Journal of Affective Disorders 183 (2015) 263–268

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Abnormal amygdala function in Parkinson's disease patients and its relationship to depression

Peiyu Huang [a], Min Xuan [a], Quanquan Gu [a], Xinfeng Yu [a], Xiaojun Xu [a], Wei Luo [b], Minming Zhang [a,*]

[a] Department of Radiology, Second Affiliated Hospital, Zhejiang University School of Medicine, China
[b] Department of Neurology, Second Affiliated Hospital, Zhejiang University School of Medicine, China

ARTICLE INFO

Article history:
Received 3 December 2014
Received in revised form
12 May 2015
Accepted 12 May 2015
Available online 21 May 2015

Keywords:
Parkinson's disease
Depression
Amplitude of low-frequency fluctuations
Functional connectivity

ABSTRACT

Depression is a common occurrence in patients with Parkinson's disease (PD). Thus, there may be a common neural mechanism underlying the two diseases. Lewy body accumulation in specific brain areas of PD patients may damage emotion-related functions, leading to depression. Among these areas, the amygdala may present with the earliest to be damaged in PD. However, it is still unclear whether amygdala structural and functional changes are related to depression in PD. We enrolled 19 depressed PD patients, 19 non-depressed PD patients, and 28 normal control subjects. Clinical assessment, including the Unified Parkinson's Disease Rating Scale, the Hamilton Rating Scale for Depression, and the Mini-Mental State Examination, was carried out on all the patients. Structural and resting-state functional brain images were also acquired to assess volumetric and functional changes of the amygdala in the patients. Results showed that although there is no significant volume change, left amygdala activity increased in the PD group compared with the normal control group, and it correlated with Hamilton Rating Scale for Depression scores. Furthermore, functional connectivity between the right amygdala and fronto-parietal areas was found to be decreased in the depressed PD patients compared with non-depressed PD patients. These results suggest that abnormal amygdala function may underlie the occurrence of depression in PD.

1. Introduction

Depression is one of the most common non-motor symptoms (Shulman et al., 2001) in patients with Parkinson's disease (PD). Although its prevalence varies according to different studies (Chaudhuri et al., 2006; Tandberg et al., 1996), there is general agreement that PD has a close relationship with depression (Aarsland et al., 2012; Moussavi et al., 2007; Reijnders et al., 2008). The cause of this close relationship between the two diseases is complicated. Negative feelings caused by the disabling symptoms is one important factor; however, much evidence also suggests that there are some common underlying brain mechanisms (Lieberman, 2006).

With the help of modern neuroimaging methods, a neural basis for depression in PD has been uncovered during the last few decades. Early studies using positron emission tomography revealed a reduction in cerebral blood flow in the prefrontal lobe, anterior cingulate gyrus, and other brain areas of depressed PD (dPD) patients (Matsui et al., 2006; Mayberg et al., 1990; Ring et al., 1994). Degenerations of the neurotransmitter systems, especially dopamine and serotonin, were also implicated by positron emission tomography studies (Ballanger et al., 2012; Remy et al., 2005; Strecker et al., 2011). Recently, the application of magnetic resonance imaging (MRI) has provided more information on understanding this mechanism. Structural alterations, including white matter degeneration and volumetric changes in the gray matter and sub-cortical structures (Cardoso et al., 2009; Feldmann et al., 2008; Li et al., 2010) were consistently reported. Evidence from functional MRI (fMRI) also helped with the understanding of regional brain activities (Wen et al., 2013) and the related brain network functions (Luo et al., 2013).

Hypothetically, the close connection between the two diseases should be related to some common pathological foundations. While Lewy body accumulation in the brain is a hallmark of PD pathology (Braak et al., 2004), there may be involvement of brain regions that participate in emotion processing, for example the amygdala (Hawkes et al., 2010). Amygdala abnormality may happen even before the clinical onset of PD symptoms, which might explain why depression can presage PD (Leentjens et al., 2003; Savica et al.,

* Correspondence to: Department of Radiology, Second Affiliated Hospital, Zhejiang University School of Medicine, No. 88 Jiefang Road, Shangcheng District Hangzhou, China, 310009. Tel./fax: +86 571 87315255.
E-mail address: zhangminming@zju.edu.cn (M. Zhang).

http://dx.doi.org/10.1016/j.jad.2015.05.029
0165-0327/

2010). Therefore, by looking into amygdala alterations in PD patients and its relationship to depression, we hoped to find a possible pathological link between the two diseases.

Previous investigation on the amygdala in PD patients revealed neuron loss and volume reduction; however, its linkage to depression in PD has not yet been fully studied, and only a few papers have tried to address this issue. Surdhar et al. (2012) found reduced amygdala volumes in dPD patients compared with non-depressed PD (ndPD) patients, but a postmortem study did not find amygdala pathology related to depression in PD (Frisina et al., 2009). These discrepancies still need to be addressed by new studies. Besides, there is a lack of investigation on the relationships between amygdala functions and depression in PD.

In the present study, we aim to investigate the structural and functional changes of the amygdala in PD patients and their relationship to depression. We hypothesize that altered amygdala structures and functions might be related to depression in PD.

