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Research Article

Functional connectivity analyses of individual hippocampal subregions in major depressive disorder with electroconvulsive therapy

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Abstract

Background: The hippocampus has been widely reported to be involved in the neuropathology of major depressive disorder (MDD). All the previous researches adopted group-level hippocampus subregions atlas to investigate abnormal functional connectivities in MDD in absence of capturing individual variability. In addition, the molecular basis of functional impairments of hippocampal subregions in MDD remains elusive.

Objective: We aimed to reveal functional disruptions and recovery of individual hippocampal subregions in MDD patients before and after ECT and linked these functional connectivity differences to transcriptomic profiles to reveal molecular mechanism.

Methods: we used group guided individual functional parcellation approach to define individual subregions of hippocampus for each participant. Resting-state functional connectivity (FC) analysis of individual hippocampal subregions was conducted to investigate functional disruptions and recovery in MDD patients before and after ECT. Spatial association between functional connectivity differences and transcriptomic profiles was employed to reveal molecular mechanism.

Results: MDD patients showed increased FCs of the left tail part of hippocampus with dorsolateral prefrontal cortex and middle temporal gyrus while decreased FC with primary visual cortex. These abnormal FCs in MDD patients were normalized after ECT. In addition, we found that functional disruptions of the left tail part of hippocampus in MDD were mainly related to synaptic signaling and transmission, ion transport, cell-cell signaling and neurogenesis.

Conclusion: Our findings provide initial evidence for functional connectome disruption of individual hippocampal subregions and their molecular basis in MDD.

Keywords: hippocampus; major depressive disorder; individual parcellation; electroconvulsive therapy; gene expression

Introduction

Major depressive disorder (MDD), a common neuropsychiatric disorder with a persistent feeling of sadness and loss of interest, is a leading cause of disability worldwide (Dick and Ferguson, 2015; Insel and Cuthbert, 2015; Stringaris, 2017). Medication is the first choice for MDD treatment while only one third of the patients relieve (Al-Harbi, 2012). Electroconvulsive therapy (ECT) is one of the most effective approaches for rapid relief of depression, especially for treatment-resistant depression and depression with suicidal tendencies (Rami-Gonzalez *et al.*, 2001; Hausner *et al.*, 2011; Leaver *et al.*, 2021). Although ECT could effectively alleviate clinical depressive symptoms for patients with MDD, it also temporally causes cognitive impairments. Thus, elucidating the brain mechanism for ECT and side effects may better direct non-invasive neuromodulation therapy for MDD.

The advent of in-vivo neuroimaging techniques has made it possible to elucidate the underlying brain structural and functional basis of depression (McGrath *et al.*, 2013). The hippocampus is a core region involved in cognition, memory, and emotion processing and plays a fundamental role in the neuropathology of depression (Zhang *et al.*, 2021; Xiao *et al.*, 2024; Zhong *et al.*, 2024). Previous studies with large samples reported collapse of hippocampal volume in patients with MDD, and the number of depressive episodes was correlated with the size of the hippocampus volume (Phillips *et al.*, 2015; Schmaal, 2016). In MDD patients after ECT, normalized hippocampal structural and functional connectivities were found and were associated with symptoms relief suggesting structural and functional recovery of hippocampus may serve as biomarkers for response of ECT (Abbott *et al.*, 2014; Joshi *et al.*, 2016). Emerging evidence has demonstrated that the hippocampus has complex functions. The dorsal hippocampus is mainly involved in memory while the ventral hippocampus plays a major role in emotion processing (Bannerman *et al.*, 2004; Satpute *et al.*, 2012). Although a previous study has explored ECT effects on

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functional couplings of hippocampal subregions using a group-level atlas in MDD patients (Bai *et al.*, 2018), increasing studies have revealed individual variability in human brain anatomy and connectivity (Wang *et al.*, 2015). Wang and colleagues employed an individual functional connectivity mapping approach to predict clinical performances for MDD patients with ECT and found that individual functional connections could predict memory impairments but group-level functional connections cannot (Wang *et al.*, 2020). In addition, a lot of studies have demonstrated that individual level functional connectivity could better predict aging, cognitive, and clinical performances (Cui *et al.*, 2020; Zhang *et al.*, 2021; Zhang *et al.*, 2022; Sun *et al.*, 2024). Thus, functional connectivity mapping of individual hippocampal subregions may better illuminate their roles in MDD and treatment response to ECT.

