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Elevated hippocampal choline level is associated with altered functional connectivity in females with major depressive disorder: A pilot study

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ABSTRACT

Metabolic and functional alterations in hippocampus have been associated with the pathophysiology of major depressive disorder (MDD). However, how the hippocampal biochemical disruptions lead to dysfunction of limbic-cortical circuit remains unclear. The present pilot study combined magnetic resonance spectroscopy (MRS) and resting-state functional magnetic resonance imaging (rs-fMRI) to investigate the hippocampal metabolic alteration and its relationship with the intrinsic functional connectivity (FC) changes in MDD. Both MRS and fMRI data were obtained from twelve women with MDD and twelve age-matched, healthy women. Bilateral hippocampi were chosen as regions of interest, in which metabolite concentrations of total choline (tCho), N-acetylaspartate and creatine were quantified. Bilateral hippocampal FC to the whole brain and its correlations with hippocampal metabolite concentrations were conducted. Females with MDD showed significantly elevated left hippocampal tCho level, and decreased anti-correlations between the left hippocampus and bilateral superior frontal gyrus (SFG), left inferior frontal gyrus, and right superior temporal gyrus. More importantly, the left hippocampal tCho level was associated with FC to the right SFG and right fusiform gyrus in healthy women, whereas it was significantly associated with FC to the right lingual gyrus in women with MDD. Our findings suggested that regional metabolic alterations in the left hippocampus might be related to the network-level dysfunction.

1. Introduction

Major depressive disorder (MDD) is a severe worldwide public health problem, characterized by persistent low mood and anhedonia (Kupfer et al., 2012). Dysfunction of the limbic-cortical pathway, which dominates emotion processing and regulation, plays an important role in MDD pathophysiology (Hamilton et al., 2011; Mayberg, 2003). As one of the most influential network models of MDD, the limbic-cortical model suggests abnormal reciprocal interactions between the limbic system and the cortex in MDD, resulting in affective and cognitive abnormalities (Kaiser et al., 2015). As an essential part of the limbic system, the hippocampal volume reduction is the most consistent brain structural alteration in MDD (Schmaal et al., 2016). However, the link between hippocampal biochemical dysfunction and abnormal network-level functional connectivity has not been investigated.

Magnetic resonance spectroscopy (MRS) provides a useful non-

Abbreviations: MDD, major depressive disorder; MI, myo-inositol; Glx, glutamate-glutamine; Gln, glutamine; Cho, choline; ECT, electroconvulsive therapy; FC, functional connectivity; FP, fronto-parietal network; ROI, region of interest; HCs, healthy controls; tCho, predominantly glycerophosphocholine and phosphocholine; tNAA, N-acetylaspartate and N-acetylaspartylglutamate; tCr, creatine and phosphocreatine; SFG, superior frontal gyrus; IFG, inferior frontal gyrus; STG, superior temporal gyrus; MTG, media temporal gyrus

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invasive tool to measure the cerebral metabolite concentrations in vivo. Altered hippocampal metabolic level has been shown in MDD patients using MRS, but the findings were heterogeneous (Wang et al., 2012; Yildiz-Yesiloglu and Ankerst, 2006). In patients with first-episode MDD, higher Myo-inositol (MI) and lower Glutamate-glutamine (Glx)/Glutamine (Gln) levels were observed in their hippocampus (Block et al., 2009; Milne et al., 2009), while other studies reported no significant hippocampal metabolite changes (Wang et al., 2012). Multiple-episode MDD patients showed increased hippocampal Choline (Cho)-containing compounds (Mervaala et al., 2000; Milne et al., 2009), whereas lower Cho level was found in other study (Ende et al., 2000). More importantly, the abnormal hippocampal Cho concentration was mediated after anti-depressant or electroconvulsive therapy (ECT) treatment in MDD and could predict the treatment outcome (Bellani et al., 2011; Block et al., 2009; Ende et al., 2000; Jorgensen et al., 2016; Wang et al., 2012). Nevertheless, MRS studies investigating the hippocampal metabolic alterations were still relatively limited and the findings varied over the course of illness and placements of hippocampal voxel. Moreover, the neurochemical changes were suggested to be accompanied by functional alterations since the pathophysiology of MDD involves multiple biological systems that influence each other (Jentsch et al., 2015; Zhang et al., 2016). Thus, studies linking regional metabolic changes to the network-level dysfunction are in need for a more comprehensive understanding of MDD pathophysiology.

As shown by a large number of resting-state functional magnetic resonance imaging (rs-fMRI) studies, the functional abnormality within distributed brain networks in MDD was associated with depression symptomatology (Kupfer et al., 2012). Alterations of functional connectivity (FC) under the resting state reflect the spontaneous neural activity and help explaining deficits in self-referential functions of MDD patients (Dichter et al., 2014). The recent meta-analysis of resting-state FC in MDD by Kaiser et al. has reported hyperconnectivity within the default network (DN) and between the fronto-parietal network (FP) and DN, as well as hypoconnectivity between FP and parietal regions (Kaiser et al., 2015). While a majority of rs-fMRI studies in depression are through data-driven whole-brain analysis, few studies adopted the region of interest (ROI) based methodology. When using the hippocampus as ROI, dysfunctional connectivity between the hippocampus and cortical regions was found in MDD (Cao et al., 2012; Lui et al., 2011; Tahmasian et al., 2013). Both medication-naïve and medicated MDD patients showed reduced FC between the hippocampus and frontal cortex (Cao et al., 2012; Lui et al., 2011; Tahmasian et al., 2013). However, the impact of biochemical changes in hippocampus on its FC alteration was never explored and merits a detailed investigation in MDD study.

