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Transcriptional patterns of amygdala functional connectivity in first-episode, drug-naïve major depressive disorder

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Previous research has established associations between amygdala functional connectivity abnormalities and major depressive disorder (MDD). However, inconsistencies persist due to limited sample sizes and poorly elucidated transcriptional patterns. In this study, we aimed to address these gaps by analyzing a multicenter magnetic resonance imaging (MRI) dataset consisting of 210 first-episode, drug-naïve MDD patients and 363 age- and sex-matched healthy controls (HC). Using Pearson correlation analysis, we established individualized amygdala functional connectivity patterns based on the Automated Anatomical Labeling (AAL) atlas. Subsequently, machine learning techniques were employed to evaluate the diagnostic utility of amygdala functional connectivity for identifying MDD at the individual level. Additionally, we investigated the spatial correlation between MDD-related amygdala functional connectivity alterations and gene expression through Pearson correlation analysis. Our findings revealed reduced functional connectivity between the amygdala and specific brain regions, such as frontal, orbital, and temporal regions, in MDD patients compared to HC. Importantly, amygdala functional connectivity exhibited robust discriminatory capability for characterizing MDD at the individual level. Furthermore, we observed spatial correlations between MDD-related amygdala functional connectivity alterations and genes enriched for metal ion transport and modulation of chemical synaptic transmission. These results underscore the significance of amygdala functional connectivity alterations in MDD and suggest potential neurobiological mechanisms and markers for these alterations.

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INTRODUCTION

Major depressive disorder (MDD) is a prevalent psychiatric illness on a global scale, marked by symptoms such as depressed mood, anhedonia, and decreased energy, which may culminate in suicidal behavior [1]. This condition not only significantly impacts the general well-being of individuals, but also has substantial repercussions on global human rights and economic conditions, leading to considerable burdens worldwide [2]. Despite extensive research, the underlying pathophysiological mechanisms of MDD remain elusive, largely due to variability in brain structure and function abnormalities, as well as diverse treatment responses [3, 4].

Understanding brain dysfunction in MDD is crucial for elucidating the disorder's pathophysiological mechanisms and developing more effective treatments [5, 6]. The emergence of resting-state functional magnetic resonance imaging (rs-fMRI) has greatly expanded our insight into the functional organization of the brain in both healthy individuals and clinical populations [7, 8]. Insights emerging from mapping intrinsic brain connectivity networks provide a potentially mechanistic framework for understanding aspects of human behavior [9, 10]. A multitude of functional brain imaging studies focusing on depressive patients have consistently revealed significant alterations within the limbic regions, notably the amygdala, throughout the various stages of depression including onset, progression, remission, and recurrence [11, 12].

The amygdala is a pivotal brain region responsible for the processing and regulation of emotions [13]. Recent research indicates a correlation between the severity of depression and abnormalities in amygdala structure and function [14, 15]. Notably, hyperactivity of the amygdala following negative emotional processing is a prominent characteristic of depressive disorders, suggesting heightened bottom-up processing in affected individuals [16]. Moreover, the amygdala establishes reciprocal connections with various cortical areas implicated in social, cognitive, and affective processing [17–19]. Specifically, bidirectional connections have been observed between the amygdala and different regions within the prefrontal cortex, such as the dorsolateral and dorsomedial areas, which play roles in cognitive and threat regulation, respectively [20–22]. Recent clinical studies have provided some evidence of reduced connectivity between the basolateral amygdala and prefrontal cortex in individuals diagnosed with MDD [23]. While previous studies have highlighted abnormalities in amygdala functional connectivity in MDD patients [23, 24], these conclusions rely on limited data and may be influenced by medication, leading to inconsistent and contested findings. Thus, it is important to validate amygdala functional connectivity alterations among first-episode, drug-naïve MDD patients in a multicenter dataset.