In this study, we aimed to use an individual functional connectivity mapping approach to reveal the role of hippocampal subregions in MDD patients after ECT and to reveal the genetic basis using the Allen Human Brain Atlas (AHBA) microarray (Arnatkeviciute *et al.*, 2018). First, we used our previously proposed group guided individual parcellation approach to define individual level hippocampal subregions. Then, functional connectivity analyses of individual hippocampal subregions in MDD patients and after ECT were executed. Finally, spatial correlations between functional connectivity changes and transcriptomic data were analyzed to reveal the molecular basis.

Materials and Methods

Subjects

The dataset of this study contains a total of 92 subjects, including 46 patients with MDD (37 females/9 males, age range from 17 to 61, mean and standard deviation = 39.9 ± 12.1 years) and 46 age- and sex-matched healthy controls (35 females/11 males, age range from 20 to 55, mean and standard deviation = 35.5 ± 11.6 years). The local ethics committee of Anhui Medical University approved the research, and all participants signed written informed consent. All the MDD patients are inpatients with treatment-resistant or acute suicidal ideation for ECT in this study. The patients with severe somatic diseases, neurological disorders, substance abuse or dependence, pregnancy, comorbidity, or other psychiatric conditions, or having previously received ECT or MRI-contraindications were excluded. The clinical performances including mini-mental state examination (MMSE), 17-item Hamilton Depression Scale (HAMD), and Hamilton Anxiety Scale (HAMA) were recorded before and after ECT.

ECT Protocols

A modified bi-frontal ECT protocol (Somatics, Lake Bluff, IL, USA) was used for MDD therapy. ECT was administrated three times a week and was applied every other day with a break over the weekends. During ECT, the patient was anesthetized using propofol. The succinylcholine and atropine were also used to relax the musculature and suppress secretion of glands. The seizure activity was monitored using electroencephalography. The treatment % energy was initially set based on the age of each participant (e.g. 50% for a 50-year-old patient), and the strength was evenly adjusted with an increment of 5% of the maximum charge (approximately 1000 millicoulombs) until seizure was detected. For details of ECT procedures for MDD treatment, refer to our previous studies (Wei *et al.*, 2014; Wang *et al.*, 2017; Li *et al.*, 2023).

Resting-State fMRI Data Acquisition and Preprocessing

Resting-state fMRI data was acquired using a 3.0T GE MRI scanner (Discovery GE750w). The patients were scanned 12–24 hours before the first ECT session and 24–72 hours after the last ECT session. The resting-state fMRI data of healthy controls were also acquired to determine functional abnormalities in MDD patients. All subjects were instructed to relax, to keep their eyes closed, to remain awake, and not to think of anything during fMRI scanning. The resting-state fMRI were scanned using a standard echo planar imaging (EPI) sequence with the following parameters: repetition time/echo time ratio = 2400/30 ms, flip angle = 90 degrees, matrix size = 64 × 64, field of view = 192 × 192 mm, 46 slices, voxel size = 3 × 3 × 3 mm^3, 217 volumes.

Resting-state fMRI data was preprocessed using the following steps. The first seven volumes were excluded and the remaining 210 volumes were registered to the first volume to correct head motion. Then, the fMRI data was transformed to Montreal Neurological Institute (MNI) space and resampled to 3 × 3 × 3mm^3. Next, all the data were smoothed with a 6mm full-width at half maximum (FWHM) Gaussian kernel. Nuisance covariates including Friston's-24 head motion parameters, white matter, cerebrospinal fluid, and global signals were regressed out and filtered with 0.01–0.1 Hz. To further exclude head motion effects, subjects with head motion exceeding one voxel were discarded. Under this criterion, no subject was excluded in this study. Moreover, scrubbing was conducted to eliminate frame-wise head motion (2 volumes before and 1 volume after) using a cubic spline interpolation if the mean frame displacement (FD) > 0.5 mm.

