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Fractional amplitude of low-frequency fluctuations is disrupted in Alzheimer's disease with depression

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HIGHLIGHTS

- Depression can reduce cognitive function in Alzheimer's disease (AD).
- AD with depression exhibited higher fALFF in several brain regions, including fusiform gyrus, caudate nucleus, and middle temporal gyrus, and lower fALFF in the supplementary motor area.
- This pattern might be an important neuropathophysiologic characteristic of depression in AD.

ABSTRACT

Objective: To explore brain activity in AD with depression (D-AD) based on fractional amplitude of low-frequency fluctuation (fALFF).
Methods: Twenty-two D-AD and 21 AD without depression patients (nD-AD) were examined by magnetic resonance imaging during resting state. Neuropsychiatric Inventory and Hamilton Depression Rating Scale were employed to assess the severity of depression. We analysed the characteristics of fALFF in D-AD differing from nD-AD. We also examined the correlation between fALFF and the depression severity.
Results: D-AD patients had higher fALFF in right fusiform gyrus, left caudate nucleus, and right middle temporal gyrus (MTG), meanwhile lower fALFF in supplementary motor area (SMA) than nD-AD patients.
Conclusions: Abnormal fALFF changes in fusiform gyrus, caudate nucleus, MTG and SMA may be important neuropathophysiologic characteristics of depression in AD.
Significance: We have clarified the potential neuropathological changes of depression in AD based on fALFF method, which is crucial for effective intervention.

1. Introduction

Depression is common in Alzheimer's disease (AD). Chi et al. (2015) and Lyketsos and Lee (2004) reported that the incidence of depression is 40%, and 80% of AD patients develop depression to some extent in the whole course. Depression in AD can reduce cognitive function, increase burden on caregivers (Zahodne et al., 2015). To date, very few antidepressants have proved effective in treating depression in AD, despite their efficacy for treating major depressive disorder (MDD) (Khundakar and Thomas, 2015). Therefore, understanding the neural mechanisms underlying depression in AD is critical for developing more effective interventions.

Although neuroimaging is one of the main tools that can help us elucidate the neuropathology of depression in AD, results using these methods have been mixed. Structural brain imaging studies have reported that D-AD have smaller gray matter volume (GMV)

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in several brain regions, including temporal and parietal lobe than nD-AD (Son et al., 2013; Lebedev et al., 2014). Hu et al. (2015) found that depression score on the Neuropsychiatric Inventory (NPI) of mild cognitive impairment and AD was associated with GMV of left middle frontal cortex (MFC). Functional brain imaging has demonstrated that hypoperfusion or hypometabolism in frontal lobe is associated with D-AD. However, results have been mixed with respect to the different sub-regions of the frontal lobe. Some studies reported that D-AD exhibited lower perfusion in MFC and dorsolateral prefrontal cortex (Holthoff et al., 2005), left anterior cingulate cortex (ACC) (Kataoka et al., 2010), right superior prefrontal cortex (Lee et al., 2006), left prefrontal cortex (Akiyama et al., 2008; Oshima et al., 2014), and bilateral superior frontal cortices (SFC) (Hirono et al., 1998) than nD-AD. Additionally, Honda et al. (2014) also reported AD patients with higher scores on the Geriatric Depression Scale had significantly more hypoperfusion in left inferior frontal cortex. In contrast, several studies found no relationship between frontal lobe changes and depression in AD. One study of Galynker et al. (2000) indicated that hypoperfusion in frontal lobe is associated with the severity of negative dementia-related symptoms, but not with depressive symptoms in patients with AD. Further, Levy-Cooperman et al. (2008) found D-AD had hypoperfusion in right SFC, bilateral MFC, and bilateral anterior cingulate cortex, but did not reach statistical significance. These inconsistencies may be related to limitations in image-analysis methods, or variations in the severity of AD and depression, and the effect of drugs.

Rest state functional magnetic resonance imaging (rs-fMRI) is an important imaging technology, which allows us to explore neuropathophysiology of MDD and AD. fMRI, based on blood-oxygenation level dependent signals, might have better temporal and spatial resolution than photon emission computed tomography. Our recently published study using homogeneity (ReHo) method showed that D-AD had lower ReHo in right precentral gyrus, SFC, MFC, and right inferior frontal cortex than nD-AD (Guo et al., 2015). Using degree centrality method, we also reported that functional connectivity was lower in the right MFC, and pre- and postcentral gyri of D-AD patients (Guo et al., 2016).

