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

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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).

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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.

analyses and between-group comparisons were first determined by thresholding the resulting t-statistic maps at $p < 0.05$ and corrected by the false discovery rate (FDR). However, due to the limitation of a small sample size in our study, we also considered the regions that did not survive the strict criteria but met a relatively loose level of $p < 0.005$, uncorrected, as significant.

FC analysis: seed region-based linear correlation methods were used to perform the FC analyses. The seed region was defined by generating a 6-mm radius in the ACC and focusing on the voxels showing the highest statistical between-group differences. The time series of each voxel in the seed region were averaged, and this was taken as the seed reference time course. A linear correlation analysis was performed by calculating the correlation coefficient between the time course of the seed region and the time series of each voxel across the whole brain. A Fisher's *r*-to-*z* transform was then performed to convert the correlation coefficient map to *z* maps (FC maps) in order to improve the normality of these correlation coefficients. The individual *z* maps were entered into a one-sample *t*-test to determine the regions that showed significant FC with the seed region for each group. Finally, a two-sample *t*-test was performed on the individual *z* maps to identify the regions that showed significant differences in FC with the seed region between the 2 groups. The same statistical approaches as those described for the analyses of ALFF in the ACC were used for thresholding the FC maps.

Relationship between ALFF and FC: because ALFF and FC are metrics that measure regional activity and remote connectivity, respectively, and ACC abnormalities in ALFF and FC are both hypothesized to be associated with the underlying pathology of depression, we were thus interested in investigating the relationship between regional ALFF and FC in the regions demonstrating between-group differences. We calculated the correlations between ALFF in the seed region of the ACC and FC in the regions showing between-group connectivity differences for all the subjects. Several regions of interest (ROIs) were defined when the intersection of voxels exceeded the threshold of the two-sample *t*-test FC comparison map, and a 6-mm radius sphere was centered at the voxel showing the highest statistical difference. For each ROI, the mean FC value was extracted by averaging the *z* values over all the voxels within the ROI for each individual subject. The ALFF values of the voxels in the seed region of the ACC were also averaged for each subject. Finally, correlation analyses were performed between the ALFF value in the seed region and the FC value in each ROI of these subjects ($p < 0.05$, Bonferroni corrected).

Relationship between CES-D and ALFF/FC measures: to examine the relationship between depressive symptom measures and neuroimaging markers, correlations between CES-D scores and ALFF/FC measures were analyzed in the StD group. The ALFF value in the seed region and FC values in the ROIs, as defined above, were used to calculate their correlations with the CES-D scores ($p < 0.05$, Bonferroni corrected).

3. Results

3.1. Demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics of each group. There were no significant differences in age, gender, or years of education ($p > 0.05$) between the NC and StD groups. There were also no significant differences between the two groups on MMSE, TMT or Stoop tests ($p > 0.05$). In addition, there was no significant correlation of these cognition variables with ALFF/FC measurements ($p > 0.05$). The CES-D scores in StD however, were significantly higher than in that in the control group ($p < 0.01$).

3.2. Regional ALFF in the ACC

Fig. 1 depicts the ALFF maps of the ACC for NC (Fig. 1A) and StD (Fig. 1B) subjects (one-sample *t*-test, corrected by FDR, $p < 0.05$). Voxels showing higher ALFF values in the ACC of both groups were located in Brodmann areas (BA) 10, 24, and 32, including the dorsal and rostral–ventral ACC regions.

Fig. 2 depicts the between-group comparison results of ALFF in the ACC (two-sample *t*-test, $p < 0.005$, uncorrected). One cluster in the adACC (18 voxels; peak MNI coordinates: 6, 27, 27; BA 32) displayed increased ALFF in the StD group. No cluster displayed significantly decreased ALFF in the StD group compared to the NC group.