Individual Hippocampal Subregions Definition

The bilateral hippocampal masks were defined using Harvard-Oxford 25% probability atlas for individual functional parcellation of hippocampus in both healthy controls and MDD patients. The hippocampal masks were re-sampled into 3-mm cubic voxel resolution for functional parcellation. The individual hippocampus subregions were identified using our proposed group guided individual functional parcellation approach which is a novel semi-supervised method for individual brain parcellation based on functional variability at individual level (Zhang *et al.*, 2021). Briefly, the whole-brain functional connectivity for each voxel of the hippocampus was first calculated. Next, the similarity for the whole brain functional connectivity maps of every pair of voxels within the hippocampus was defined using eta^2 to obtain a similarity matrix for each subject. Then, all the similarity matrices were averaged across all the subjects to obtain a mean similarity matrix. This average similarity matrix was fed into our proposed adaptive affinity propagation algorithm to obtain the group-level parcellation results for hippocampus. Based on the group-level parcellation result, the average similarity vector of each subregion across all voxels within this subregion was calculated and was taken as a new clustering center. Finally, the litekmeans method was applied to cluster the similarity matrix into different subregions in each individual with the group-parcellation derived clustering centers.

Resting-State Functional Connectivity Analyses for Individual Hippocampal Subregions

Resting-state functional connectivity (RSFC) maps of the hippocampal subregions in each individual were calculated using Pearson correlation coefficient between the average time series of each hippocampus subregion and the time series of each voxel

Table 1: Demographic and clinical variables of the MDD patients and HCs.

Variables	MDD	HC	P value
Number of subjects	46	46	
Gender (male/female)	9/37	11/35	0.61
Age (mean ± SD)	39.91 ± 12.25	35.48 ± 11.77	0.08
Number of treatment (mean ± SD)	8.57 ± 2.01		
HAMD scores (mean ± SD)		1.83 ± 1.97	[a]1.66×10^{-40}, [b]1.92×10^{-7}, [c]2.47×10^{-21}
Before ECT	23.85 ± 5.98		
After ECT	6.74 ± 5.57		
HAMA scores (mean ± SD)		2 ± 2.03	[a]6.21×10^{-33}, [b]5.58×10^{-7}, [c]7.05×10^{-18}
Before ECT	22.11 ± 6.96		
After ECT	6.83 ± 5.72		
MMSE scores (mean ± SD)			[a]0.0017, [b]1.73×10^{-4}, [c]0.32
Before ECT	28.38 ± 1.89	29.47 ± 1.16	
After ECT	28.08 ± 2.03		

The *P* values were obtained by a Chi-square test for gender, and two-sample t-tests for age. MDD, major depressive disorder; HC, healthy controls; HAMD, Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety; MMSE, Mini Mental State Examination; ECT: electroconvulsive therapy. [a] Comparison between HC and MDD patients before ECT using two-sample t-test. [b] Comparison between HC and MDD patients after ECT using two-sample t-test. [c] Comparison between MDD patients before and after ECT using paired t-test.

of the rest brain. The Fish r-to-z transformation was applied to improve the normality. To identify functional connectivity difference of each hippocampal subregion between healthy controls and MDD patients, two-sample *t*-tests with age as covariate were applied and significant level was determined using false discovery rate (FDR) method with $p < 0.05$. To explore treatment effect of ECT, the average functional connectivities of brain regions showing RSFC differences with hippocampal subregions were calculated for different groups. Two-sample t-tests with age as covariate and paired *t*-tests were performed to reveal RSFC differences between healthy controls and MDD patients after ECT and between MDD patients before and after ECT, respectively. The significant differences were corrected using FDR method with $p < 0.05$. To determine whether the functional connectivity differences were associated with clinical performances, correlations analyses were performed between functional connectivity or changes of functional connectivity and clinical scores.

Associations between Changes of Functional Connectivity and Gene Expression

The microarray data of human gene expression provided by AHBA (http://human.brain-map.org), including 6 donated adult brains (35 females/11 males, age from 24 to 57), were downloaded. All the data were preprocessed by Arnatkeviciute et al. (2019). A total of 58 692 probes collected 20 737 unique gene expression data from 3702 spatially distinct samples in the brain, and 45 821 genes provided corresponding Entrez IDs and GeneSymbol annotations. In addition, MNI coordinates of 3702 spatial samples were provided for linkage with neuroimaging data. Using the 1000 whole-brain parcellation map proposed by Schaefer *et al.*, (2018), the gene expression was evenly mapped to each subregion of the cortex. Given that only two right hemisphere gene expression datasets were acquired, we analyzed the gene expression data of the 500 subregions in the left hemisphere. The statistical *t*-value maps between MDD and healthy groups of the hippocampal subregions were mapped to 500 parcels in left hemisphere. The average *t*-value for each parcel was calculated and a 1×500 vector was obtained. Then, the spatial Pearson correlation coefficients between each gene's expression level and statistical *t*-value of the 500 parcels were calculated. The spin test was used to eliminate the spatial autocorrelation. The significantly associated genes for changes of functional connectivity were identified using the Bonferroni corrected method with $p < 0.01$.