Recent studies have highlighted the substantial influence of genetic factors on the development of human brain networks

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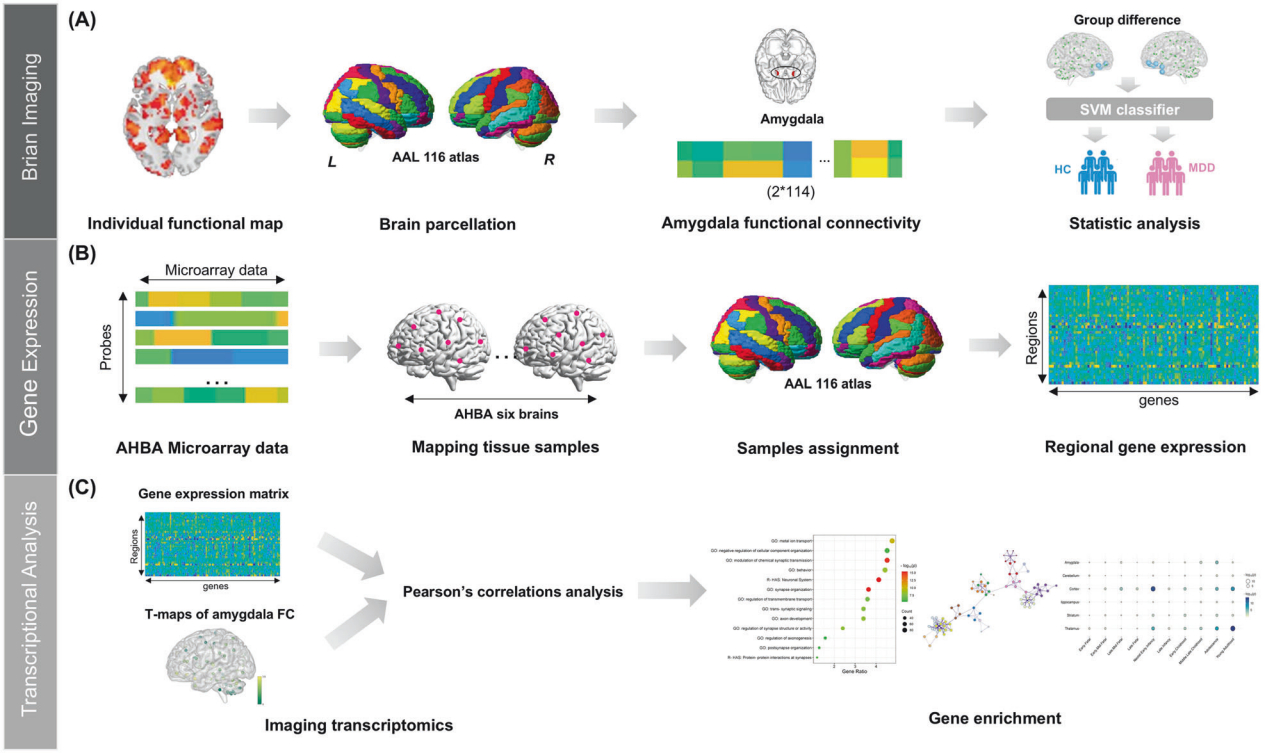

Fig. 1 Overview of the study design. A Brain imaging analysis. Amygdala functional connectivity was determined by extracting mean BOLD signals utilizing the AAL atlas and computing Pearson correlation coefficients between the bilateral amygdala and other brain regions. Amygdala functional connectivity was used for group-level comparison and individual-level classification. **B** Gene expression. The gene expression data was obtained from the AHBA and underwent comprehensive preprocessing for analysis across the entire brain using the AAL atlas, resulting in a regional gene expression matrix. **C** Transcriptional analysis. Pearson's correlation analysis was conducted to establish connections between MDD-related abnormalities in amygdala functional connectivity and gene expression data. Subsequently, enrichment analyses were performed on significant gene lists to reveal relevant biological pathways, cell types, and developmental genes. AAL Automated Anatomical Labeling, AHBA Allen Human Brain Atlas, BOLD blood oxygen level dependent, MDD major depressive disorders, HC healthy controls.

[25, 26]. Multiple lines of evidence indicate that the onset of MDD is intricately linked to a complex interplay of genetic and epigenetic elements [27, 28]. Genome-wide association studies (GWAS) have also identified numerous genetic loci that are correlated with MDD [29]. Nevertheless, the precise mechanisms through which genetic factors modulate brain activity in MDD remain elusive. The advent of a comprehensive whole-brain atlas of gene expression, derived from the Allen Human Brain Atlas (AHBA) database, has opened new avenues for probing the intricate relationship between disease-related gene expression at the micro-level and broader brain alterations observed across diverse psychiatric conditions [30–32]. Furthermore, neuroimaging traits, serving as intermediate phenotypes, are believed to be closer to the genetic underpinnings of MDD [33]. Consequently, there has been a growing body of imaging transcriptomics research aiming to elucidate the complex mechanisms contributing to MDD by linking brain structural and functional changes to gene expression data [31, 34, 35]. Numerous studies have pinpointed genes linked to anomalies in resting-state brain function, shifts in cerebral blood flow, and modifications in structural brain networks in individuals with MDD [31, 35–37]. Nevertheless, there are currently no relevant studies to establish the association between gene expression and amygdala functional connectivity alterations in MDD.