In the present pilot work, we focused on the study of metabolic and functional changes in the hippocampus of MDD patients by combing MRS and rs-fMRI methodologies. Considering the gender difference in clinical symptoms of MDD patients (Kuehner, 2003), we only included female patients and matched female healthy controls (HCs) to eliminate the confounder of gender. Metabolite concentrations in bilateral hippocampi were quantified and compared to HCs. We used bilateral hippocampi as seed ROIs and calculated their FC to the whole brain. More importantly, the correlations between the hippocampal metabolic level and altered FC were measured. We hypothesize that there is a linkage between MDD patients' hippocampal metabolite changes and its FC alterations with other brain regions.

2. Material and methods

2.1. Subjects

Twelve female outpatients with major depressive disorder (MDD) were recruited in Shanghai Mental Health Center (SMHC). All patients fulfilled ICD-10 (the tenth revision of International Classification of Diseases) diagnosis criteria for MDD (current episode of depression without history of manic episode) (Mussigbrodt et al., 2000). Diagnosis was verified by a senior psychiatrist. Six females with recurrent MDD were taking anti-depressant medications (2 duloxetine, 2 citalopram, 1 paroxetine, 1 mianserin) and six were unmedicated, first-episode. The total course of disease was 26.1 ± 7.9 months. Twelve age and education-matched female healthy controls were recruited by local advertisements. All healthy controls were screened by a senior psychiatrist and had no personal or family history of psychiatric illness. Other exclusive criteria for both groups include history of any substance or alcohol abuse, severe neurological or physical disease, or pregnancy. No individual had a history of tobacco use.

The experimental protocol was approved by the Ethics Committee in SMHC in compliance with the Helsinki Declaration. Written informed consent was obtained from each participant before the experiments. All subjects participated in the assessments of Hamilton Rating Scale for Depression (HAMD) and Hamilton Rating Scale for Anxiety (HAMA) by a senior psychiatrist (Williams, 2001). Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS) were self-rated (Knight et al., 1983). All subjects had no MRI contraindications and underwent MRI scanning on the same day of screening assessments. The demographic and clinical characteristics for both groups are illustrated in Table 1.

2.2. MRI data acquisition

MRI data were obtained on a Siemens 3.0-T Verio MRI scanner (MR B17, Siemens AG, Erlangen, Germany) with a 32-channel head coil in SMHC. To minimize head motion, foam padding was placed around each subject's head. T1-weighted images, resting-state fMRI images and ^{1}H MRS data were sequentially acquired with the following parameters.

2.2.1. T1-weighted images

Structural T1-weighted images were acquired using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence with repetition time (TR) = 2530 ms, echo time (TE) = 3.65 ms, field of view (FOV) = 256 mm, voxel size = 1 mm × 1 mm × 1 mm, 224 coronal slices, slice thickness = 1 mm, flip angle = 7°, GRAPPA acceleration factor of 2 and scan time for about 4 min.

2.2.2. Resting-state fMRI

Before the acquisition of fMRI data, each subject was instructed to close their eyes and not to think systematically during the whole scan. Resting-state fMRI images were acquired using echo planar imaging (EPI) sequence (TR= 2000 ms, TE = 30 ms, a 90° flip angle, FOV= 220 mm, voxel size=3.4 mm × 3.4 mm × 4 mm, and slice number = 36). The scanning time is about 6 min.

Table 1
Demographic and clinical characteristics of patients with major depressive disorders (MDD) and healthy controls (mean ± S.D.)

Measurement	MDD patients	Healthy controls	*t* value	*p* value
Cases	12	12	–	–
Age (years)	35.42 ± 9.50	35.08 ± 8.49	0.09	0.93
Handedness (right/left)	12/0	12/0		-
Education (years)	12.75 ± 3.60	13.50 ± 2.61	−0.59	0.57
Medication	6/12 medicated	–	–	–
Course of disease (months)	26.1 ± 7.9	–	–	–
HAMD	23.00 ± 2.90	0.33 ± 1.16	25.22	<0.001
HAMA	11.17 ± 1.95	0.44 ± 1.00	17.03	<0.001
SDS	0.53 ± 0.10	0.30 ± 0.05	7.10	<0.001
SAS	46.92 ± 10.81	27.58 ± 5.28	5.57	<0.001

Abbreviations: SD: standard deviation; HAMD: Hamilton Rating Scale for Depression; HAMA: Hamilton Rating Scale for Depression; SDS: Self-rating Depression Scale; SAS: Self-rating Anxiety Scale.

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