Gene Enrichment Analysis

ToppGene (https://toppgene.cchmc.org/) provides a convenient tool for Gene ontology (Go) enrichment analysis for significantly associated genes with changes of RSFC. Enrichment analysis was executed to identify biological function including molecular functions, biological processes, and cellular components (Carbon *et al.*, 2021). The Kyoto Encyclopedia of Genes and Genomes (KEGG) was used to identify biological pathways. The significance for gene enrichment analysis was determined using Fisher's exact tests and corrected using the FDR method with $p < 0.05$.

Results

Demographic and Clinical Characteristics

Table 1 summarizes the demographic and clinical characteristics of all participants. There were no significant differences in sex and age between MDD patients and HC. Patients with MDD had significantly higher depressive load before and after ECT compared to HCs, and ECT led to a significant reduction in depressive symptoms in MDD. Patients with MDD also had significantly higher anxiety load before and after ECT compared to HCs, and ECT led to a significant reduction in anxiety symptoms in MDD. MMSE scores were significantly lower in MDD patients before and after ECT compared to HCs while there was no significant difference in MDD patients before and after ECT.

Individual Parcellation of the Bilateral Hippocampus

Group-level and individual-level functional parcellation of the bilateral hippocampus in the healthy controls and depressive patients were obtained by our previously proposed individual par-

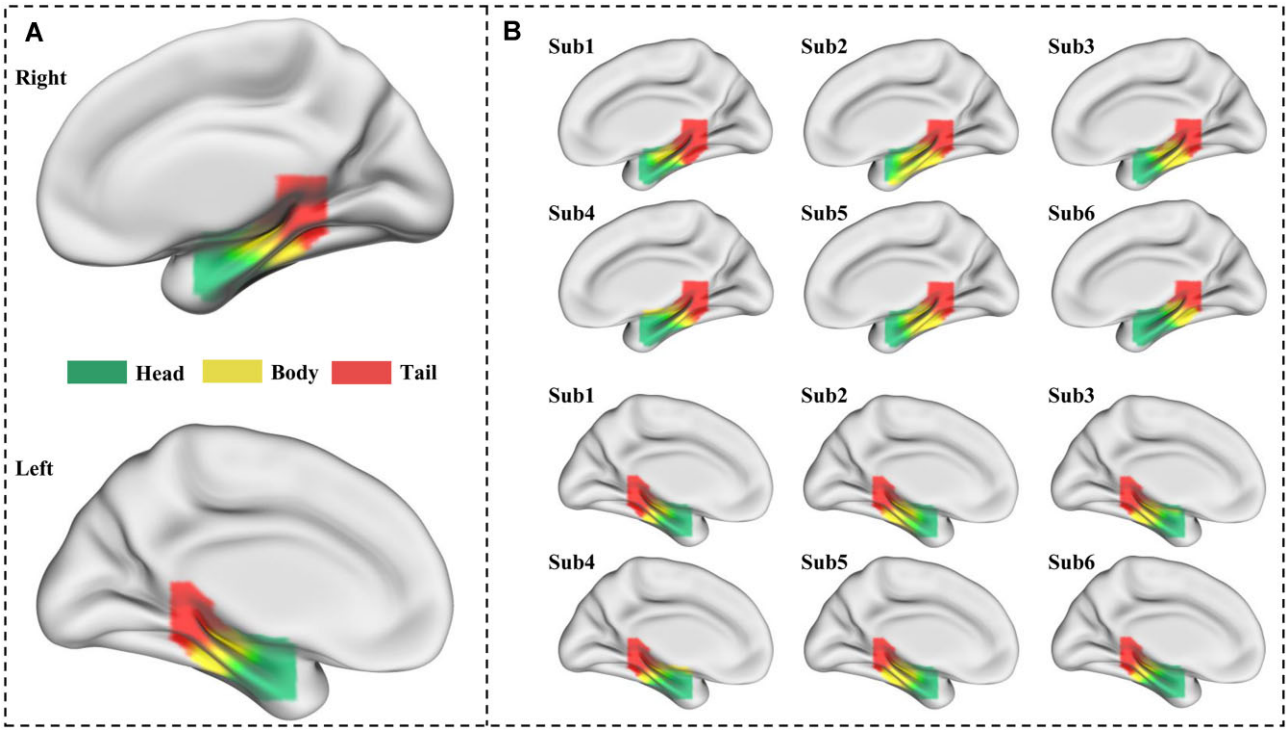

Figure 1: The group-level and individual-level parcellation of hippocampus. The group-level and six randomly selected individual level parcellation of bilateral hippocampus were shown. The hippocampus was parcellated into head, body, and tail parts from anterior to posterior axis.

