Psychiatry Research: Neuroimaging 222 (2014) 29–36

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Altered local activity and functional connectivity of the anterior cingulate cortex in elderly individuals with subthreshold depression

Rui Li [a,b,c], Zhenling Ma [a,d], Jing Yu [a,e], Yong He [f], Juan Li [a,b,c,*]

[a] Center on Aging Psychology, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China
[b] Magnetic Resonance Imaging Research Center, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China
[c] Research Center of Emotion Regulation, Beijing Normal University, Beijing 100875, China
[d] School of Nursing, Peking Union Medical College, Beijing 100144, China
[e] School of Psychology, Southwest University, Chongqing 400715, China
[f] State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China

ARTICLE INFO

Article history:
Received 8 June 2013
Received in revised form
23 February 2014
Accepted 24 February 2014
Available online 4 March 2014

Keywords:
fMRI
Resting state
Anterior cingulate
Depression

ABSTRACT

The anterior cingulate cortex (ACC) is recognized as a key structure in the pathogenesis of depression. This study aimed to investigate the resting-state regional activity and functional connectivity of the ACC in a community sample of elderly individuals with subthreshold depression (StD). We employed resting-state functional magnetic resonance imaging to acquire data from 19 elderly subjects with StD and 18 normal controls. We used a regional amplitude of low-frequency fluctuation (ALFF) analysis and a correlation-based functional connectivity (FC) approach to explore changes in local activity and remote connectivity of the ACC in StD. Compared to controls, the StD group demonstrated increased ALFF in the anterior portion of the dorsal ACC (adACC). The adACC also displayed increased FC with the dorsolateral prefrontal cortex and supplementary motor area and decreased FC with several subcortical regions. The FC levels of the adACC displayed a trending correlation with self-reported depressive symptoms. This study is the first to reveal the ACC changes in resting-state activity and connectivity in the elderly with StD, suggesting that altered ALFF/FC of the adACC is an important feature of StD.

1. Introduction

Geriatric depression has been conceptualized as a neurologic disorder resulting from the dysfunction of the frontal-subcortical circuits that govern mood and cognition (Mayberg et al., 1999; Alexopoulos, 2002; Ajilore et al., 2014; Kumar et al., 2013). Neuroimaging studies of patients with depression have demonstrated that subthreshold depressive symptoms, referred to as subthreshold depression (StD), in older adults is accompanied by structural brain changes, including the frontal volume reductions (Kumar et al., 1997, 1998; Taki et al., 2005), frontal asymmetry decrements (Kumar et al., 2000), white matter lesions (Mackin et al., 2013a), and decreased regional cerebral blood flow in the frontal regions (Dotson et al., 2009) as well as functional activity alterations (Ma et al., 2013).

The anterior cingulate cortex (ACC) is an essential part of the frontal-subcortical circuit, and it plays a modulatory role in cognition and emotion (Vogt et al., 1992; Bush et al., 2000). Numerous neuroimaging studies have reported that geriatric depression is closely associated with structural (Ballmaier et al., 2004; Bae et al., 2006; Elderkin-Thompson et al., 2009), functional (Aizenstein et al., 2009), and metabolic (Mayberg et al., 1999; Alexopoulos et al., 2012) abnormalities of the ACC. Recent molecular and neuroimaging studies have further theorized that altered baseline or resting-state activity in the ACC is associated with psychological abnormalities observed in patients with depression (Dantzer et al., 2008; Horn et al., 2010; Khundakar et al., 2011).

The ACC is an anatomically and functionally heterogeneous region (Vogt et al., 1992; Bush et al., 2000; Pizzagalli, 2011; Shackman et al., 2011). Previous neuroimaging studies have suggested that the dorsal ACC (dACC), also known as the middle cingulate cortex, and the rostral–ventral ACC are specialized for cognitive and affective processes, respectively (Bush et al., 2000). In depression, decreased metabolism or hypoactivity has been reported in the dACC (de Asis et al., 2001; Drevets et al., 2002), whereas increased metabolism or hyperactivity has been reported in the subgenual region of the rostral ACC (Mayberg et al., 1999).