In this study, we aimed to identify amygdala functional connectivity patterns linked with MDD and explore associated transcriptional profiles (Fig. 1). Using a multicenter neuroimaging dataset of 573 individuals, we first compared amygdala functional connectivity between first-episode, drug-naïve MDD patients and healthy controls (HC). Next, we developed individual-level machine learning models utilizing amygdala functional connectivity to diagnose MDD. Lastly, we investigated connectome-transcriptome associations using AHBA. Our hypotheses were: (1) amygdala functional connectivity abnormalities would be evident in MDD patients; (2) amygdala functional connectivity could effectively diagnose MDD at the individual level; (3) MDD-related amygdala connectivity alterations would correlate with gene expression profiles in relevant biological pathways, cell types, and developmental genes.

MATERIALS AND METHODS

Phenotypic and imaging dataset

The study comprised 210 drug-naïve first-episode MDD patients and 363 age- and sex-matched HC who were part of the DIRECT Consortium [38, 39] (Supplementary Table 1; Supplementary Fig. 1), utilizing publicly available brain imaging data of depression (http://rfmri.org/REST-meta-MDD). Patients met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or International Classification of Diseases 10 (ICD-10) criteria for MDD, with a Hamilton Rating Scale for Depression (HAMD) score ≥14 points and ages between 18 and 65 years. Exclusion criteria included missing demographic information, poor image quality, and excessive head motion. Detailed criteria were provided in the Supplementary Materials. Ethics approval was obtained from respective site committees, and written consent was obtained from all participants before testing. Brain image preprocessing followed a standardized protocol using DPARSF software (http://www.rfmri.org/), involving removal of the first 10 volumes, slice timing correction, head motion realignment, covariate regression, normalization to the Montreal Neurological Institute (MNI) template, and

application of a bandpass filter (0.01–0.1 Hz), as outlined in the Supplementary Materials (Supplementary Table 2).

Brain imaging analysis

Region of interest (ROI) based amygdala functional connectivity construction. In this study, the whole brain was parcellated into 116 regions using the Automated Anatomical Labeling (AAL) atlas [40]. Based on prior literature highlighting the amygdala's significance in MDD [41], it was selected as a key region for connectivity analysis. To establish ROI based amygdala functional connectivity, mean blood oxygen level dependent (BOLD) signals were extracted from preprocessed fMRI data for each of the 116 ROIs. Pearson correlation coefficients were then, respectively computed between the mean time series of the bilateral amygdala and other whole-brain ROIs. Subsequently, Fisher r-to-z transformation was applied to identify functional connections between the bilateral amygdala and other whole-brain ROIs. Finally, we could obtain the functional connectivity map (2×114) in the left and right amygdala.

Group differences in amygdala functional connectivity. We utilized the GRETNA toolbox to assess group differences in amygdala functional connectivity [42]. Specifically, we separately compared the functional connectivity of the left and right amygdala between HC and MDD, while controlling for sex, age, and education level. Benjamini–Hochberg False Discovery Rate (BH-FDR) was applied to adjust the P-values, with significance set at $P_{\text{BH-FDR}} < 0.05$.

Classification performance based on amygdala functional connectivity. The classification task aimed to distinguish between MDD patients and HC using a Gaussian support vector machine (SVM) model trained on significantly different amygdala functional connectivity between the two groups. Initially, the datasets were divided into training and test sets (7:3 ratio). Subsequently, within the training set, a 10-fold cross-validation method was employed to split the data into internal training and validation sets (9:1 ratio) to optimize the training model. Finally, the model's performance was evaluated using the test set, with the final area under the receiver operating characteristic curve (AUC) and accuracy serving as metrics to assess classification performance. The detailed steps are described in the Supplementary Materials.

