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Abnormal degree centrality in Alzheimer's disease patients with depression: A resting-state functional magnetic resonance imaging study

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ABSTRACT

Depression is common in Alzheimer's disease (AD) and occurs in AD patients with a prevalence of up to 40%. It reduces cognitive function and increases the burden on caregivers. Currently, there are very few medications that are useful for treating depression in AD patients. Therefore, understanding the brain abnormalities in AD patients with depression (D-AD) is crucial for developing effective interventions. The aim of this study was to investigate the intrinsic dysconnectivity pattern of whole-brain functional networks at the voxel level in D-AD patients based on degree centrality (DC) as measured by resting-state functional magnetic resonance imaging (R-fMRI). Our study included 32 AD patients. All patients were evaluated using the Neuropsychiatric Inventory and Hamilton Depression Rating Scale and further divided into two groups: 15 D-AD patients and 17 non-depressed AD (nD-AD) patients. R-fMRI datasets were acquired from these D-AD and nD-AD patients. First, we performed a DC analysis to identify voxels that showed altered whole brain functional connectivity (FC) with other voxels. We then further investigated FC using the abnormal DC regions to examine in more detail the connectivity patterns of the identified DC changes. D-AD patients had lower DC values in the right middle frontal, precentral, and postcentral gyrus than nD-AD patients. Seed-based analysis revealed decreased connectivity between the precentral and postcentral gyrus to the supplementary motor area and middle cingulum. FC also decreased in the right middle frontal, precentral, and postcentral gyrus. Thus, AD patients with depression fit a 'network dysfunction model' distinct from major depressive disorder and AD.

1. Introduction

The most significant non-cognitive features of Alzheimer's disease (AD) are the behavioral and psychological symptoms of dementia (BPSD). Of all the BPSD, the prevalence of depression is the highest, at 40% (Chi et al., 2015). It increases burdens on caregivers, reduces quality of life, and leads to more rapid decline and higher mortality in patients. However, there are very few medications that are useful for treating depression in patients with AD (Khundakar and Thomas, 2015). Therefore, understanding the brain abnormalities in AD patients with depression (D-AD) is crucial for developing effective interventions.

The development of neuroimaging techniques has provided a tool for detecting brain changes in AD patients with depression. Using single photon emission computed tomography, studies have shown that D-AD patients have hypoperfusion in the right orbitofrontal, inferior frontal, superior frontal, bilateral middle frontal, and anterior cingulate gyrus (ACG) (Honda et al., 2014; Levy-Cooperman et al., 2008). ^{1}H-magnetic resonance spectroscopy and diffusion tensor imaging (DTI) studies have also shown that depression in AD is associated with specific neurochemical and white matter changes. Tsai et al. (2013) found that Geriatric Depression Scale-Short Form scores correlated positively with the choline/creatine (Cr) ratio in the left dorsolateral prefrontal cortex (DLPFC), and myo-inositol/Cr in both the left and right cingulate gyrus. Di Paola et al. (2015)) also found that depression severity was related to fractional anisotropy (FA) and mean diffusivity (MD) at the level of the corpus callosum rostrum. The processing of emotion and cognition is based on a network of integrative information from several brain regions (Smith and Lane, 2015; Wang et al., 2015). Resting-state functional magnetic resonance imaging (R-fMRI) studies have shown that brain functional alterations in major depressive disorder (MDD) are not limited to regional changes but are exhibited at the level of functional integration within the prefrontal-limbic network. This includes the amygdala, ventral striatum, DLPFC, ventrolateral prefrontal cortex, medial prefrontal cortex (mPFC), and ACG, which are involved in both

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the processing and regulation of emotion (Kupfer et al., 2012). AD patients appear to have a disrupted default mode network (DMN), which is a well-established network that includes brain regions such as the posterior cingulated cortex (PCC), precuneus, mPFC, inferior parietal cortex, medial temporal cortex, and hippocampus (Zhong et al., 2014). Using the amplitude of low-frequency fluctuations (ALFF) analysis method, Liang et al. (2014) found that ALFF changes in the PCC and precuneus were significantly correlated with emotional states, as measured by the Geriatric Depression Scale, in mild cognitive impairment (MCI) and AD patients. In our recently published study (Guo et al., 2015), a regional homogeneity (ReHo) method was used to measure the regional characteristics of AD patients with depression. The results showed that compared with non-depressed AD (nD-AD) patients, those with depression had decreased ReHo in the right precentral, superior frontal, and middle frontal gyrus (MFG), and in the right inferior frontal cortex. Based on these findings, we hypothesized that these changes observed in regions related to DMN and the prefrontal-limbic network may be a disease biomarker in D-AD patients.