cellation methods. Similar to our previous results, the bilateral hippocampus were parcellated into three subregions including head, body, and tail parts of hippocampus at group level (Fig. 1A). Using the group-level parcellation results as new clustering centroid, three-way individual-level parcellation results of hippocampus were defined. Six randomly selected individual parcellation maps of hippocampus were displayed and significant individual anatomical variations of hippocampus subregions were observed (Fig. 1B).

Functional Connectivity Differences of Hippocampal Subregions in MDD and ECT Effects

To identify functional connectivity abnormalities of each hippocampal subregion in MDD patients, two-sample *t*-tests for whole brain functional connectivity maps of hippocampal subregions were performed between MDD patients and healthy controls. Compared to healthy controls, MDD patients showed significantly increased functional connectivities of the left tail part of hippocampal subregion with left dorsolateral prefrontal cortex [dlPFC, peak MNI: (-33, -18, 54)] and left middle temporal gyrus [MTG, peak MNI: (-66, -30, -27)] while significantly reduced functional connectivity of the left tail part of hippocampal subregion with primary visual cortex [V1, peak MNI: (15, -81, -9)] (Fig. 2A). There were no other significant functional connectivity differences with other hippocampal subregions between MDD patients and healthy controls.

To explore ECT effects on functional connectivities of hippocampal subregions, the average functional connectivities of brain regions showing functional connectivity differences with hippocampal subregions found above were calculated in healthy controls and MDD patients before and after ECT. Compared with MDD patients before treatment, ECT could effectively decrease functional connectivities of the left tail part of the hippocampal subregion with left dlPFC and left MTG and increase functional connectivity of the left tail part of the hippocampal subregion with V1 (Fig. 2B). After ECT, MDD patients showed similar connectivity patterns as HCs, suggesting ECT could normalize the abnormal functional connectivity in MDD patients.

To determine whether functional connectivity differences are associated with clinical performances, correlation analyses were performed and found that functional connectivities between the left tail part of the hippocampal subregion and V1 were negatively correlated with HAMD and HAMA scores in MDD patients after ECT (Fig. 2C).

Molecular Basis Underlying Changes of Functional Connectivity of Hippocampal Subregion

Using spatial association analysis between statistical map and gene expression data, 880 significantly associated genes with changes of functional connectivities of the left tail part of hippocampal subregion were identified. Enrichment analysis revealed that these genes are closely associated with MDD, schizophrenia, cognitive disorders, and epilepsy (left panel in Fig. 3). Moreover, the biological processes of these genes were also found to be mainly involved in neurogenesis, cell-cell signaling, ion transport and its regulation, and synaptic and trans-synaptic signaling (right panel in Fig. 3).

Discussion

Using our proposed individual functional parcellation approach, individual functional subregions of the hippocampus and individual functional connectivity are mapped for both HCs and MDD

