}), neuron projection ($P = 7.50 \times 10^{-3}$), and glutamatergic synapse ($P = 0.011$). The gene set enrichment analysis results were shown in Fig. 3 and Table S3.

3.5. FER-related genes are specifically expressed in neuron

By performing the cell type-specific expression analysis, FER-related genes were overexpressed in neurons, especially in layer 6 neurons ($P = 0.023$, BH-FDR corrected) and Cort+ neurons ($P = 0.004$, BH-FDR corrected) in cortex under a pSI threshold of 0.05 (Fig. 4).

3.6. FER-related genes are specifically expressed in brain tissue

Tissue-specific expression analysis was performed to further understand the tissue-specific expression of FER-related genes. Those genes were significantly enriched in brain tissue ($P = 8.27 \times 10^{-8}$, BH-FDR corrected), blood vessel tissue ($P = 1.65 \times 10^{-4}$, BH-FDR corrected), and overy tissue ($P = 4.67 \times 10^{-4}$, BH-FDR corrected) under a pSI threshold of 0.05 (Fig. 4). Brain tissue was the most significant, even under a more stringent pSI threshold of 0.001 ($P = 2.87 \times 10^{-4}$, BH-FDR corrected).

3.7. PPI Network associated with FER-related genes

Under the interaction confidence score at 0.4, a network containing 149 nodes and 86 edges was constructed which is significantly more than the 41 edges created by chance ($P = 4.82 \times 10^{-10}$) (Fig. 5). multiple comparison corrections Using the MCC method in the CytoHubba, the top five key genes in the PPI network were identified as hub genes, including neurexin 2 (*NRXN2*), cholinergic receptor nicotinic alpha 4 subunit (*CHRNA4*), neuroligin 1 (*NLGN1*), acetylcholinesterase (*ACHE*), and Src family tyrosine kinase (*FYN*). Enrichment analysis of the PPI network indicated that the genes were mainly enriched in the following biological process: positive regulation of synaptic transmission ($P = 1.3 \times 10^{-5}$, FDR-corrected), modulation of chemical synaptic transmission ($P = 1.3 \times 10^{-5}$, FDR-corrected), and nervous system development ($P = 2.3 \times 10^{-3}$, FDR-corrected); and in the following cellular components: synapse ($P = 5.21 \times 10^{-5}$, FDR-corrected), distal axon ($P = 4.6 \times 10^{-3}$, FDR-corrected), and cell junction ($P = 7.4 \times 10^{-3}$, FDR-corrected).

3.8. FER-related genes are related to psychiatric diseases

Based on GWASs of AD (Jansen et al., 2019), ADHD (Demontis et al., 2019), ASD) (Grove et al., 2019), SCZ (Schizophrenia Working Group of the Psychiatric Genomics, 2014), BP (Stahl et al., 2019), and MDD (Wray et al., 2018), with an uncorrected threshold of $P < 0.05$, 1,675 AD-related genes, 2,440 ADHD-related genes, 1,442 ASD-related genes, 2,021 MDD-related genes, 5,099 SCZ-related genes, and 3,098 BP-related genes were selected for conducting psychiatric diseases enrichment analysis. We found that those genes are significantly enriched for ADHD ($P = 0.02$, Bonferroni corrected), ASD ($P = 0.03$, Bonferroni corrected), SCZ ($P = 2.87 \times 10^{-5}$, Bonferroni corrected), BP ($P = 0.04$, Bonferroni corrected), and MDD ($P = 0.003$, Bonferroni corrected), but not significant for AD ($P = 0.2$, Bonferroni corrected) (Fig. 5).

4. Discussion

This study carried out an across-sample transcriptome-neuroimaging spatial association analysis between the FER-related brain activation and gene expressions in the human brain. A total of 153 genes were identified to associate with FER-related brain activation. Enrichment analyses showed that these FER-related genes are mainly overexpressed in the brain, especially in the neurons, and closely related to the cell junction, neuron development, and synaptic function. Diseases enrichment analyses confirmed that these genes were associated with psychiatric diseases with emotion impairments.

Consistent with previous works using the HCP dataset (Barch et al., 2013; Hariri, Tessitore, et al., 2002), we found that the FER task could robustly activate the emotion-related brain regions such as the amygdala in all ten groups. Moreover, the activation pattern was also consistent with many previous studies on the expression recognition tasks (Fusar-Poli et al., 2009; Phan et al., 2002; Vytal & Hamann, 2010). These results demonstrated that emotion task in the HCP could stimulate reliable FER-related brain activation.