3.3. FC network of the adACC

Based on our results, the adACC was defined as the seed region for the whole brain FC analysis. This was used to further confirm whether a widespread abnormal connectivity existed with the areas showing increased ALFF in the StD subjects. Fig. 3 demonstrates the FC maps of the adACC in the NC and StD subjects (one-sample *t*-test, $p < 0.05$, corrected by FDR). The connectivity patterns of the adACC in both groups appeared very similar. The regions showing significant FC with the adACC included the middle/inferior/superior frontal gyrus, inferior parietal lobe, superior temporal gyrus, insula, hippocampus, thalamus, and cerebellum.

Fig. 4 depicts the results of the between-group FC comparison with the adACC. The results demonstrated that 6 clusters displayed altered connectivity to the adACC in the StD group (two-sample *t*-test, $p < 0.005$, uncorrected). Compared to the NC group, the StD group displayed increased FC in the left dorsolateral prefrontal cortex (DLPFC) and right supplementary motor area (SMA). Decreased FC was observed in 4 clusters in the right hemisphere: the inferior orbitofrontal gyrus, pallidum, thalamus, and anterior insula. The 6 regions showing abnormal FC in the StD group were defined as ROIs, and the details of these regions are listed in Table 2.

3.4. Relationship between regional ALFF and remote FC

We further examined the relationship between local activity in the adACC and the remote FC in the regions demonstrating between-group differences across all 37 subjects. As shown in Fig. 5, the right thalamus displayed decreased FC in the StD group, and we observed a significant negative correlation between its FC to the adACC and the regional ALFF value in the adACC ($r = -0.443$,

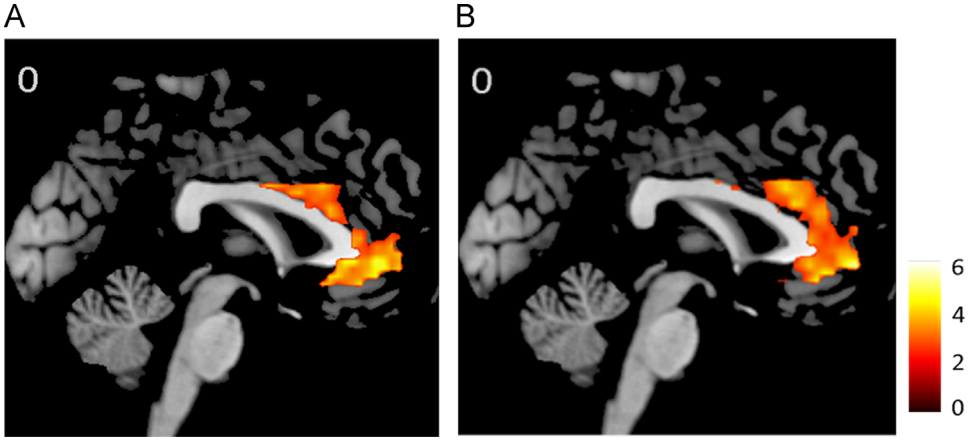

Fig. 1. Sagittal view of ALFF maps of the ACC in NC (A) and StD (B). *T* score bar is shown on the right.

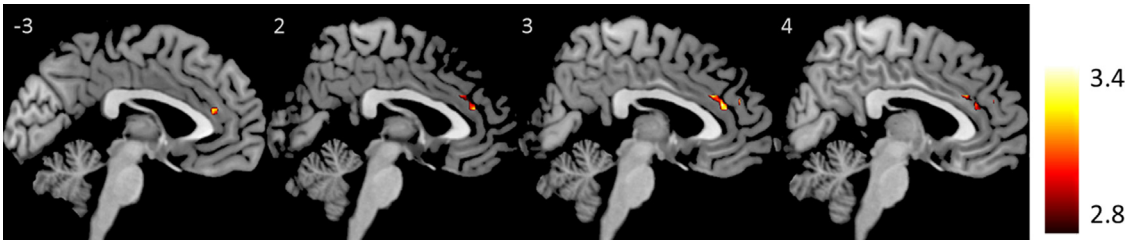

Fig. 2. Sagittal view comparing ALFF between the NC and StD groups. The figure shows increased ALFF in the adACC of StD subjects compared to control subjects. *T* score bar is shown on the right.