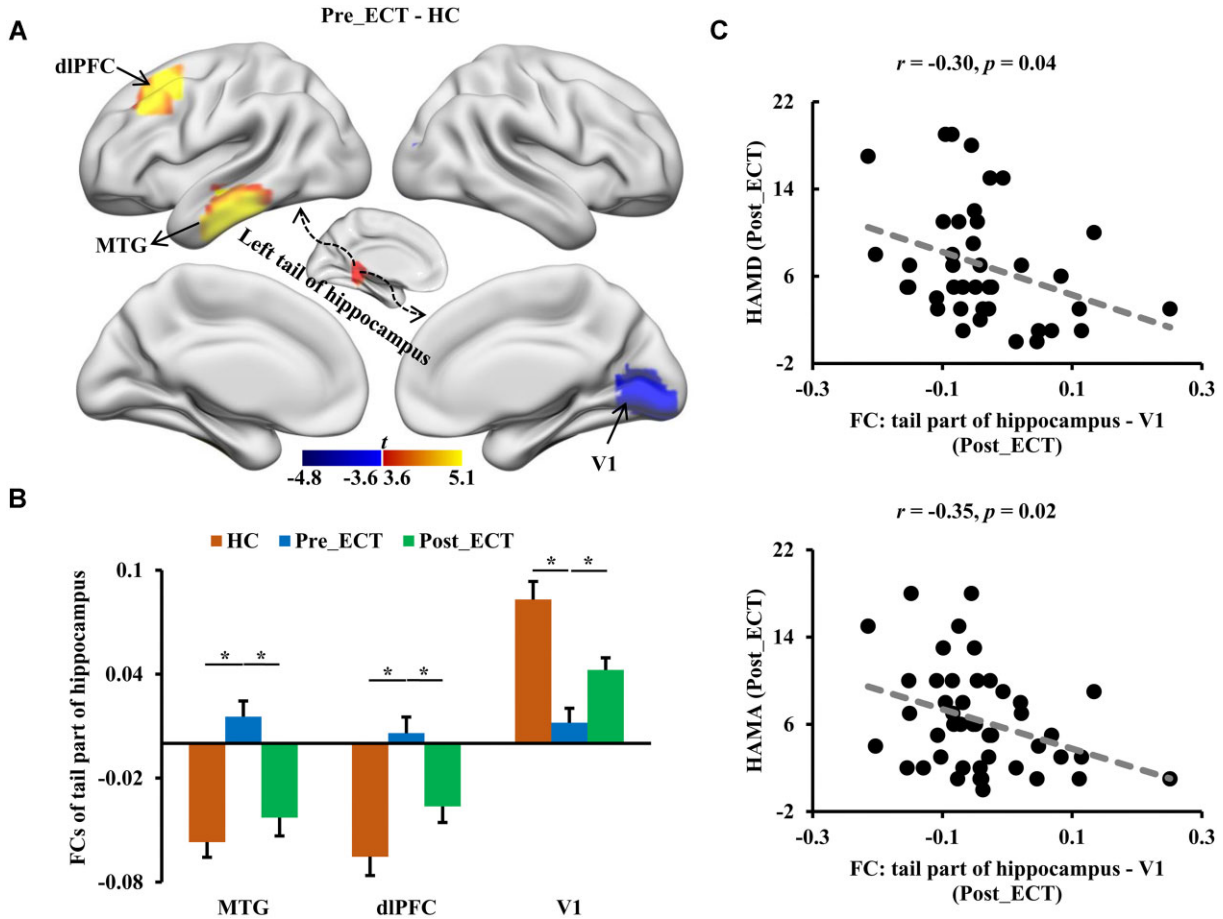

Figure 2: Altered functional connectivity (FC) of the tail part of the hippocampus in MDD patients. (A) Compared with healthy controls, MDD patients before ECT (Pre_ECT) showed increased FCs of the left tail part of hippocampus with left dorsolateral prefrontal cortex (dlPFC) and left middle temporal gyrus (MTG), while decreased FC of the left tail part of hippocampus with right primary visual cortex (V1). (B) In MDD patients after ECT (Post_ECT), we found that ECT could normalize the abnormal FCs in MDD patients. (C) The decreased FCs between left tail part of hippocampus and right V1 were negatively correlated with depression and anxiety loads in MDD patients after ECT (Post_ECT).

