Sci. Bull.
DOI 10.1007/s11434-016-1205-9

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Article

Life & Medical Sciences

Brain activity in Parkinson's disease patients with mild cognitive impairment

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Received: 15 August 2016 / Revised: 6 November 2016 / Accepted: 7 November 2016

Abstract Mild cognitive impairment (MCI) is common in patients with Parkinson's disease (PD), yet the underlying neural mechanisms of this disease state remain unclear. We investigated alterations in the spontaneous brain activity of PD patients with MCI (PD-MCI) relative to cognitively normal PD patients (PD-CN) and healthy control (HC) subjects. In this work, 13 PD-MCI patients, 16 PD-CN patients, and 16 HC subjects completed resting state functional MRI. Spontaneous brain activity was measured by calculating amplitude of low frequency fluctuation (ALFF) values across the whole brain. Between-group differences and correlations between ALFF values and cognitive test scores were analyzed. ALFF values decreased in the right superior temporal gyrus and increased in the left middle temporal gyrus and left superior frontal gyrus of PD-MCI patients compared with PD-CN patients. In the PD-MCI group, ALFF values in the left middle temporal gyrus were negatively correlated with Montreal Cognitive Assessment and vocabulary test scores, and the ALFF values in the left superior frontal gyrus were negatively correlated with vocabulary test scores. Our study demonstrates that PD-MCI is associated with abnormal spontaneous brain activity in the temporal and frontal lobes. These findings inform the underlying neural mechanism of cognitive impairment in PD.

Keywords Parkinson's disease · Mild cognitive impairment · Resting state functional MRI · Low frequency fluctuation

1 Introduction

Cognitive impairment is a common non-motor symptom in Parkinson's disease (PD). The severity of cognitive impairment in PD ranges from mild cognitive impairment (MCI) to dementia [1], and most notably affects executive function, attention, working memory, and visuospatial as well as language domains [2]. The incidence of MCI is estimated to be between 20 % and 40 % in the early phase of PD [3], and patients with MCI have a higher risk of developing dementia than those without MCI [4].

An increasing number of studies have focused on the mechanisms and risk factors associated with PD-MCI. Several studies used neuroimaging to determine whether specific neural changes are associated with PD-MCI. Atrophy of the temporal, parietal, and frontal cortices [5, 6], the thalamus [7], and the hippocampus [8] has been reported in PD-MCI. In addition, reduced fraction anisotropy values [9] and increased white matter hyper intensity

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Electronic supplementary material The online version of this article (doi:10.1007/s11434-016-1205-9) contains supplementary material, which is available to authorized users.

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burden have been identified in PD-MCI patients [10]. A longitudinal study suggested that frontal cortical thinning might be an early indicator of future cognitive decline and the transition of MCI to dementia in PD patients [11]. In contrast, Ukban et al. [12] used fMRI to longitudinally assess neural changes associated with altered working-memory in a population-based cohort of PD patients and found that the evolution of cognitive impairment was associated with posterior cortical changes such as decreased blood-oxygen level-dependent (BOLD) signal intensity in the right fusiform gyrus, right vermis, and left inferior temporal cortex, as well as increased BOLD signal intensity in the right parietal cortex and left prefrontal cortex.

While the abovementioned studies provided useful information about the neural correlates of cognitive impairment in PD, current knowledge of the mechanisms underlying PD-MCI remains limited. For example, no study to date has investigated patterns of spontaneous brain activity related to MCI in PD patients. The amplitude of low frequency fluctuation (ALFF) in BOLD signal on resting state fMRI can be used to characterize spontaneous brain activity [13]. The fMRIALFF (0.01–0.08 Hz) values were used to examine baseline brain activity in children with attention deficit hyperactivity disorder [14]. Hou et al. [15] found that spontaneous brain activity in PD patients was altered in two frequency bands, slow-4 (0.027–0.073 Hz) and slow-5 (0.010–0.027 Hz), using the ALFF method. Moreover, Hu et al. [16] used ALFF values to compare differences in neural activity among depressed PD patients, non-depressed PD patients, and healthy control subjects, and concluded that ALFF values in the left median cingulated cortex were significantly elevated according to depressive status. ALFF values have also been used to investigate intrinsic neural oscillations in PD patients on and off of L-dopa therapy [17] and to distinguish PD patients from healthy control subjects [18]. Accordingly, we used this method in the present study to investigate whether PD-MCI is associated with abnormal spontaneous brain activity.

2 Methods and materials

2.1 Subjects and methods

In total, 31 PD patients and 17 age- and gender-matched healthy control (HC) subjects were recruited for participation in this study. Of these, we excluded 2 PD patients and 1 HC subject due to remarkable head motion (head motion >3 mm or rotary motion >3°) on fMRI. Thus, 29 PD patients and 16 HC included in the final analysis.

PD was diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [19] and evaluated by the MDS Unified Parkinson's Disease Rating Scale III (MDS-UPDRSIII) and the Hoehn–Yahr disability scale.

A series of neuropsychological examinations were used to evaluate impairments in specific cognitive domains including memory [the memory section of the Alzheimer's Disease Assessment-Cognitive Part (ADAS-cog)], attention (remembering the order and reverse order of a number series), visuospatial ability (Webster's building blocks), and global cognition [the Montreal Cognitive Assessment (MoCA), Beijing Version]. PD-MCI was diagnosed according to the Movement Disorders Society Task Force guidelines [20] and impairment in at least two neuropsychological tests represented by two scores $\geq$1.5 standard deviations below the mean value of the appropriate norm in the same domain or in different domains. Patients who did not fulfill these criteria for MCI were classified as cognitively normal (PD-CN). The MoCA score was $\geq$26 in all PD-CN and HC subjects.

All experiments were performed according to the Declaration of Helsinki and were approved by the Institutional Review Board of Xuanwu Hospital in Beijing, China. Additionally, all subjects provided written informed consent for study participation.

2.2 Functional MRI acquisition

All MRI data were acquired using a SIEMENS Trio 3-T scanner. fMRI scans were acquired following a 12-h period of medication withdrawal in all patients. Resting state functional images were obtained using an echo-planar imaging (EPI) sequence with the following settings: repetition time = 2000 ms, echo time = 40 ms, voxel size = 4.0 × 4.0 × 4.0 mm, slice thickness = 4.0 mm, axial slices = 28 layers, flip angle = 90°, and scanning time = 8 min.

2.3 Data preprocessing

All preprocessing was performed using the Data Processing Assistant for RS-fMRI (DPARSF) version 2.0. The first 10 time points were discarded to allow for scanner calibration and subject acclimation. The remaining data were slice-time corrected and aligned to the first image of each session for motion correction. Images were then spatially normalized to a standard brain space template (the Montreal Neurological Institute template). Functional volumes were resampled to 3.0 × 3.0 × 3.0 mm isotropic voxels and finally images were smoothed with an 8-mm full-width at half maximum Gaussian filter to increase the signal-to-noise ratio. Linear trends were removed and every voxel was band-pass filtered ($0.01 < f < 0.08$ Hz) to remove the effects of low-frequency drift and high-frequency noise.