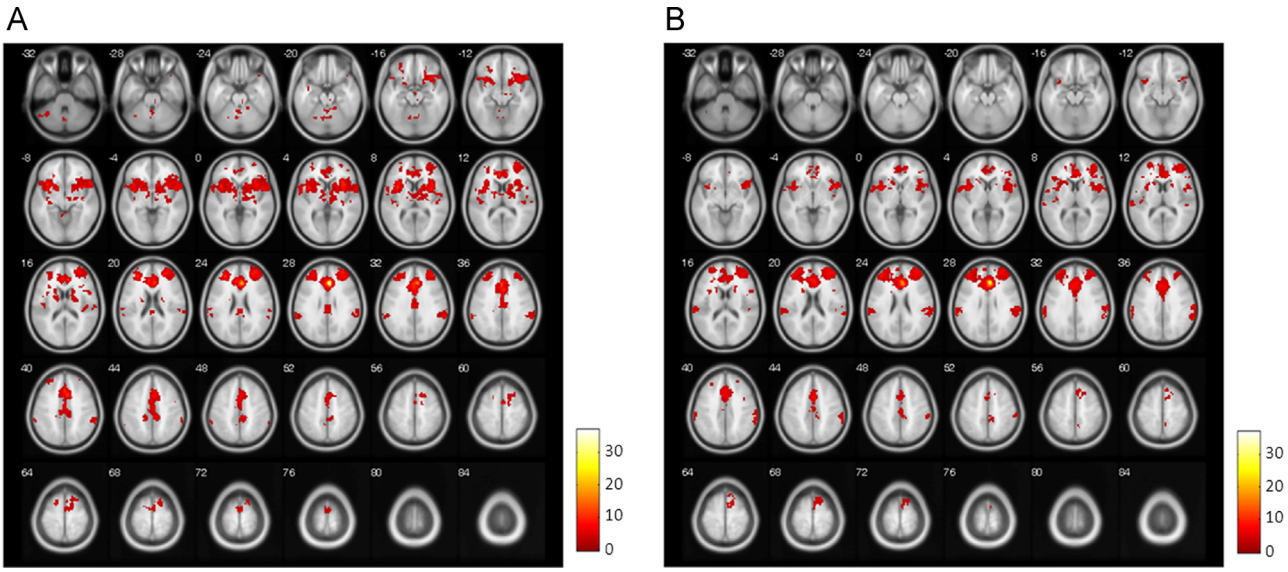

Fig. 3. Slice view of the FC maps of the adACC in NC (A) and StD (B). *T* score bar is shown on the right.

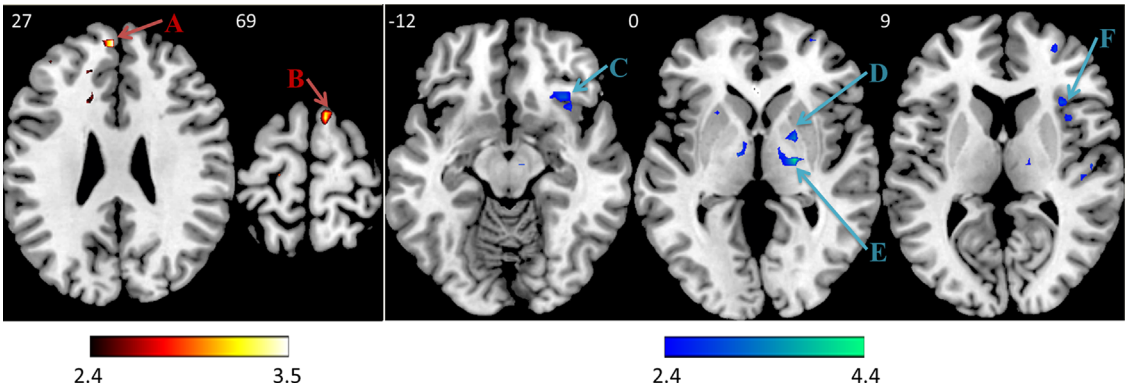

Fig. 4. Slice view comparing FC in the NC and StD groups. The red and blue clusters show the regions with respective increased and decreased FC in StD compared to controls. A, left DLPFC; B, right SMA; C, right inferior orbitofrontal cortex; D, right pallidum; E, right thalamus; and F, right anterior insula. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

$p < 0.05$, Bonferroni corrected). The right SMA showed increased FC in the StD group. We also observed a positive correlation trend between its FC to the adACC and the regional ALFF value in the adACC ($p < 0.05$, uncorrected).

