NeuroImage: Clinical 11 (2016) 658–666

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

The volumetric and shape changes of the putamen and thalamus in first episode, untreated major depressive disorder

Yi Lu[a], Hongmin Liang[a], Dan Han[a], Yin Mo[a], Zongfang Li[a], Yuqi Cheng[b], Xiufeng Xu[b], Zonglin Shen[b], Chunyan Tan[a], Wei Zhao[a], Yun Zhu[a], Xuejin Sun[a,*]

[a] Department of Medical Imaging, The First Affiliated Hospital, Kunming Medical University, Kunming, Yunnan, China
[b] Department of Psychiatry, The First Affiliated Hospital, Kunming Medical University, Kunming, Yunnan, China

ARTICLE INFO

Article history:
Received 6 November 2015
Received in revised form 26 March 2016
Accepted 13 April 2016
Available online 14 May 2016

Keywords:
Major depressive disorder
Volumetric analysis
Shape analysis
Putamen
Thalamus

ABSTRACT

Previous MRI studies confirmed abnormalities in the limbic-cortical-striatal-pallidal-thalamic (LCSPT) network or limbic-cortico-striatal-thalamic-cortical (LCSTC) circuits in patients with major depressive disorder (MDD), but few studies have investigated the subcortical structural abnormalities. Therefore, we sought to determine whether focal subcortical grey matter (GM) changes might be present in MDD at an early stage. We recruited 30 first episode, untreated patients with major depressive disorder (MDD) and 26 healthy control subjects. Voxel-based morphometry was used to evaluate cortical grey matter changes, and automated volumetric and shape analyses were used to assess volume and shape changes of the subcortical GM structures, respectively. In addition, probabilistic tractography methods were used to demonstrate the relationship between the subcortical and the cortical GM. Compared to healthy controls, MDD patients had significant volume reductions in the bilateral putamen and left thalamus (FWE-corrected, $p < 0.05$). Meanwhile, the vertex-based shape analysis showed regionally contracted areas on the dorsolateral and ventromedial aspects of the bilateral putamen, and on the dorsal and ventral aspects of left thalamus in MDD patients (FWE-corrected, $p < 0.05$). Additionally, a negative correlation was found between local atrophy in the dorsal aspects of the left thalamus and clinical variables representing severity. Furthermore, probabilistic tractography demonstrated that the area of shape deformation of the bilateral putamen and left thalamus have connections with the frontal and temporal lobes, which were found to be related to major depression. Our results suggested that structural abnormalities in the putamen and thalamus might be present in the early stages of MDD, which support the role of subcortical structure in the pathophysiology of MDD. Meanwhile, the present study showed that these subcortical structural abnormalities might be the potential trait markers of MDD.

1. Introduction

Major depressive disorder (MDD) is a highly prevalent complex neuropsychiatric condition characterised by a broad range of symptoms, with a yearly increase in morbidity and a high risk of mortality (Raes et al., 2006; Sullivan et al., 2000). Approximately 50–75% of MDD patients experience more than one clinically significant episode in their lifetimes (Association, A.P., 2000), and subsequent episodes reduce the effectiveness of antidepressant medication (Angst, 1999). Early studies suggested that psychological treatments earlier in life and at earlier stages of illness reduced the rate of recurrence of depressive episodes (Kaymaz et al., 2008). Therefore, understanding the pathophysiology of MDD at the time of the first episode may provide insights into prevention and early treatment for this debilitating illness.