* Corresponding author at: Center on Aging Psychology, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, No. 16 Lincui Road, Chaoyang District, Beijing 100101, China. Tel.: +86 10 6486 1622; fax: +86 10 6487 2070.
E-mail address: lijuan@psych.ac.cn (J. Li).

http://dx.doi.org/10.1016/j.pscychresns.2014.02.013
0925-4927

However, recent imaging findings have suggested that the anterior portion of the dACC (adACC) acts as a processing hub for both negative affect and cognitive control (Shackman et al., 2011). In a resting-state functional magnetic resonance imaging (fMRI) study of major depression, the adACC was recognized as an essential region of the dorsal nexus that displays increased depression-associated connectivity with the following 3 different brain networks: the default mode network (DMN), cognitive control network, and affective network (Sheline et al., 2010).

Previous investigations of the regional power of baseline activity, called the amplitude of low-frequency fluctuation (ALFF), in resting-state fMRI, have found that the ACC and several other DMN regions display higher ALFF values (Zang et al., 2007). Moreover, it has recently been reported that patients with depression exhibit abnormal resting-state ALFF in the ACC (Guo et al., 2012). Furthermore, resting-state fMRI studies have widely reported high correlations of baseline activity, which is usually called resting-state functional connectivity (FC), between different brain regions belonging to the same neuroanatomical or functional systems (Greicius et al., 2003; Koyama et al., 2010). In patients with depression, abnormal resting-state FC in the ACC has recently been demonstrated, such as decreased pregenual ACC–dorsomedial thalamus connectivity (Anand et al., 2009), decreased pregenual ACC–anterior insula connectivity (Horn et al., 2010), and increased subgenual ACC–thalamus connectivity (Greicius et al., 2007). Thus, these previous studies have provided evidence that both regional ALFFs and FC patterns of the ACC are associated with the underlying pathology of depression. However, it remains largely unclear whether these abnormal regional and FC patterns appear in individuals with StD.

Evidences in support of an important role of the ACC in depression are mainly from neuroimaging studies of patients with clinical depression. Previous epidemiological studies have reported that older individuals with StD are at an increased risk of developing major depression (Beekman et al., 2002), and older adults with StD also show declines in heath and overall functioning, which may yield increased healthcare utilization and low quality of life (Judd et al., 2002; Lyness, 2008; Vahia et al., 2010). However, we speculated that the abnormalities in ACC function observed in clinical depression may already exist at an earlier stage, which is the preclinical StD stage. Therefore, the aim of the present study was to employ fMRI to investigate baseline or resting-state alterations that may occur in the ACC of elderly individuals with StD. Our research focused on changes in the regional activity of the ACC as well as on any potential connectivity alterations of this area compared to other regions. Low-frequency (0.01–0.08 Hz) blood oxygen level-dependent (BOLD) fluctuations of control and StD subjects during resting-state conditions were used to determine the following: (1) the specific locations of any abnormal baseline activity that might be associated with StD; and (2) the resting-state FC networks associated with the regions displaying abnormal ALFF (seed regions). Furthermore, we investigated the relationship between two potential fMRI metrics that may be useful for diagnosing StD and calculated their correlations with depressive symptoms, as measured by a self-reported scale.

2. Methods

2.1. Subjects

Nineteen elderly subjects with StD and 18 healthy normal control (NC) subjects from the local communities were included in the study. These subjects were previously used to investigate the regional homogeneity characteristics of whole-brain spontaneous fluctuations (Ma et al., 2013). Each subject was assessed using a standardized clinical evaluation protocol that included the Center for Epidemiologic Studies Depression Scale (CES-D), the Mini Mental State Examination (MMSE), the Trail Making Test (TMT) part A and B, and the Stroop tests with the Word and Color–Word subtasks. We used the CES-D to measure the depressive symptoms in the subjects. With reference to the previously reported inclusion criteria for StD (Cuijpers et al., 2006, Vahia et al., 2010, Yu et al., 2012), all elderly StD subjects had a CES-D score of 8 or more, and they did not meet the DSM-IV diagnostic criteria for major depression. In contrast, all NC subjects had a CES-D score of 5 or less. To exclude any potential cognitive impairment, all subjects met the MMSE cutoff of 24 or more (Shu et al., 2012; Li et al., 2013). We note that there were only two subjects who were with MMSE score of 24, and the others were all with MMSE score ≥ 26. The mean CES-D score in the StD group was 16.4 [range, 8–26; standard deviation (S.D.)= 4.9], and the mean CES-D score in the NC group was 1.1 (range, 0–5; S.D.= 1.6). None of our samples met the DSM-IV diagnostic criteria for MDD or had history of prior depressive episodes. Participants were excluded from this study if they had a past history of mental illness, neurological disorder, drug abuse, moderate to serious hypertension, or known systematic disease. During the study, none of the participants was taking antidepressants or any other psychotropic medications. The clinical and demographic characteristics of all of the subjects are shown in Table 1.