3.5. Relationship between ALFF/FC measures and CES-D scores

The relationship between the fMRI-based measures, ALFF and FC, and depressive symptom levels (CES-D scores) were examined in the StD group. We did not find any significant correlations between regional ALFF values and the adACC and CES-D scores. At a more liberal threshold level ($p < 0.05$, uncorrected), we observed a trending negative correlation between the FC in the right anterior insula and the CES-D scores ($r = -0.402$, $p = 0.088$) (Fig. 6). We note here that after controlling for the variable Group, this tendency became more evident in all 37 subjects ($r = -0.355$, $p = 0.035$), possibly due to the increase in sample size. However, the sample size in the present study was not large enough to

Table 2
Regions showing between-group FC differences.

Comparison	Regions	L/R	BA	Peak MNI location			Maximal *t*-value	Cluster size (voxels)
				x	*y*	*z*		
StD > NC	Dorsolateral prefrontal cortex	L	9/10	−3	54	27	3.54	8
	Supplementary motor area	R	6	9	12	69	3.41	7
StD < NC	Inferior orbitofrontal gyrus	R	47	33	24	−12	3.14	7
	Pallidum	R		21	0	0	3.50	7
	Thalamus	R		21	−12	0	4.39	13
	Anterior insula	R	13	33	21	9	3.05	7

Note: L, left; R, Right.

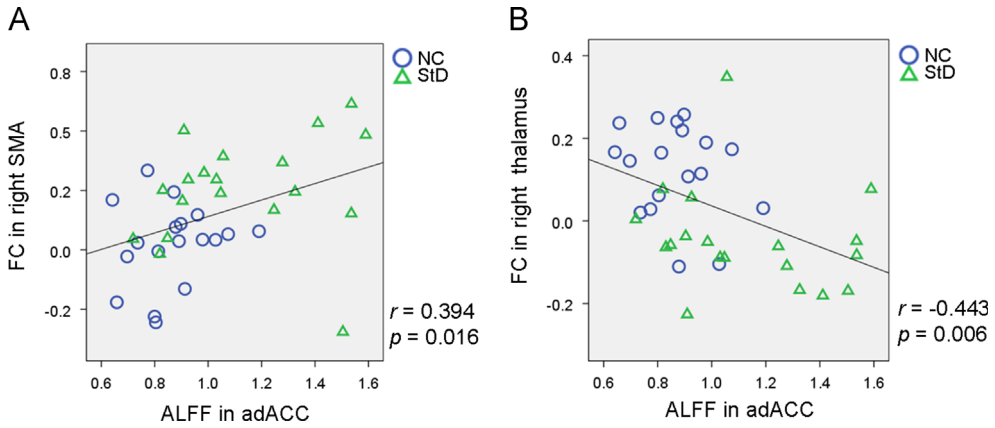

Fig. 5. Scatter plots of the significant relationship between ALFF and FC with the adACC ($p < 0.05$). A shows a significant positive correlation between ALFF in the adACC and the FC in right SMA, while B shows a significant negative correlation between ALFF in the adACC and FC in the right thalamus. Circular and triangular dots represent the data from the NC and StD groups, respectively.

provide sufficient statistical power to describe the relationship between them.