Whereas the pathophysiology of MDD remains unknown, computational analyses of brain structural MRIs, especially voxel-based morphometry (VBM) and volumetric analyses, are beneficial for understanding the relationship between structural changes and pathologic processes in MDD. In previous VBM reports, volume reductions in the frontal regions, especially the anterior cingulated cortex, orbitofrontal and prefrontal cortices, and the hippocampus, have the most consistent results in MDD patients (Bora et al., 2012; Lai, 2013; Serra-Blasco et al., 2013; Zou et al., 2010). Especially, the hippocampal volume reductions were considered to be an early potential marker in first-episode patients with MDD (Frodl et al., 2002b). Besides, larger volumes of amygdala were also found in first-episode patients with MDD (Frodl et al., 2002a; Frodl et al., 2003), and correlated positively with the severity of depressive state (van Eijndhoven et al., 2009). These investigations indicated that the anatomical structure changes are in accordance with the hypothesis of abnormality in the cortic-limbic circuit (Malykhin et al., 2012; Mayberg, 1997), which may contribute to the pathophysiology of MDD. Although the hippocampus, a part of

* Corresponding author at: Department of Medical Imaging, The First Affiliated Hospital, Kunming Medical University, No. 295 Xichang RD., Kunming 650032, Yunnan, China.
E-mail address: sunxuejinkm@126.com (X. Sun).

http://dx.doi.org/10.1016/j.nicl.2016.04.008

the subcortical grey matter (GM), had been particularly well studied in MDD patients, several studies recently demonstrated that the functional and structural abnormalities of other subcortical GM associated with affective processing, especially the striatum (Heller et al., 2009) and thalamus (Webb et al., 2014), may also be associated with MDD. For example, the caudate nucleus is one of the central loci for reward-based behavioural learning, and therefore is intricately involved in pleasure and motivation (Haruno et al., 2004). There were also a few studies demonstrating that MDD may be associated with a neuropathological process affecting neurocircuitry involving the connections between the frontal cortex, striatum, thalamus and the related parts of the limbic system within the limbic-cortico-striatal -thalamic-cortical (LCSTC) circuits (Yeh et al., 2010) or the limbic-cortical-striatal-pallidal-thalamic (LCSPT) network (Drevets et al., 2008; Sheline, 2000), suggesting the involvement of some subcortical structures in the pathology of MDD. However, only the structural abnormality of the hippocampus was found in most VBM studies, and the structural abnormalities of other subcortical nuclei, especially the striatum and thalamus, were not well studied.

Recently, many studies demonstrated that traditional VBM analyses of structural MRIs were not sensitive to subtle changes in the subcortical GM (Menke et al., 2014; Nemmi et al., 2015). A few studies began to use the vertex-based shape analysis for exploring the morphological changes of the subcortical GM in Parkinson and Alzheimer's disease (Menke et al., 2014; Štepán-Buksakowska et al., 2014), providing useful information about the location and pattern of morphological changes of the subcortical GM. Because shape analysis can precisely localise regional shape deformations in the subcortical GM and detect changes that are not found in VBM and volumetric analyses, they are now increasingly used to study subcortical GM in a variety of neurological and psychiatric disorders. In this context, shape analyses could provide a sensitive, quantitative biomarker for focal subcortical GM atrophy.

This present study aims to determine whether focal subcortical GM changes are present at the early stage of MDD or not and to elucidate their relationships with clinical severities. To minimise confounding factors that are known to possibly affect GM changes, we only recruited untreated, first episode MDD patients. Specifically, voxel-based morphometry (VBM), automated volumetric and vertex-based shape analyses will be used to assess focal, subtle changes of the subcortical GM. In addition, probabilistic tractography will be used to demonstrate the relationships between subcortical and cortical GM.

2. Materials and methods

2.1. Subjects

This was a retrospective study and the ethics committee of Kunming Medical University approved the study protocol. In this study, 35 first episode and drug-naive patients were recruited from the psychiatry department of the First Affiliated Hospital of Kunming Medical University, but five of the 35 patients were excluded due to obvious structural abnormalities detected by T2-weighted MRI. Ultimately, 30 first episode and drug-naive patients (15 women and 15 men, age range 18–52 years; 100% right handed; education years range = 12–23) were recruited. Two experienced psychiatrists independently made the diagnosis of MDD according to the diagnostic assessment using the Structured Clinical Interview for DSM-IV-Patient Edition (SCID-P). All of the MDD patients also had a score of 18 or greater (scores range: 18–34) on the 17-item Hamilton Depression Rating Scale (HDRS). Those patients that had other comorbid Axis I and Axis II psychiatric disorders, such as schizophrenia, bipolar affective disorder, and personality disorders, were excluded from this study according to the SCID-I and SCID-II assessments. The MDD patients included in the study never received anti-depressive medications before the MRI examinations. All patients involved in the study provided written informed consent.