Degree centrality (DC), measured by R-fMRI, has recently gained great attention. This graph-based measurement of network organization reflects the number of instantaneous functional connections between a region and the rest of the brain within the entire connectivity matrix of the brain. Thus, it can assess how much a node influences the entire brain and integrates information across functionally segregated brain regions. Therefore, voxel-wise centrality maps have provided novel insights into the patterns and complexity of functional connectivity in several diseases, such as schizophrenia (Wheeler et al., 2015), MDD (Shen et al., 2015), and Parkinson's disease (Baggio et al., 2014).

In our recent study (Guo et al., 2015), the ReHo method was used to measure the regional characteristics of AD patients with depression, but the DC measure was not calculated. Therefore, focusing on network architecture, the current study aimed to investigate the intrinsic dysconnectivity pattern in whole-brain functional networks at the voxel level, in AD patients with depression. First, we performed DC analysis to identify voxels that showed altered FC with other voxels. Then, we conducted further FC analyses using the regions that showed significant alterations in the DC analysis, to provide detailed information regarding the connectivity between a voxel and the particular regions that were changed.

2. Materials and methods

2.1. Patients

This study was approved by the Ethics Committee of Tongde Hospital of Zhejiang Province, China. All patients (or their legal representatives) completed formal written consent prior to the MR scanning. The participants were 32 AD patients who met the criteria for a diagnosis of probable AD according to the National Institute on Aging-Alzheimer's Association guidelines (McKhann et al., 2011), scored 20–24 on the Mini-Mental State Examination, and 1 on the Clinical Dementia Rating scale (CDR). All patients were right-handed, had more than 6 year education, and were aged 65–80 years. Patients were excluded if they had a history of alcoholism, neurological disorders, or psychiatric disorders. Participants were also excluded if dual-echo MR images showed two or more hyperintense lesions with diameters of ≥5 mm, or more than four hyperintense lesions with diameters of 0–5 mm.

2.2. The assessment of depression

Depression was confirmed using the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (Gmitrowicz and Kucharska, 1994). Depression severity was evaluated using the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1967) and Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). A HAMD score of ≥7 and a D-NPI score of ≥4 indicate clinically significant symptoms (Schneider et al., 2001). We classified the AD patients who were diagnosed with depression as the depressed AD group D-AD, and those who were not as non-depressed AD (nD-AD). All scales were administered by trained clinical neuropsychologists.

2.3. MRI scan

Imaging data were acquired using a 3T Siemens scanner (Siemens Magnetom Verio; Siemens Medical Systems, Erlangen, Germany) at the Tongde Hospital of Zhejiang Province. All patients were placed in a birdcage head coil and foam padding fitted to reduce head motion. They were asked to stay still, keep their eyes closed, and not think of anything in particular. Functional 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 × 64, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, and field of view (FOV) = 200 × 200 mm^2. Each condition consisted of 200 functional volumes. In addition, anatomical T1-weighted whole brain magnetization-prepared rapid gradient echo images were obtained using the following parameters: 128 sagittal slices, slice thickness/gap = 1/0 mm, in-plane resolution = 512 × 512, TR = 1900 ms, TE = 2.48 ms, inversion time (TI) = 900 ms, flip angle = 9°, and FOV = 256 × 256 mm^2.

2.4. Data processing

All R-fMRI data preprocessing was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting State fMRI (http://www.restfmri.net). Prior to preprocessing, the first 10 volumes of the functional images were discarded to remove initial transient effects and to allow the participant to adjust to the scanner noise. Then, the remaining R-fMRI images were acquired with slice timing for the acquisition delay between slices and head motion correction. All participants had less than 1.5 mm maximum displacement in x, y, or z and 1.5° of angular motion during the whole R-fMRI scan. All realigned images were acquired with spatial normalization and then resampled to 3-mm isotropic voxels. The resulting normalized functional images were spatially smoothed using an isotropic Gaussian filter (6-mm FWHM). All smoothed images were filtered using typical temporal bandpass (0.01–0.08 Hz) to reduce low-frequency drift, physiological high-frequency respiratory and cardiac noise. Linear trends were removed within each time series. Finally, several sources of spurious variances were removed by linear regression, including six head motion parameters, along with average signals from cerebrospinal fluid and white matter.

2.5. DC calculation

For the calculation of voxel-wise DC, we performed voxel-based whole-brain correlation analysis on the preprocessed R-fMRI data, as has been well described in previous studies (Li et al., 2016). Pearson's correlation coefficients (r) were computed between all pairs of brain voxels in the gray matter mask. We then converted the Pearson's correlation data to normally distributed Fisher's Z-scores and constructed the whole-brain functional network by thresholding each correlation at $r > 0.25$ (Buckner et al., 2009a). The DC for a given voxel was calculated as the sum of the significant connections in at the individual level. Finally, the voxel-wise DC values were also transformed into a Z-score map using the Fisher-Z transformation to improve normality. Because of the uncertainty of interpretation and detrimental effects on test-retest reliability, only positive correlations were considered in the DC calculations.

To examine the between-group DC difference, a two sample *t*-test was performed between the two groups using REST. AlphaSim, a