Gene expression dataset and preprocessing

The gene expression data utilized in this study was sourced from six neurotypical adult donors in AHBA (http://human.brain-map.org) (Supplementary Table 3) [43]. The gene microarray data from brain tissue samples underwent preprocessing using the abagen (https://www.github.com/netneurolab/abagen) toolbox following a recommended pipeline [44, 45]. Specifically, reannotation of genetic probes was conducted based on established guidelines, and intensity-based filtering was applied to exclude probes with values below the background noise threshold, set at 50%. For genes indexed by multiple probes, we selected the probe that demonstrated the most consistent regional variation across donors, ensuring differential stability. Each tissue sample was spatially registered to MNI (https://github.com/chrisfilo/alleninf) coordinate space based on the T1-weighted images of individual donors, and subsequently assigned to specific brain regions according to their MNI coordinates. The microarray data was then integrated with the parcellation consisting of 116 brain regions defined by the AAL atlas, allowing for gene expression analysis to be conducted across the entire brain. Gene expression values were normalized for each donor using the scaled robust sigmoid (SRS) method and then averaged across brain regions. Finally, a gene expression map (112 regions × 15,633 genes) was obtained for further transcription-neuroimaging association analysis. Of note, four regions were discarded because no tissue samples were assigned to these regions.

Transcription-neuroimaging association analysis

To ascertain variations in amygdala functional connectivity among distinct groups within a specified brain tissue sample, we analyzed the discrepancies in amygdala functional connectivity between cases and controls, utilizing T-values derived from 114 regions. It is important to note that self-connections of the amygdala were not included in the analysis. Pearson's correlations were utilized to assess the relationship between the gene expression matrix and the amygdala functional connectivity case-control T-vector. Correction for multiple comparisons was conducted using BH-FDR method. To further test whether the number of the identified genes was significantly greater than the random level, a spatially-constrained permutation test (i.e., spin test, $n = 1000$) was conducted to establish the significance of our results. The detailed steps are described in the Supplementary Materials.

Enrichment analysis was performed to uncover the biological pathways linked to MDD. The Gene Ontology (GO), Reactome, and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases integrated into Metascape were utilized to examine significant gene sets (https://metascape.org/gp/index.html#/main/step1) [46]. Additionally, CSEA tool was employed to investigate the expression profiles of identified genes in different cell types, brain regions, and developmental stages, with the objective of identifying specific patterns of overexpression in MDD (http://doughertytools.wustl.edu/CSEAtool.html) [47]. All enrichment analyses were adjusted for the false discovery rate using $P_{\text{BH-FDR}} < 0.05$ to ensure statistical rigor.

Validation analyses

We implemented a leave-one-site-out cross-validation approach to assess the potential impact of specific sites on our findings. This involved systematically excluding one dataset at a time and utilizing the remaining three datasets as a subset for statistical analysis. In each subset, we performed T-tests across 114 regions to generate T-value maps, assessing whole-brain case-control differences. Pearson correlation was used to examine the spatial congruence of regional differences between each subset and the full dataset.

RESULTS

Brain imaging analysis

Group differences in amygdala functional connectivity. Compared to HC, individuals with MDD demonstrated reduced FC between the right amygdala and various brain regions, including the left orbital parts of the middle frontal gyrus (MFG), left orbital parts of the superior frontal gyrus (SFG), bilateral orbital parts of the inferior frontal gyrus (IFG), right medial SFG, right medial orbital parts of the SFG, bilateral gyrus rectus, and left temporal pole (comprising the superior temporal gyrus and middle temporal gyrus) ($P_{\text{BH-FDR}} < 0.05$) (Fig. 2A). Only reduced FC between the left amygdala and left temporal pole (i.e., superior temporal gyrus) was observed in MDD compared to HC ($P_{\text{BH-FDR}} < 0.05$) (Fig. 2B).

Classification performance based on amygdala functional connectivity. The classification performance of the model, utilizing amygdala functional connectivity to distinguish MDD patients from HC, was evaluated using a 10-fold cross-validation method. The classifier achieved an accuracy of 72% (Fig. 3A) and exhibited an AUC of 0.74 (Fig. 3B). The 10-fold cross-validation method was employed to ensure the robustness of the classifier by reducing overfitting and providing a reliable estimate of the model's performance, enhancing the generalizability and stability of the classification results.

Imaging transcriptomics analysis

Transcriptional profiles related to altered amygdala functional connectivity in MDD. Gene-wise cross-region spatial correlation analyses were performed between gene expression data and amygdala functional connectivity difference maps for both the right and left amygdala. Using a significance threshold of $P_{\text{BH-FDR}} < 0.05$, a total of 3624 genes were found to be associated with case-control amygdala functional connectivity alterations in the right amygdala, while 2419 genes were associated with alterations in the left amygdala. Of these, 2059 genes showed consistent spatial correlations with amygdala functional connectivity alterations in both the right and left amygdala. The reliability of this association was confirmed through spatially-constrained permutation tests.