4. Discussion

In this study, we observed increased regional ALFF in the adACC in elderly individuals with StD compared to elderly controls. In StD subjects, the adACC displayed increased FC with the left DLPFC and right SMA and decreased FC with the inferior orbitofrontal cortex, anterior insula, thalamus, and pallidum. Moreover, we observed that higher ALFF in the adACC correlated with increased connectivity in the right SMA and decreased connectivity in the right thalamus, suggesting a possible intrinsic relationship between regional activity changes and remote connectivity alterations. The correlation analyses of the fMRI metrics and depressive symptoms demonstrated an obvious negative trending correlation between FC values in the right anterior insula and the CES-D scores of the StD group. Our results highlighted the potential for using resting-state fMRI as a biomarker of StD in older adults.

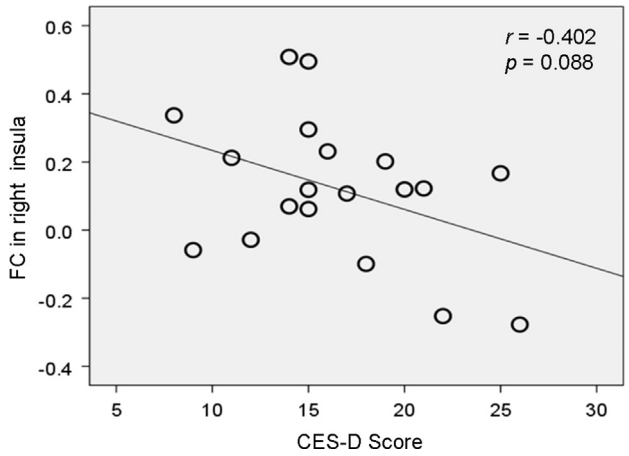

Fig. 6. Scatter plots of the negative relationship between FC in the right insula with the CES-D scores in the StD group. Each circular dot represents the data from 1 elderly StD participant.

4.1. Increased ALFF in the adACC of elderly individuals with StD

It has been demonstrated that neurobiological changes in the ACC play a role in the symptomatology of depression (Drevets, 2001; Davidson et al., 2002). In this study, we demonstrated altered resting-state spontaneous activity in the adACC, reflected by increased ALFF in elderly individuals with StD. Because the adACC has recently been suggested to act as a process hub for negative emotion and cognitive control (Aizenstein et al., 2009), the altered ALFF found in this critical region may be an important characterization feature of StD in elderly individuals. To the best of our knowledge, this is the first reporting of this finding.

Increased ALFF in the adACC may represent higher metabolic processing or neural hyperactivity in this area in StD individuals compared to controls. The increased activity of the ACC, including the dorsal (Bench et al., 1995; Buchsbaum et al., 1997; Mayberg et al., 1999) and rostral (Mayberg et al., 1997; Pizzagalli, 2011) regions, has usually been observed in patients in remission from major depression. In patients with clinical major depression, the dorsal regions have generally been reported to show decreased activity (de Asis et al., 2001; Drevets et al., 2002). It appears that

the regional activity changes we observed in the adACC of StD individuals may be different from those found in patients with clinical depression but similar to changes found in depression-treatment responders. Magnetic resonance spectroscopy studies have demonstrated increased glutamate, a major excitatory neurotransmitter tightly coupled to fMRI BOLD activity (Bonvento et al., 2002) and involved in the physiology of emotional problems (Sanacora et al., 2008), in the early stages of depressive disorder (Grimm et al., 2012), while it has been shown to progressively decrease in depressed patients (Sanacora et al., 2003). The increased regional ALFF values in the adACC may therefore be an important potential fMRI marker for subjects suffering from StD. To further elucidate the role of the adACC in depression, a longitudinal study is required in the future.