This study was approved by the Ethics Committee of the Institute of Psychology of the Chinese Academy of Sciences. All subjects provided written informed consent.

2.2. Data acquisition

Functional images were acquired under resting-state conditions with a 3-T Siemens scanner equipped for echo planar imaging (EPI) at the Imaging Center for Brain Research in Beijing Normal University. For each participant, 160 EPI functional volumes were collected. The following parameters were used: time repetition (TR), 3000 ms; time echo (TE), 30 ms; flip angle, 90°; field of view, 200×200 mm^2; 45 axial slices; thickness, 3.0 mm; gap, 0.6 mm; in-plane resolution, 64×64; and voxel size, $3.125 \times 3.125 \times 3.0$ mm^3. During the scan, subjects were instructed to keep their eyes closed and to think of nothing in particular. To aid in the localization of functional data, a high-resolution, three-dimensional T1-weighted structural image was also acquired for each subject with the following parameters: 176 slices; resolution, 256×256; voxel size, $1 \times 1 \times 1$ mm^3; TR, 1900 ms; TE, 2.2 ms; and flip angle, 9°.

2.3. Data preprocessing and analysis

Resting-state fMRI data analyses were processed with the Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI V2.0 Basic Edition (Yan and Zang, 2010).

Preprocessing: data preprocessing included slice timing correction, within-subject spatial realignment, between-subject spatial normalization to the Montreal Neurological Institute (MNI) coordinate space with $3 \times 3 \times 3$ mm^3 resampling, spatial smoothing with a 4-mm Gaussian kernel, linear detrending, and temporal band-pass filtering (0.01–0.08 Hz).

ALFF analysis: Fast Fourier Transform was first applied to each voxel to transfer the time series to a frequency domain for calculating the power spectrum, which was then square rooted and averaged across the low-frequency band (0.01–0.08 Hz). The averaged square root of the resting-state spontaneous activity at 0.01–0.08 Hz was defined as the ALFF. For standardization, the ALFF value of each voxel was divided by the global mean ALFF value. One-sample *t*-tests were then performed on each group to demonstrate the voxels that were significantly larger than 1 in the ACC area, which was defined by the Anatomical Automatic labeling atlas toolbox (Tzourio-Mazoyer et al., 2002). To detect the locations of between-group ALFF differences in the ACC, two-sample *t*-tests were performed. We applied a two-step approach for thresholding the statistical maps of the within-group analyses and between-group comparisons. The statistical maps of the within-group

Table 1
Characteristics of the StD, and healthy controls.

Characteristics	StD	NC	*p* Value
N (M/F)	19 (7/12)	18 (8/10)	0.64[a]
Age, years	66.5 ± 5.7	66.4 ± 3.9	0.96[b]
Education, years	13.2 ± 2.7	13.5 ± 2.8	0.75[b]
CES-D	16.4 ± 4.9	1.1 ± 1.6	< 0.01[b]
MMSE	28.3 ± 1.6	28.8 ± 1.5	0.26[b]
TMT A	31.05 ± 12.32	34.31 ± 9.66	0.38[b]
TMT B	19.10 ± 3.31	20.79 ± 5.57	0.35[b]
Stroop, word	19.10 ± 3.31	20.79 ± 5.57	0.27[b]
Stroop, color–word	29.21 ± 6.92	32.14 ± 7.62	0.23[b]

[a] *p* Value for gender distribution was obtained by χ^2test.
[b] *p* Values were obtained by *t*-test.