Another important method of analyzing rs-fMRI data is to examine the spontaneous low-frequency fluctuations (LFF) of the human brain. LFF amplitude (ALFF) and fractional LFF amplitude (fALFF) are thought to reflect the strength of intrinsic spontaneous brain activity. ALFF represents the amplitude in the low-frequency band (e.g., 0.01–0.08 Hz) (Zang et al., 2007). Although ALFF is effective at detecting LFF, it may also include LFF fluctuations over 0.1 Hz (Zou et al., 2007). fALFF, normalized indexes for the ALFF, can measure LFF specifically within a specific frequency range (Zou et al., 2007).

Given the nervous system deficits revealed in studies of MDD and D-AD, activity change in the temporal and frontal regions might be associated with D-AD. To test this hypothesis, we analyze the characteristics of fALFF from rs-fMRI data, and reveal changes of brain activity in D-AD.

2. Materials and methods

2.1. Patients

The participants included 43 AD patients who met the diagnostic criteria for dementia as a result of Alzheimer's disease (recommended by the National Institute on Aging-Alzheimer's Association workgroup for probable AD (McKhann et al., 2011)), scored between 20 and 24 on the Mini-Mental State Examination, and scored 1 on the Clinical Dementia Rating. The severity of depression was quantified using the 17-item Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1967). Depressed subjects met DSM-IV criteria for MDD (Gmitrowicz and Kucharska, 1994) and had a score of 7 or greater on the HAMD-17. Participants were also administered the depression domain of Neuropsychiatric Inventory (D-NPI) (Cummings et al., 1994), and D-NPI scores $\geq$4 are indicative of clinical significance referring to the recommendations of clinical trials (Schneider et al., 2001). Education of every participant was more than six years, and age ranged from 65 to 80. Participants who had history of alcoholism or psychiatric disorders, or were taking antidepressant drugs were excluded. Ethics Committee of Tongde Hospital of Zhejiang Province approved this study. Every participant (or his/her legal guardian) signed informed consent.

2.2. MRI scanning

Imaging data was acquired using a 3T Siemens scanner (Siemens Magnetom Verio; Siemens Medical Systems, Erlangen, Germany) with an 8-channel birdcage head coil and foam padding to reduce head motion. All participants were informed to stay still, keep their eyes closed, and not think of anything in particular. Bold fMRI images were obtained using an echo-planar imaging sequence with the following parameters: 33 axial slices, thickness/gap = 4.8/0 mm, in-plane resolution = 64 $\times$ 64, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, and field of view (FOV) = 200 $\times$ 200 mm^2. Each acquisition consisted of 200 brain volumes. A 3D high-resolution T1-weighted anatomic image was also acquired using a magnetization-prepared rapid gradient echo images with the following parameters: 128 sagittal slices, slice thickness/gap = 1/0 mm, in-plane resolution = 512 $\times$ 512, TR = 1900 ms, TE = 2.48 ms, inversion time (TI) = 900 ms, flip angle = 9°, and FOV = 256 $\times$ 256 mm^2.

2.3. Data processing

Functional images were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and DPARSF (http://www.restfmri.net). Before preprocessing, the first 10 volumes of functional images were discarded to allow the signal to reach equilibrium and to allow participants to adjust to the scanner noise. The remaining rs-fMR images were corrected for acquisition delays (slice timing), realigned before spatial normalization (nonlinear registration), and smoothed (FWHM 6 mm). All smoothed images were filtered using a typical temporal band pass to reduce the effects of low-frequency drift and high-frequency noise, and to extract frequencies below 0.08 Hz. After that, the data were detrended to remove the linear trends within the time series. Finally, several sources of spurious variance, including six head-motion parameters and the average signals from cerebrospinal fluid and white matter, were regressed out as covariates.

2.4. fALFF calculation

fALFF was calculated using REST software (http://www.rest-fmri.net). The preprocessed time series were first converted to a frequency domain with a fast Fourier transform and the power spectrum was obtained. The square root of the power spectrum was computed at each frequency of the power spectrum and the averaged square root was obtained across 0.01–0.08 Hz at each voxel. Finally, fALFF was calculated as the ratio of the low-frequency power spectrum (0.01–0.08 Hz) to the power spectrum of the entire frequency range.

2.5. Statistical analyses

To explore the differences in fALFF between the groups, a second-level random-effect two-sample t test was performed on