Enrichment analyses. Enrichment analyses using GO biological process, Reactome, and KEGG were performed to elucidate the

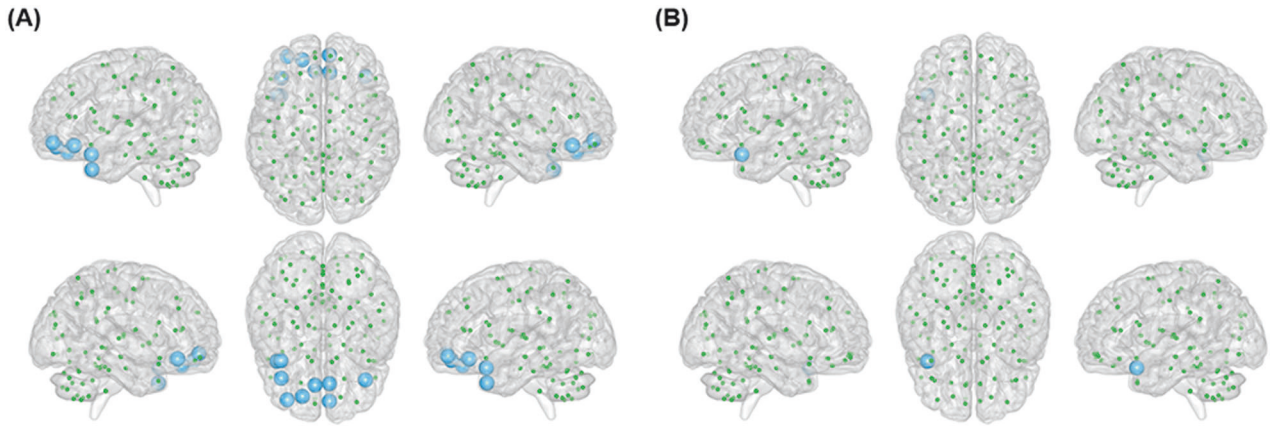

Fig. 2 Differences in amygdala functional connectivity between MDD and HC. A Brain regions showing significant differences in left amygdala-based functional connectivity between MDD and HC. **B** Brain regions showing significant differences in right amygdala-based functional connectivity between MDD and HC. Non-significant regions are depicted in green. Blue spheres represent significant decreases (MDD < HC), while red spheres represent significant increases (MDD > HC). MDD major depressive disorders, HC healthy controls.