Although candidate gene studies and GWAS revealed some genetic loci associated with emotion, the studies usually provide limited insight into the transcriptional mechanism of emotion. An alternate method is the across-sample transcriptome-neuroimaging spatial association analysis which was widely used to investigate transcriptional mechanisms of cognitive activities and psychiatric disorders (Forest et al., 2017; Ritchie et al., 2018; Xie et al., 2020). It has been demonstrated that this method could reliably link neuroimaging maps from living brains with gene expression from postmortem brains (Berto, Wang, Germi, Lega, & Konopka, 2018; Forest et al., 2017; M. Hawrylycz et al., 2015).

To increase the reliability of the results, we randomly divided the 203 subjects into two groups, and this step was repeated five times. Finally, 153 genes that exhibited association with FER-related brain activation in the same direction in all ten groups were defined as the FER-related genes. We further compared the FER-related genes with the other cognitive task-related genes to evaluate whether 153 genes were specific to the FER. Our results indicated that FER-related genes were partly different from the other cognitive task-related genes, and FER shared some genes with working memory (48 genes), language (69 genes), and social cognition (40 genes). These results suggested that FER might have some specific regulatory genes and might be also modulated by some genes related to other cognitive functions. This explanation was supported by the previous studies that showed emotion had shared some similar neuroanatomical and neurophysiological basis with language, social cognition, and working memory. For instance, a research demonstrated a strong positive correlation between emotional competence and language competence in children (Beck, Kumschick, Eid, & Klann-Delius, 2012). Emotion shared bilateral prefrontal function with working memory in an fMRI study (Mitchell, 2007). Robust correlations were found between social cognition skills and facial processing (Petroni et al., 2011). Enrichment analyses revealed that FER-related genes are mainly overexpressed in the brain, especially neurons. GO enrichment showed that FER-related genes were mainly associated with anterograde trans-synaptic signaling, cell junction organization, chemical synaptic transmission, and neurodevelopment

including neuron projection development, neuron development, and nervous system development. And a couple of cellular components including synapse, distal axon, and neuron projection showed significant association. Those findings highlighted the importance of the genes modulating the synaptic functions, neuronal structures, and development in FER processing. For example, *MET* in the term nervous system development, which encodes Met Receptor Tyrosine Kinase, was known to affect facial expression perception (Lin et al., 2012) and could increase the risk for ASD (Abrahams et al., 2013; Campbell et al., 2007; Campbell et al., 2006; Jackson et al., 2009). *CTNNB1* in the term neuron development, which encodes catenin beta 1, is associated with fear-memory consolidation, ASD, and anxiety-related behavior (Dong et al., 2016; Maguschak & Ressler, 2008; Wang et al., 2017). *SHANK2* (H3- and multiple ankyrin repeats protein 2), a gene involved in ASD (Bavamian et al., 2015), is related to cell junction organization and chemical synaptic transmission. A PPI network was constructed using 153 FER-related genes. The top five most connecting key genes were identified, including *NRXN2*, *CHRNA4*, *NLGN1*, *ACHE*, and *FYN*. Those genes may play an important role in emotion recognition. For instance, *CHRNA4*, which encodes cholinergic receptor nicotinic alpha 4 subunit, is associated with negative emotion (Markett, Montag, & Reuter, 2011), ADHD (Lasky-Su et al., 2008), and depression (Tsai et al., 2012). A previous GWAS study showed that rs1044396 polymorphism in *CHRNA4* is related to several conceptualizations of negative emotionality. *NRXN2* encoding neurexin 2, a kind of neuronal adhesion protein, is important in neurotransmitter secretion and synaptic cell adhesion (Missler et al.) and is associated with ASD and SCZ (Gauthier et al., 2011; Mohrmann, Gillessen-Kaesbach, Siebert, Caliebe, & Hellenbroich, 2011; Tromp, Mowry, & Giacomotto, 2021). Previous studies suggested that *NLGN1*, encoding neuroligin 1, was associated with many psychiatric disorders related to emotion such as PTSD, MDD, ASD, SCZ (Feng, Akladious, & Hu, 2016; Glessner et al., 2009; Kilaru et al., 2016; Lewis et al., 2010; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Sudhof, 2008; Yue et al., 2011). *FYN* is a member of the Src family of nonreceptor-type tyrosine kinase and is essential for fear memory and anxiety (Isosaka et al., 2008; Skelton et al., 2003). For example, fear memory was impaired in FYN-deficient mice (Isosaka et al., 2008). Previous work indicated that stress-induced alternative splicing of the *ACHE* gene was important for contextual fear and synaptic plasticity (Nijholt et al., 2004). Enrichment analysis of the PPI network indicated that the FER-related genes were mainly overexpressed in cell junction, nervous system development, and synapse, consistent with the GO enrichment results.