4.2. Altered FC with the adACC in elderly patients with StD

Consistent with its role as a process hub for negative affect and cognitive control (Shackman et al., 2011), we observed that the adACC was functionally connected with the frontoparietal and SMA regions, which are involved in cognitive control and executive functions (Devinsky et al., 1995; Carter et al., 1999; Hatanaka et al., 2003). We also observed that it was functionally connected with the orbitofrontal cortex, insula, thalamus, and hippocampus, which are implicated in emotional regulation (Drevets and Raichle, 1998; Menon and Uddin, 2010; Cauda et al., 2011). The FC comparison of the adACC demonstrated that the StD group displayed increased connectivity for the left DLPFC and right SMA and decreased connectivity for the right orbitofrontal gyrus, pallidum, thalamus, and anterior insula. It is worth noting that some of these regions, including the dorsolateral prefrontal, orbitofrontal, and insular cortices, have also shown StD-related abnormalities in regional homogeneity in our prior paper from this dataset (Ma et al., 2013). This suggested that, beyond the regional activity alterations observed in the adACC, the altered widespread remote connectivity for this region was also related to StD.

Increased connections in the DLPFC and SMA regions have previously been demonstrated in major depression using both resting- (Zhou et al., 2010) and task-based (Frodl et al., 2010) fMRI. The DLPFC plays an important role in the circuitry of emotional control; it monitors attention resources and guides emotional responses together with the dorsal ACC regions and other parietal regions (Bush et al., 2000; Taylor and Fragopanagos, 2005). The involvement of increased adACC–DLPFC connectivity in depression is particularly supported by a resting-state fMRI study that has identified these regions as the dorsal nexus linking the DMN, cognitive control network, and affective networks; they have highlighted the important role of increased adACC–DLPFC connectivity in depressive symptomatology (Sheline et al., 2010). In addition, numerous neuroimaging studies have also revealed hyper baseline metabolism (Phillips et al., 2003), increased resting-state connectivity (Sheline et al., 2010; Zhou et al., 2010), and increased activation (Grimm et al., 2008) in the DLPFC of patients with major depression. The SMA is also an important region that is functionally connected with the adACC (Stevens et al., 2011), and the connectivity between them has been speculated to be involved in conveying information about negative affect from the adACC to the motor areas involved in expressing emotion or executing goal-directed behavior (Shackman et al., 2011). The SMA has been found to have increased connectivity with the cognitive control network (Zhou et al., 2010) and increased regional activity (Liu et al., 2012) during resting-state conditions of geriatric depression.

The psychological explanation for these increased connections with the adACC is far from clear; however, it was speculated by Sheline et al. (2010) that it might represent excessive introspection, increased vigilance, or a disability to focus on cognitive tasks in these subjects because it is the overlap region of default-mode, cognitive control, and affective networks. Here, increased connections with the adACC were observed in each of these networks, as has also been reported for major depression (Sheline et al., 2010; Zhou et al., 2010). Given that the adACC has been ascribed the crucial hub for negative affection and cognitive control in the ACC (Shackman et al., 2011), the identification of increased resting-state ALFF in this area of elderly individuals with StD may provide further support for this speculation.

Not only was increased regional ALFF activity observed in the adACC, but increased connectivity with other regions was also detected. Moreover, the between-group FC comparison revealed decreased connectivity of the adACC with regions in the right hemisphere, including the orbitofrontal cortex, anterior insula, thalamus, and pallidum, in the StD group. The more distributed right hemisphere abnormalities found in these regions have consistently been demonstrated by reduced cortical thickness or volume reductions in patients with geriatric depression (Mackin et al., 2013b; Sexton et al., 2013), suggesting a role for these regions in the pathophysiology of depression. Neuroimaging studies have also demonstrated that these regions play important roles in emotion-processing circuits and that they connect with the ACC area (Bush et al., 2000; Stevens et al., 2011). The orbitofrontal cortex is linked to the processing of rewards and punishments (Kringelbach and Rolls, 2004). Recently, an fMRI study of emotional facial recognition tasks has reported less connectivity between the orbitofrontal cortex and the dorsal ACC in patients with major depression (Frodl et al., 2010). The anterior insula is involved in all subjective feelings and is activated jointly with the ACC during emotional experiences (Craig, 2009). Hypoactivation to negative affective pictures (Lee et al., 2007) and reduced resting-state regional coherence (Liu et al., 2010) in the right insula have been reported in fMRI studies of depression. The pallidum and thalamus are two subcortical regions that are centrally involved in the functional and anatomical circuitry of mood disorders (Drevets et al., 1992; Price and Drevets, 2010). Relevant studies have reported decreased pallidum volume in young depressed suicide attempters (Vang et al., 2010) and reduced pallidal and thalamic volumes in subjects with geriatric depression (Andreescu et al., 2008). A resting-state fMRI study of major depression also reported decreased dorsal ACC–thalamus connectivity (Anand et al., 2005), suggesting the involvement of the thalamus in the progression of depression. Therefore, along with the increased connections with the adACC, decreased connectivity also constitutes the imaging features that characterize elderly patients with StD.