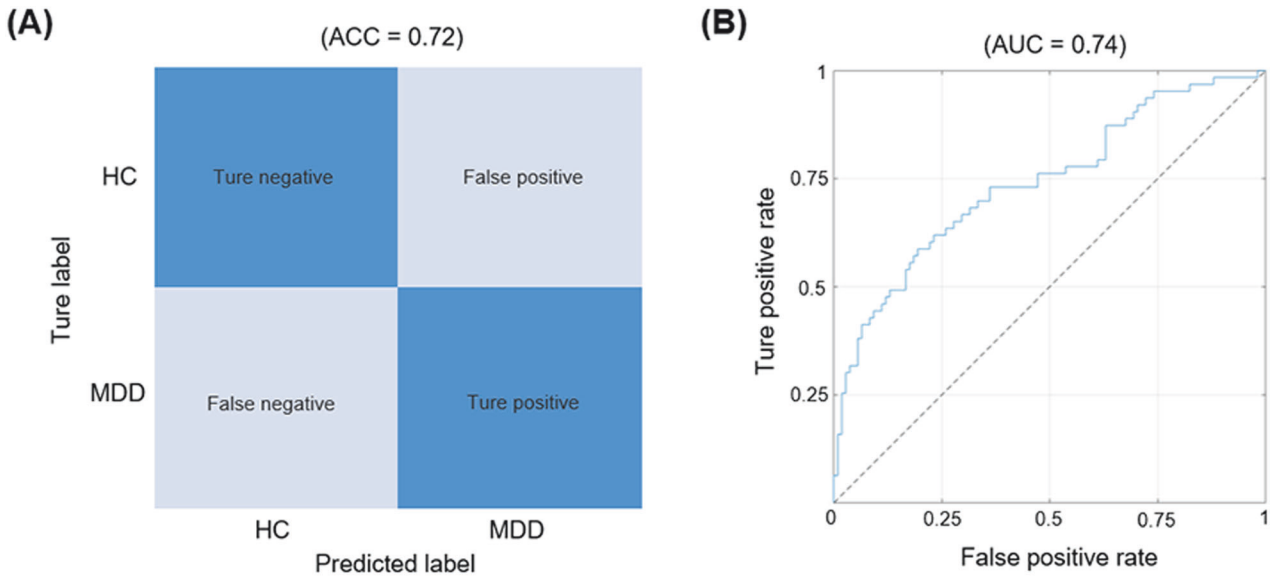

Fig. 3 Classification performance for MDD identification. A The confusion matrices for the classifier. **B** The receiver operating characteristic curve for the classifier. ACC accuracy, AUC area under the receiver operating characteristic curve, MDD major depressive disorder, HC healthy controls.

biological functions of genes reliably linked to alterations in amygdala functional connectivity in MDD. Following the removal of discrete clusters, these genes exhibited significant enrichment in various biological processes ($P_{\text{BH-FDR}} < 0.05$). The most prominent processes were related to metal ion transport and modulation of chemical synaptic transmission, both of which had the highest gene counts and significance (Fig. 4A, B).

CSEA indicated that the 2059 identified genes showed significant enrichment in Glt25d2 neurons ($P = 1.17 \times 10^{-4}$) and Ntsr+ neurons ($P = 1.47 \times 10^{-4}$) within the cortex (Fig. 4C). Subsequently, we explored whether these genes displayed enrichment in specific human brain regions or developmental stages. Analysis of developmental gene expression revealed that these genes were expressed in the brain starting from early/mid fetal development, encompassing various brain regions such as the cortex and subcortex (including the thalamus, striatum, and amygdala) (Fig. 4D). Notably, their expression was particularly pronounced during neonatal and early infancy, adolescence, and young adulthood stages.

Validation analysis

Overall, the patterns of amygdala functional connectivity differences remained similar even after removing any one of the four datasets (Supplementary Fig. 2). Specifically, both the right and left amygdala functional connectivity T-maps from the validation analysis showed significant correlations with the corresponding T-value maps from the main analysis (all $P < 0.001$).

DISCUSSION

Utilizing a multicenter MRI dataset, this study represents the first to unveil the transcriptional pattern of amygdala functional connectivity disruption in first-episode, drug-naïve major depressive disorder. Consistently with our hypothesis, significant amygdala functional connectivity abnormalities were observed in MDD patients compared to HC. Notably, at the individual level, features of amygdala functional connectivity demonstrated considerable efficacy in distinguishing between MDD patients and HC. Moreover, by investigating the relationship between amygdala functional connectivity abnormalities and brain gene