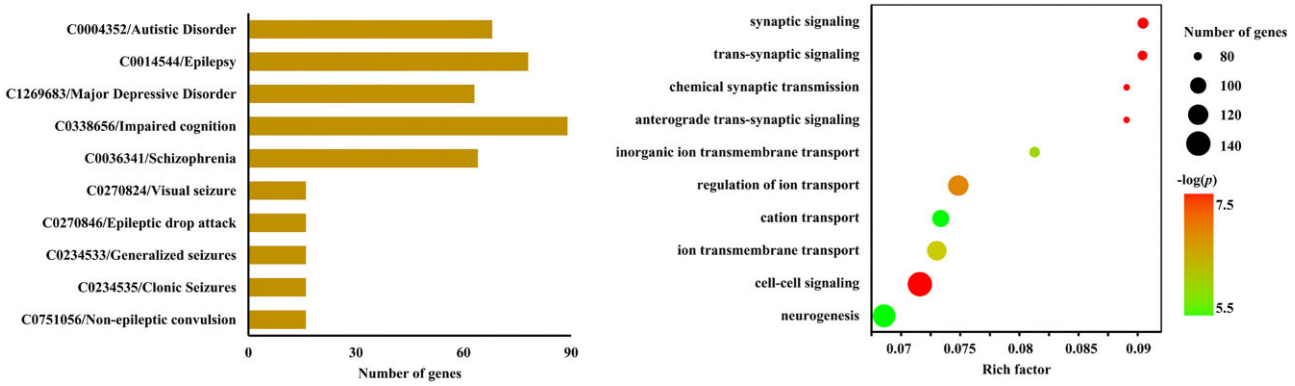

Figure 3: Enrichment analysis for the associated genes. Using spatial correlation analysis, the genes associated with changes of functional connectivity of the left tail part of hippocampus in MDD patients, compared to HCs, were identified. Enrichment analysis of these genes found that they are mainly related to the brain disorders of impaired cognition, epilepsy, autism disorder, schizophrenia, and MDD (left panel). These genes were mainly involved in biological processes including neurogenesis, cell-cell signaling, synaptic signaling, regulation of ion transportation, and so on (right panel).

patients. Individual functional connectivity analyses reveal significantly changed functional connectivity of hippocampal subregions in MDD patients and that ECT could normalize these abnormal functional connections. Importantly, by combining transcriptomic data, we establish the molecular basis for these changes of functional connectivity in MDD patients. Taken together, we provide initial evidence for the functional abnormality of individual hippocampal subregions in MDD patients and how ECT modulates these functional disruptions at individual level. The associated genes with changes of functional connectivity of hippocampal subregions may improve understanding of the role of the hippocampus in the neuropathology of MDD.

Individual Hippocampal Subregions Mapping for ECT

The hippocampus has been demonstrated to be a heterogeneous region composed of different subregions which play distinct roles in human behavior, emotion, and cognition (Robinson *et al.*, 2015; Zhang *et al.*, 2021). A recent ECT study using a hippocampus atlas to define three functional subregions including emotion, cognition, and perceptual function found that ECT increased functional connectivity of the emotional hippocampal subregion with left middle occipital gyrus and the right medial temporal gyrus while decreasing functional connectivity of the cognitive hippocampal subregion with bilateral angular gyrus in MDD patients (Bai *et al.*, 2018). In another study, Hao and colleagues also segmented the hippocampus into three subregions—cornu ammonis, dentate gyrus, and subiculum—and found different subregions showing different changes of whole brain resting-state functional connectivity pattern in MDD patients (Hao *et al.*, 2020). Similar findings were found by Cole *et al.* (2010) which reported that the collapse of hippocampal subregions in patients with MDD and atrophy mainly concentrates in subiculum and cornu ammonis subregions. However, all the aforementioned studies are based on group-level hippocampus parcellation results leading to inaccurate functional connectivity mapping (William *et al.*, 2015). Given the large individual variations in the functional neuroanatomy of high-order cognition-related brain areas, group-level functional subregion analysis cannot well characterize individual behavioral differences (Wang and Liu, 2014). Thus, mapping personalized functional connectivity of hippocampal subregions at the individual level could better characterize functional abnormalities of the hippocampus in depression and guide precision therapy. In this study, we applied our proposed individual hippocampus parcellation algorithm to define hippocampal functional subregions at the individual level, which will be beneficial to future studies to identify important roles of the hippocampus in neuropsychiatric disorders from an individual perspective.

Hippocampus in Depression

The key role of the hippocampus in MDD has been well documented. A lot of previous studies have reported hippocampal atrophy in patients with MDD (Vakili *et al.*, 2000; Sheline *et al.*, 2002; Colla *et al.*, 2007), and hippocampal volume was closely correlated with severity, number of episodes, and duration of depression (Sheline *et al.*, 2019). In MDD patients after treatment such as taking antidepressants and ECT, the volume of the hippocampus increases significantly (Malykhin *et al.*, 2010; Leif *et al.*, 2018), and hippocampal subregion volume could predict ECT outcomes in MDD (Cao *et al.*, 2018; Gbyl *et al.*, 2021; Xu *et al.*, 2023). In addition to structural changes of the hippocampus, MDD patients also showed altered hippocampal functional connectivity with prefrontal and parietal cortices and the changed functional connectivity was correlated with the duration of MDD (Cao *et al.*, 2012). In addition, Barch and colleagues reported that preschool poverty changed hippocampal connectivity patterns leading to school-age depression (Barch *et al.*, 2016). Recently, a study used the connections of the hippocampus to left inferior frontal gyrus and precuneus to predict the therapeutic effect of antidepressants for patients with MDD (Xiao *et al.*, 2021). All these studies indicate that the hippocampus has a close relationship with the onset, duration, and severity of depression. In our study, we found that MDD patients showed increased functional connectivity between the tail part of the hippocampus and dorsolateral prefrontal cortex, as well as the middle temporal cortex, while exhibiting decreased functional connectivity with the primary visual cortex. Interestingly, we found that the functional connectivities of the tail part of hippocampus with primary visual cortex were negatively correlated with depression and anxiety severity. For these MDD patients after ECT, the abnormal functional connectivities of hippocampal subregions were normalized. This result is supported by a previous study which found that the tail of the hippocampus volume is a prognostic biomarker for antidepressant treatment outcomes in patients with MDD and concluded that volume decline of the tail part of the hippocampus may relate to a cumulative imprint of previously long-lasting untreated depressive episodes (Nogovitsyn *et al.*, 2020). Our findings provide new supporting evidence for the important role of the hippocampus, especially the left tail part of the hippocampus, in disease onset and severity in MDD patients and the functional connectivity of the tail part of the hippocampus may serve as a biomarker for response or remission of depression.