FER deficits have been observed in individuals with ASD (Harms et al., 2010), SCZ (Kohler, Walker, Martin, Healey, & Moberg, 2010; Kring & Elis, 2013), BP (Kohler et al., 2011), and MDD (Bourke et al., 2010; Demenescu, Kortekaas, den Boer, & Aleman, 2010). In this study, the FER-related genes showed significant enrichment for the psychiatric conditions with heavy emotion impairments such as ADHD, ASD, SCZ, BP, and MDD. However, AD showed no significance. These results suggested that FER-related genes were associated with psychiatric diseases, which might help understand the mechanism of the FER impairments in these psychiatric disorders.

Several limitations should be mentioned in this study. First, transcriptome data was extracted from the left cerebral hemispheres of six postmortem adult brains in AHBA. The small sample size might bias our findings. Second, gene expression data and FER-related brain activation data were derived from the

different subjects. Although gene expression patterns were confirmed to be conserved across individuals (M. Hawrylycz et al., 2015; Zeng et al., 2012), this influence could not be completely ruled out. To reduce this impact, we randomly divided neuroimaging data into two groups and repeated it five times. Only genes that exhibited consistently significant associations in the same direction in ten groups were defined as FER-related genes. Finally, causal effects between gene expression and FER-related brain activation could not be clarified by this transcription-neuroimaging association analysis.

5. Conclusion

This study identified 153 significant FER-related genes using the transcriptome-neuroimaging spatial association analysis. Enrichment analyses revealed that FER-related genes are mainly enriched in the brain, especially neurons, and might be associated with cell junction organization, synaptic functions, and nervous system development regulation, indicating that FER was a complex polygenetic biological process involving multiple pathways. Moreover, these genes exhibited higher enrichment for psychiatric diseases with heavy emotion impairments. This study provided new insight into understanding the FER-related biological mechanisms and might be helpful to explore treatment methods for emotion-related psychiatric disorders.

Declarations

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Conflicts of interest: All authors claim that there are no conflicts of interest.

Ethics approval: The HCP study was ethically approved by the Washington University Institutional Review Board (IRB).

Consent to participate: Written informed consents were provided by all subjects.

Consent for publication: Not applicable.

Availability of data and material: The participants of facial expression recognition were from the Human Connectome Project (https://www.humanconnectome.org/). Group-level activations were calculated using the SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). The gene expression data were available in the 2010 Allen Institute for Brain Science (http://human.brain-map.org).

Code availability: The online tool g: Profiler (https://biit.cs.ut.ee/gprofiler) was used to perform enrichment analysis for FER-related genes. Tissue-specific expression analysis and cell type-specific

expression analysis were carried out using the online tool Tissue-specific expression analysis (TSEA) (http://genetics.wustl.edu/jdlab/tsea/) and cell type-specific expression analysis (CSEA) tool (http://genetics.wustl.edu/jdlab/csea-tool-2/). The protein-protein interaction network was constructed using the STRING database version 11.0 (https://string-db.org/).

Authors' contributions: Z.W., F.L., W.Q., and Q.Z. designed research; Z.W., Y.J., and Y.F. performed research; W.Q., H.L., W.Z., K.X., F.L., and Q.Z. provided guidance and advice; Z.W., X.D., and Y.J. analyzed data; and Z.W., W.Q., and Q.Z. wrote the paper.