2. Material and methods

2.1. Subjects

Two groups of PD patients (with and without depression, 21 for each group) were recruited from the Department of Neurology, Second Affiliated Hospital of Zhejiang University. Diagnosis of PD was made by a senior neurologist according to UK PD Brain Bank criteria. Unipolar depression was diagnosed by an experienced psychiatrist according to DSM-IV criteria. Scores of the Unified Parkinson's Disease Rating Scale (UPDRS), the Hamilton Rating Scale for Depression (HRSD), and the Mini-Mental State Examination (MMSE) were obtained from all subjects. Anti-parkinsonian medicine was terminated at least 12 h prior to the imaging scans. Table 1 shows detailed characteristics of the two groups. For exclusion criteria, we ruled out any subjects who had other neurologic or psychiatric disorders or brain trauma at any time in their lives. After the initial assessment, 4PD patients (2 depressed and 2 non-depressed) were excluded for having low MMSE scores. Twenty-six normal controls (NC) matched for age and sex were also enrolled. All the subjects had signed written informed consent before study. This research was approved by the Medical Ethic Committee of Zhejiang University.

2.2. Image acquisition

All the scans were performed on a 3.0 T GE Signa MR scanner in the Department of Radiology, Second Affiliated Hospital of Zhejiang University. Ear plugs and foam pads were used to reduce noise and head motion. Blood oxygenation level dependent (BOLD) images were acquired using GRE-EPI sequence (TR=2 ms, TE=30 ms, flip angle=13°, FOV=256 × 256 mm^2, voxel size=1 × 1 × 1 mm^3). A total of 185 resting-state BOLD images were acquired from each subject. Anatomical images acquired after the functional imaging consisted of a 3-D GRE T1-weighted sequence (TR/TE=5100 ms/1.2 ms; FOV=24 × 24 cm; matrix=256 × 256; slices=124; thickness=1.2 mm; and space=0 mm). Subjects were instructed to relax with their eyes closed without falling asleep, and without directed systematic thought. This was confirmed after completion of scanning.

Table 1
Demographic data.

	NC	dPD	ndPD	*P*
Age (*y*)	54.5 ± 15.4	55.1 ± 13.7	54.8 ± 9.2	0.988
M/F	9/19	10/9	10/9	0.253[a]
Duration (*y*)	–	5.2 ± 4.8	4.6 ± 5.0	0.713
UPDRS	–	57.7 ± 22.4	50.8 ± 22.4	0.349
H&Y stage	–	2.6 ± 0.7	2.3 ± 1.0	0.258
HRSD	–	19.9 ± 7.9	2.2 ± 1.5	0.000[b]
MMSE	–	27.2 ± 2.2	27.3 ± 2.6	0.895

UPDRS: Unified Parkinson's Disease Rating Scale; H&Y stage: Hoehn and Yahr stage; HRSD: Hamilton Rating Scale for Depression; MMSE: Mini-Mental State Examination.

[a] Chi-square test.

[b] Indicates significant difference between the dPD and ndPD group.

2.3. Image processing

Amygdala volumes were calculated by automated FreeSurfer segmentation to avoid subjective bias (Bertoni and Sclavi, 2010; Hanson et al., 2012; Morey et al., 2009; Nugent et al., 2013). Functional alterations were assessed by using resting-state fMRI and amplitude of low-frequency fluctuations (ALFF), a method developed by Zang et al. (Yu-Feng et al., 2007). ALFF examines low-frequency blood-oxygen level fluctuations within a specific frequency range (0.01–0.08 Hz), which are related to regional spontaneous neuron activities. ALFF has been widely applied to brain imaging studies on neuropsychiatric disorders, such as epilepsy (Zhang et al., 2010), schizophrenia (Hoptman et al., 2010), and depression (Liu et al., 2012). Besides local amygdala activities, we also tried to investigate the coordination between amygdala and other brain regions. This was achieved by using functional connectivity (FC), which calculates the temporal correlations between amygdala activities and activities of the other areas (Friston, 2011).

2.3.1. Volume calculation

Automated segmentation and labeling of the amygdala was performed using FreeSurfer (v5.3.0). This uses an affine rigid linear transformation and combines information about voxel intensity relative to a probability distribution for tissue classes, with information about the spatial relationship of the voxel to the location of neighboring structures obtained from a manually labeled atlas. Details of FreeSurfer subcortical segmentation are described in Fischl (2012). After getting the whole brain segmentations, the amygdala regions were returned to native space using the FreeSurfer library function mri_label2vol and the transformation matrix generated at the previous registration step.

2.3.2. Pre-processing of BOLD images

Preprocessing was performed using Data Processing Assistant for Resting-State fMRI (DPARSF, by YAN Chao-Gan, http://www.restfmri.net) and Resting-State fMRI Data Analysis Toolkit (REST, V1.8, http://www.restfmri.net). The first 10 images were excluded from the analysis. The remaining images were corrected for slice timing with the middle slice as a reference, realigned to remove head motion, normalized into the standard space using DARTEL, and resampled with 3 × 3 × 3 mm^3 voxel size. The resulting images were then smoothed using a 6-mm Gaussian kernel and proceeded to the next step.

2.3.3. ALFF calculation

ALFF values were calculated by using REST (State Key Laboratory of Cognitive Neuroscience and Learning in Beijing Normal University; http://resting-fmri.sourceforge.net). In brief, after band-pass filtering (0.01–0.08 Hz) and linear-trend removal, the time series was transformed to the frequency domain by using fast Fourier transformation, and the power spectrum was obtained. Then, the power spectrum obtained by FFT was square root-transformed and averaged across 0.01–0.08 Hz at each voxel. The averaged square root of activity in this frequency band was taken