A total of 30 healthy control subjects (HCs), matched for age, gender and number of years of education, were also recruited from Kunming, but four of the 30 HCs were also excluded due to obvious structural abnormalities detected by T2-weighted MRI. Ultimately, 26 healthy control subjects (HCs) were recruited. They were screened using a diagnostic interview, the Structured Clinical Interview for DSM-IV Nonpatient Edition (SCID-NP), to rule out current or past DSM-IV Axis I disorders. They were also interviewed to affirm that there was no history of psychiatric illness in their first-degree relatives. All subjects were right-handed and without severe or acute medical conditions physically based on clinical evaluations and medical records. All of the healthy control subjects involved in the study provided written informed consent.

2.2. Magnetic resonance imaging acquisition

All participants were scanned on a Philips 3T achieva TX scanner with an eight-channel head coil. A high-resolution 3D TFE sequence was acquired with the following parameters: TR = 7.7 ms, TE = 3.6 ms, matrix = 228 × 228, FOV = 250 mm × 250 mm, 230 axial slices, acquisition time = 6 min 53 s. A diffusion tensor image sequence was applied with the following parameters: TR = 7173 ms, TE = 78 ms, matrix = 115 × 115, FOV = 230 mm × 230 mm, 50 axial slices, slice thickness = 3 mm, diffusion directions = 32, acquisition time = 9 min 7 s. In addition, axial T2-weighted MR images were acquired with the parameters: TR = 2500 ms, TE = 80 ms, matrix = 332 × 225, FOV = 250 mm × 220 mm, slice thickness = 6 mm, 18 axial slices, acquisition time = 55 s. The anatomical MR images were re-evaluated for any structural abnormalities and were reported as normal in all subjects.

2.3. Voxel-based morphometry

T1-weighted 3D TFE data were analysed using FSL-VBM (Douaud et al., 2007), an optimised voxel-based morphometry protocol (Good et al., 2001) carried out using FSL tools (Smith et al., 2004). First, structural images were brain-extracted. Then, a tissue-type segmentation was carried out. The resulting grey matter partial volume images were then aligned to MNI152 standard space using the affine registration tool FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001), followed by nonlinear registration using FNIRT. Second, the registered images were averaged to create a study-specific template. Then, we registered all the grey matter images to the template, and smoothed these modulated segmented images using an isotropic Gaussian kernel with a sigma of 3 mm. Finally, the voxel-wise GLM was applied using an analysis of covariance (ANCOVA), and the effects of age and gender were regressed out. The statistical threshold was set at $p < 0.05$, corrected for multiple comparisons (family-wise error, FWE) using the cluster-wise approach. In addition, the associations between GM volume changes and clinical variables (Hamilton Depression Rating Scale (HDRS) score) were also explored (FWE-corrected, $p < 0.05$).

2.4. Subcortical grey matter volumetric analysis

We segmented the bilateral hippocampus, amygdala, accumbens nucleus, caudate nucleus, pallidum nucleus, putamen nucleus and thalamus, respectively, from each subject's T1 3D TFE image using FMRIB's Integrated Registration and Segmentation Tool (FIRST), part of FMRIB's Software Library (FSL 5.0.8, http://www.fmrib.ox.ac.uk/fsl).

For each subject, brain tissue volume, normalised for subject head size, was estimated with SIENAX, part of FMRIB's Software Library. SIENAX starts by extracting brain and skull images from the single whole-head input data. The brain image is then affine-registered to the MNI152 space (using the skull image to determine the registration scaling); this is primarily aimed at obtaining the volumetric scaling factor, to be used for normalisation of head size.

The results of each step of the image processing, most importantly the subcortical segmentation, were carefully examined to ensure