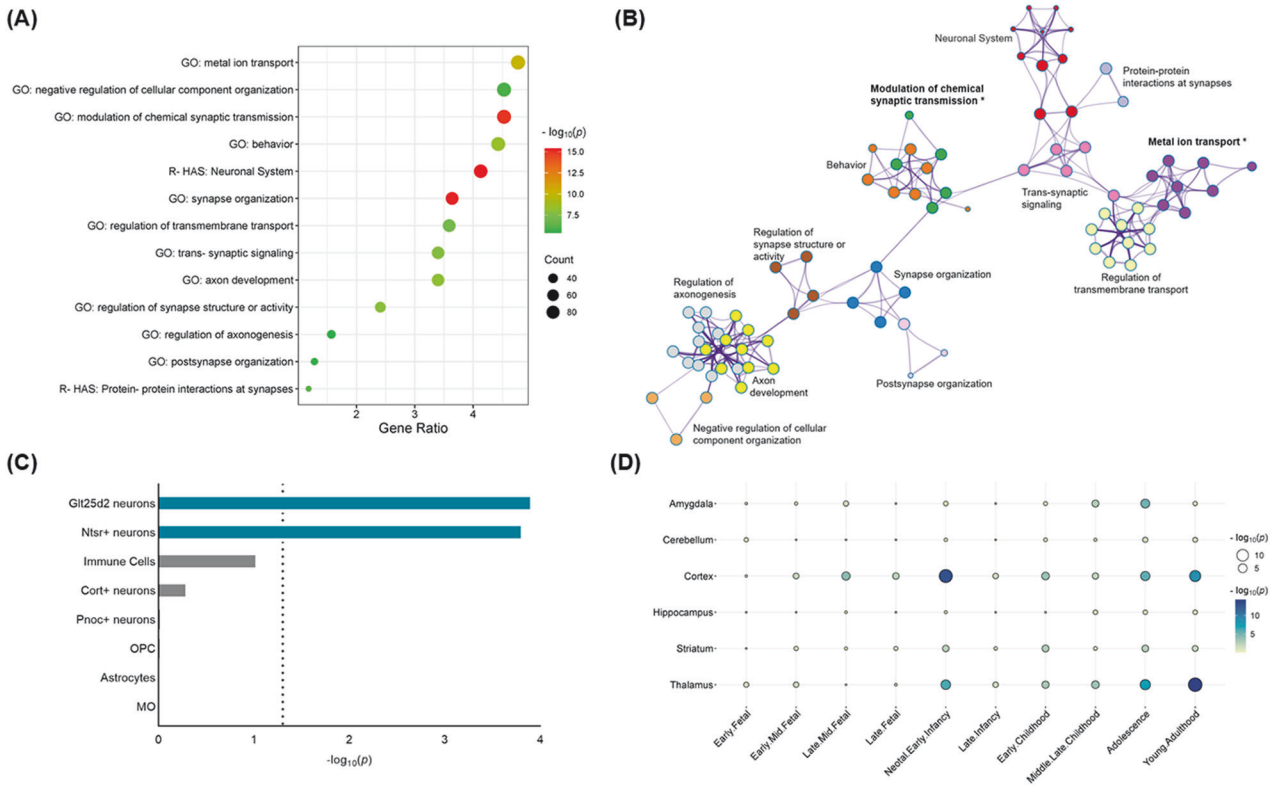

Fig. 4 Transcriptional patterns associated with MDD-related amygdala functional connectivity alterations. A Enrichment for the significant genes. Bubble size represents the number of overlapping genes with each annotation (GO term, Reactome gene set, or KEGG pathway), while color indicates significance level (BH-FDR corrected). **B** Enrichment network shows intra-cluster and inter-cluster similarities of enriched annotations. Each term is represented by a node, with size indicating the number of input genes and color representing cluster identity. The most prominent processes—related to metal ion transport and modulation of chemical synaptic transmission—are highlighted in bold and marked with an asterisk (*), as they had the highest gene counts and significance. **C** CSEA of the significant genes list (BH-FDR corrected). **D** Developmental gene expression enrichment analysis of the significant genes list. Bubble size and color both represent significance level (BH-FDR corrected). GO gene ontology, R-HAS Reactome-Homo sapiens, KEGG Kyoto Encyclopedia of Genes and Genomes, CSEA cell-type single-cell expression analysis, BH-FDR Benjamini–Hochberg false discovery rate, MO myelinating oligodendrocyte, OPC oligodendrocyte progenitor cells.

expression patterns, we discovered that amygdala functional connectivity abnormalities associated with MDD were linked to biologically relevant pathways. These prominent pathways were related to metal ion transport and modulation of chemical synaptic transmission. Furthermore, we observed preferential expression of these genes in distinct cell types and brain regions. These findings underscore the robustness of amygdala functional connectivity signatures in individuals with MDD, establishing a crucial link between neuroimaging and transcriptome data. This integration offers novel insights into the neurobiological mechanisms underlying MDD.

Regional abnormalities in amygdala functional connectivity were identified in the orbitofrontal cortex (OFC) (including left orbital parts of MFG, left orbital parts of SFG, bilateral orbital parts of IFG, and right medial orbital parts of the SFG), medial prefrontal cortex (PFC) (i.e., right medial SFG), bilateral gyrus rectus, and left temporal pole. Functional connectivity of the amygdala with these regions have been widely reported in MDD [23, 48–50]. OFC and medial PFC, pivotal regions within the PFC, played crucial roles in the onset and progression of depression [51]. They were involved in various functions including reward processing, attention, perception, emotional processing, and executive function. Numerous preclinical and clinical studies have indicated that the consistently impairments in PFC was one of the most important characteristic in MDD [51]. Compared to healthy children, children with a higher risk of MDD, as well as those currently diagnosed with MDD, exhibited reduced functional connectivity between the right dorsolateral prefrontal cortex and the amygdala [52]. This observed alteration in connectivity corresponds to a pathway previously associated with the regulation of emotional responses in adult MDD [53]. Furthermore, there is evidence suggesting that the temporal pole and gyrus rectus are implicated in various high-level cognitive processes, including language and semantic processing, socio-emotional processing, autobiographical memory, facial recognition, and analysis and recognition of complex objects [54–56]. Our previous study results indicated that these cognitive functions were somewhat compromised in MDD [57]. Therefore, we speculate that the disrupted functional connectivity between the amygdala and the temporal pole and gyrus rectus may heighten susceptibility to depressive symptoms, potentially by affecting cognitive processes. Crucially, these aberrant amygdala functional connectivity patterns hold potential for effectively identifying individuals with MDD at the individual level. This further emphasizes the diagnostic value of these specific amygdala functional connectivity patterns for MDD identification.