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Figures

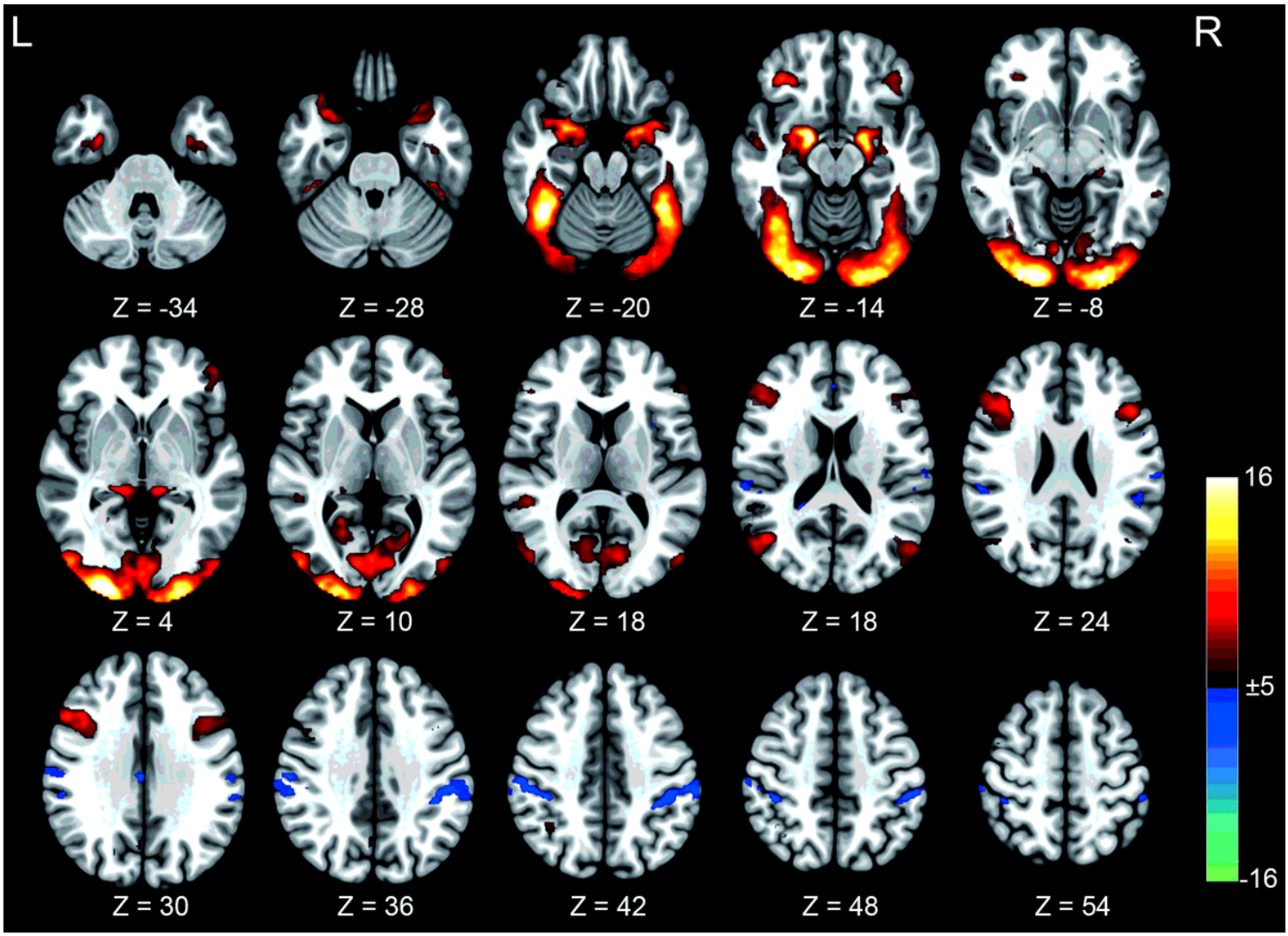

Figure 1

The group-level activation maps of group one in the facial expression recognition task. The color bar represents t-values of brain activation.