Molecular Basis of Hippocampus in MDD

The Allen Human Brain Atlas microarray dataset provides a unique opportunity to reveal molecular basis of macroscopic neuroimaging phenotypes (Yang *et al.*, 2023; Chen *et al.*, 2024; Yu *et al.*, 2024). Recently, we analyzed static and dynamic functional connectivity changes of default mode network and identified the genes associated with these functional alterations to reveal the molecular basis of ECT for depression (Li *et al.*, 2023). In this study, using functional connectivity analysis for individual hippocampal subregions, we revealed changed functional connectivity of the tail part of the hippocampal subregion in MDD patients compared to healthy controls. We linked these functional changes to the human transcriptomic data and identified the associated genes for alterations of functional connectivity. The following enrich analysis revealed that these genes were mainly involved in synaptic signaling and transmission, ion transport, cell-cell signaling, and neurogenesis. Our findings provide the initial evidence for the individual functional connectivity changes of hippocampal subregions and identified the molecular basis for these individual functional connectivity abnormalities in MDD patients, which may facilitate better understanding of the role of the hippocampus in neuropathology of depression.

There are some limitations of our study. First, the neuroimaging-transcriptome association analysis only used the left hemispheric genes' expression profiles to avoid sampling bias, since only two donors had samples in the right hemisphere, which may affect our findings about the molecular basis underlying functional differences of the hippocampal subregion in MDD. Our findings should therefore be further validated in future studies. Second, since the transcriptomic data are not from our enrolled subjects, the interpretation of the molecular basis for functional changes needs to be approached with caution. Third, the sample size of this study is not large, and the findings need to be further validated. Fourth, we did not separate the patients with MDD into treatment-resistant and suicidal attempt subgroups, which may bring confounds of our findings. Fifth, we parcellated the hippocampus using functional MRI at the resolution of 3 mm cubic voxel. Given that the hippocampus is small, the obtained functional subregions of the hippocampus may not be ideal.

Conclusion

In this study, group level guided individual functional hippocampal subregions were mapped and individual functional connectivity changes of the left tail part of the hippocampal subregion

with dorsolateral prefrontal cortex, middle temporal gyrus, and primary visual cortex were found in MDD patients. In addition, we found that ECT could normalize these abnormal functional connectivities in MDD. Importantly, we linked changes of functional connectivity of hippocampal subregions to transcriptomic profiles to reveal the molecular mechanism for the functional abnormalities in MDD patients. The associated genes were mainly related to synaptic signaling and transmission, ion transport, cell-cell signaling, and neurogenesis. This study revealed functional connectome disruption of individual hippocampal subregions in MDD patients and their molecular basis. Our findings will facilitate uncovering the molecular basis of depression and guide precious therapy for MDD.

Author contributions

Hui Sun (Data curation, Formal analysis, Software, Visualization, Writing - original draft), Dundi Xu (Formal analysis, Methodology, Visualization, Writing - original draft), Qinyao Sun (Formal analysis, Visualization), Tongjian Bai (Data curation), Kai Wang (Conceptualization, Resources, Supervision), Jiaojian Wang (Conceptualization, Investigation, Supervision, Writing - review & editing), Jiang Zhang (Conceptualization, Project administration, Supervision, Writing - review & editing), and Yanghua Tian (Conceptualization, Data curation, Resources, Supervision, Writing - review & editing)

Conflict of Interest Statement

None declared.

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