In transcription-neuroimaging association analysis, we identified alterations in amygdala functional connectivity associated with changes in gene expression enriched in metal ion transport and modulation of chemical synaptic transmission. Metal ion transport is crucial for regulating cell metabolism and influencing disease progression. [58]. Specifically, mitochondrial metal ion channels and transporters could serve as potential therapeutic targets for MDD and metabolic diseases [58, 59]. Dysregulation of metal ion

homeostasis can impact neurotransmitter systems and synaptic plasticity, contributing to the cognitive and emotional symptoms of MDD [60–63]. Synaptic transmission, essential for synaptic plasticity, is also implicated in the neurobiology of depression [64, 65] Disruptions in synaptic transmission, critical for neuronal communication and plasticity, likely contribute to the observed neural connectivity changes in MDD [65]. This supports the effectiveness of synaptic modulators in antidepressant treatments, as many antidepressants function by modulating serotonergic neurotransmission at the synaptic level [66]. Our findings suggest that targeting both metal ion transport channels and synaptic transmission mechanisms could be promising therapeutic strategies for MDD. Further investigation into drugs that modulate these pathways may lead to the development of novel, more effective treatments.

Utilizing single-cell expression data, our investigation revealed that genes consistently associated with amygdala functional connectivity alterations in MDD exhibited significant expression in Glt25d2 neurons and Ntsr+ neurons. This specific neuronal expression pattern aligns with previous research underscoring the significant role of neurons in mediating the genetic influence on functional connectivity [67–69]. Evidence suggests that Glt25d2 and Ntsr+ neurons are constituents of the pyramidal neuron population [70, 71], and their neuropathological abnormalities are intricately linked to the pathophysiology of MDD [72]. Moreover, developmental enrichment analyses revealed that these genes were expressed not only in the cortex but also in several subcortical regions in MDD. The enriched time window for the expression of these genes spanned a broad range of developmental stages, from early/mid fetal development to young adulthood. This suggests that the susceptibility to MDD may potentially manifest during earlier developmental stages than previously anticipated, extending beyond young adulthood [31].

Several limitations warrant consideration in our study. Firstly, the gene expression data were obtained from six healthy adult donors without MDD. Differences in gene expression between depressed patients and healthy individuals, as well as sex variations, may impact the interpretation of connectome-transcriptome associations. Then, our study employed a cross-sectional design, which restricts our ability to establish causal relationships between amygdala functional connectivity and MDD. Future prospective longitudinal studies are needed to provide deeper insights into causal relationships and a more comprehensive understanding.

In summary, our findings confirm our hypothesis of amygdala functional connectivity alterations in MDD, facilitating individual-level identification of the disorder. Additionally, our investigation into connectome-transcriptome associations revealed MDD-related genes enriched for metal ion transport and modulation of chemical synaptic transmission. These insights significantly contribute to our understanding of the neurobiological mechanisms in MDD and offer novel avenues for prevention and intervention strategies.

DATA AVAILABILITY

Phenotypic and imaging datasets were sourced from the publicly available brain imaging depression consortium (http://rfmri.org/REST-meta-MDD). Human gene expression data supporting this study's findings are accessible in the Allen Human Brain Atlas database (http://human.brain-map.org/static/download).

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YL: Conceptualization, Methodology, Formal Analysis, Writing–Original draft preparation & Editing. ML: Formal Analysis, Review & Editing. BZ, WQ, YG and YJ: Review & Editing. JL: Conceptualization, Methodology, Supervision, Resources, Writing–Review & Editing.

COMPETING INTERESTS

The authors declare no competing interests.

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