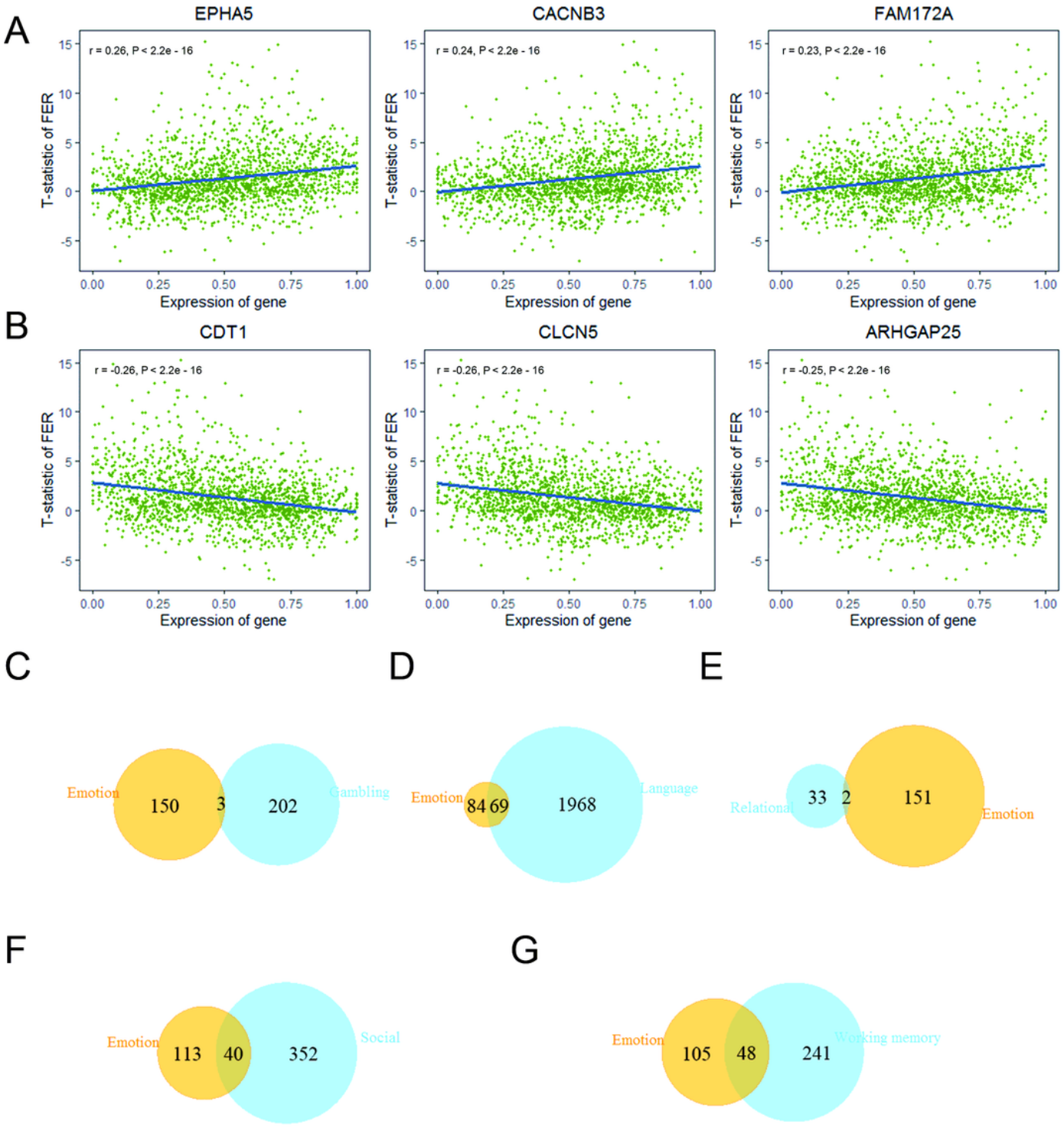

Figure 2

Representative correlation maps between emotion-activation and gene expression and the numbers of FER-related genes overlapped with other cognitive task-related genes. (A-B) Representative correlation maps between emotion-activation and gene expression across 3702 samples. (A) Three representative genes with positive correlation. (B) Three representative genes with negative correlation. The x-axis is the gene expression value. The y-axis is the t-value of group-level brain activations. The name of each gene is

shown on the top of each scatter plot. (C-G) The numbers of FER-related genes overlapped with other cognitive task-related genes (P < 0.05, Bonferroni corrected). (C) Gambling task, (D) Language task, (E) Relational task, (F) Social task, (G) Working memory task.