Finally, the findings of abnormal FC and enhanced ALFF in StD were actually derived from the examination of the ACC at 2 different analytical levels. The higher ALFF in the adACC suggested regional changes in StD, while the altered FC indicated abnormalities in the connectivity between the adACC and other remote brain regions. Intriguingly, we found that the 2 different metrics appeared to be intrinsically linked. We observed that high ALFF in the adACC correlated with increased FC in the right SMA and decreased FC in the right thalamus. This suggests that regional activity changes and remote connectivity alterations with the adACC might be 2 mutually concomitant processes. Together, the local activity changes in the adACC and the connectivity abnormalities observed during resting-state conditions constituted dual evidence for a crucial role of the adACC in the pathogenesis of elderly subjects with StD.

4.3. Relationship between ALFF/FC markers and individual depressive levels

Besides functioning as a novel perspective for understanding the mechanisms underlying various neuropsychological disorders,

resting-state fMRI is also useful for identifying potential noninvasive biomarkers for an early clinical diagnosis of disease, as well as the rapid evaluation of related treatments. In this study, we assessed the potential use of ALFF and FC as markers for StD and observed the two above-mentioned intrinsically accompanying processes of increased regional ALFF in the adACC and remote connectivity changes with this area at resting-state in elderly individuals. However, when we examined the relationship between ALFF and FC with the self-reported depressive symptoms in the StD group, we found no significant correlation between ALFF in the adACC and CES-D scores and only a trending negative correlation between the FC in the right insula and the CES-D scores. We speculate that the sample size used in this study was not large enough to provide sufficient statistical power to describe the relationship between them.

4.4. Limitations

Several limitations should be noted. First, the definitions of StD are really divergent across different studies. The assessment of StD in our study was primarily based on the CES-D scores (Cuijpers et al., 2006, Vahia et al., 2010, Yu et al., 2012). Although some other studies reported that CES-D score more than 16 corresponded to the criteria of major depressive disorder, the StD subjects with higher CES-D scores in the present study however did not fulfill the DSM-IV diagnostic criteria for major depression as determined by professional psychiatrists. A further longitudinal study is required in the future to track whether the subjects with higher CES-D scores would move towards clinical depression, and to observe the trajectory of ACC activity and connectivity changes. Second, the sample size of the present study was relatively small. It may have limited us in providing results of the between-group connectivity differences with stringent statistical power and in finding more significant correlations between imaging variables and individuals' depressive symptoms. Therefore, our results require replication in larger independent sample studies. Third, recent evidence has shown that vascular factors, such as cardiovascular disease and diabetes, play a role in late-life depression (Valkanova and Ebmeier, 2013). However, a potential influence of these factors on the present results could not be excluded. Further analysis is required to evaluate the effects of vascular risk factors. Finally, the current study explored the functional activity/connectivity abnormalities of the ACC in StD under the resting-state condition. No attempt was made in this study to examine if the cause of the ACC dysfunction in StD was functional, structural, or both. Further examinations that combine both fMRI data and structural data, such as white matter integrity, or diffusion tensor imaging data may help improve the understanding of the neurobiological mechanisms of StD in older adults.

In summary, this study highlights the crucial role of the adACC in elderly subjects with StD through a dual investigation of local activity exploration and remote functional connectivity analyses and provides a new perspective for uncovering the underlying mechanisms of StD. The findings also suggest the potential use of fMRI markers for the characterization of StD.

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