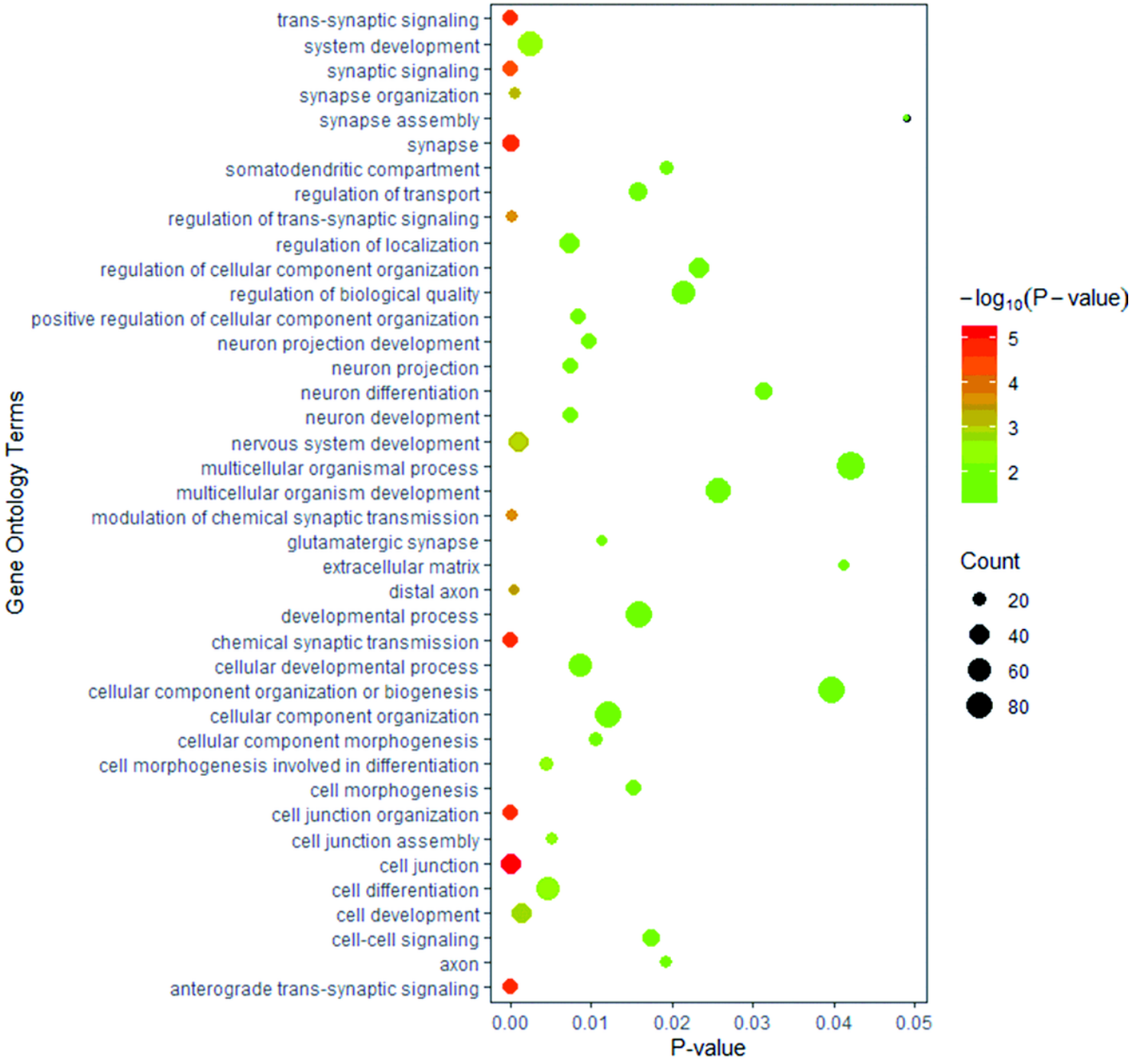

Figure 3

GO enrichment for the 153 FER-related genes (P < 0.05, Bonferroni corrected). The size of each bubble represents the number of FER-related genes enriched in the GO terms. The x-axis represents -log10 P (Bonferroni corrected). The y-axis represents gene ontology terms. GO, gene ontology.

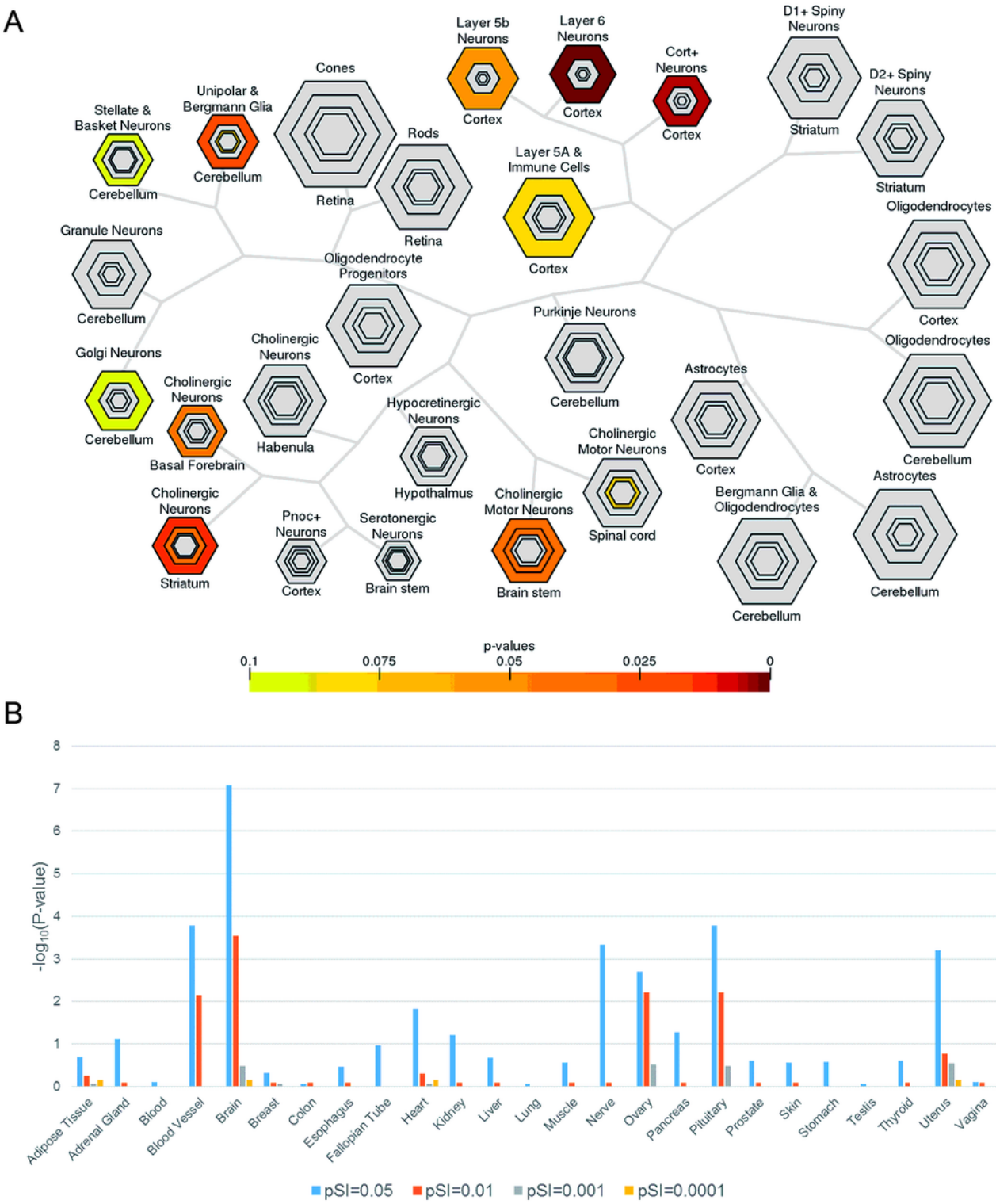

Figure 4

Cell type-specific expression analysis and tissue-specific expression analysis of FER-related genes. (A) Cell type-specific expression analysis. The size of the bullseyes represented pSI values (i.e., pSI = 0.05, 0.01, 0.001, and 0.0001). The color represented the P values (BH-FDR correction). (B) Tissue-specific expression analysis of FER-related genes. The colors represent the pSI = 0.05, 0.01, 0.001, and 0.0001. The y-axis represents -log10 P (BH-FDR corrected).

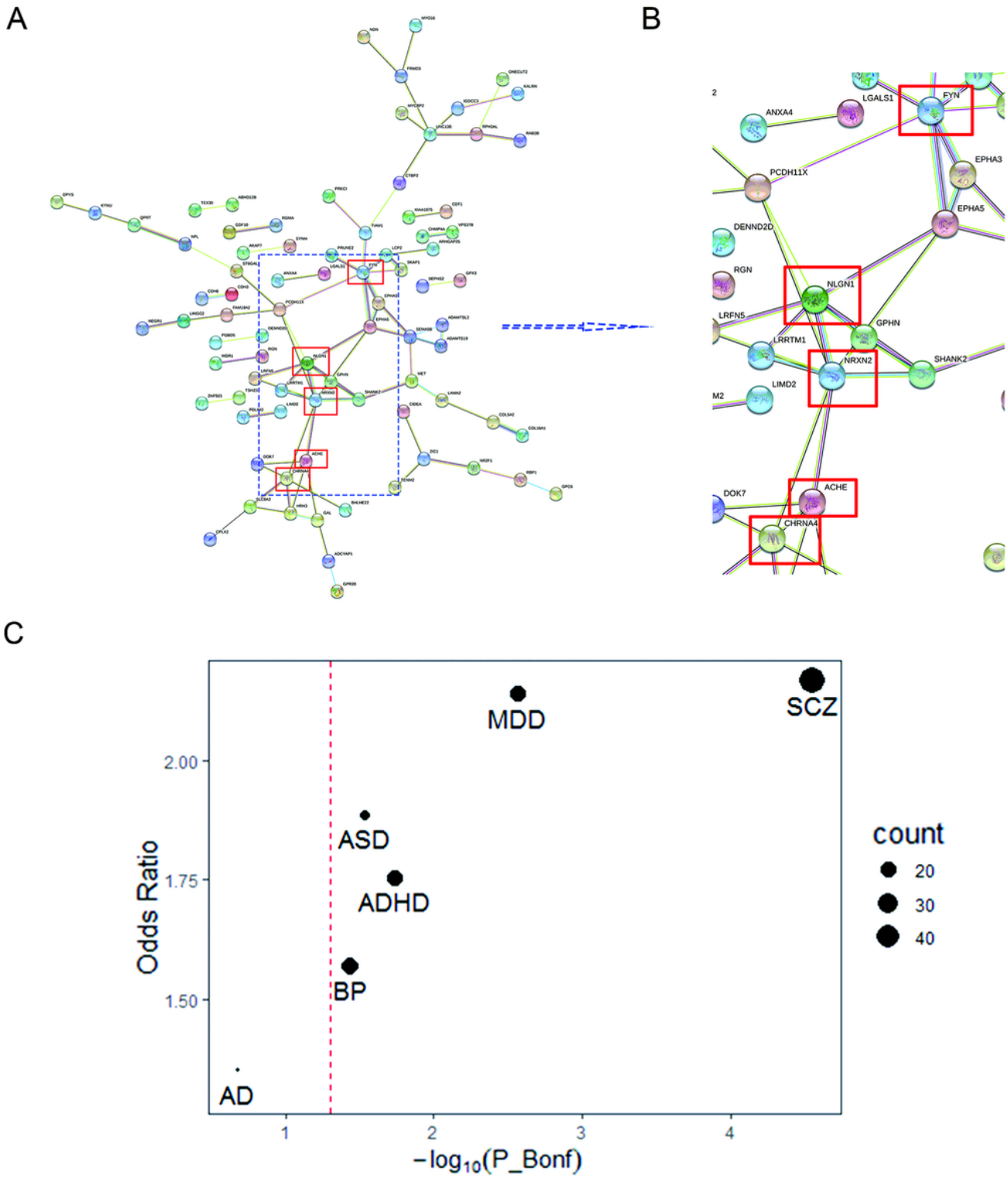

Figure 5

Protein-protein networks and enrichment of FER-related genes for common psychiatric disorders. (A-B) Protein-protein networks constructed using the 153 FER-related genes. Each node represents a protein, and an edge represents an interaction between two proteins. (A) The whole PPI network constructed using 149 FER-related genes. (B) The representative hub genes: NRXN2, CHRNA4, NLGN1, ACHE, and FYN. (C) Enrichment of FER-related genes for common psychiatric disorders. The size of each bubble

represents the number of FER-related genes overlapped with genes associated with common psychiatric disorders. The x-axis represents -log10 (P, Bonferroni corrected). The y-axis represents odds ratio values. The red line represents P = 0.05.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS1.tif
- FigureS2.tif
- SupplementaryTable1.xlsx
- SupplementaryTable2.xlsx
- SupplementaryTable3.xlsx
- Supplementarymaterials.docx