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Research report

Abnormal functional connectivity in patients with vascular cognitive impairment, no dementia: A resting-state functional magnetic resonance imaging study

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ABSTRACT

The functional connectivity (FC) method was used to investigate the changes in the resting state of patients with vascular cognitive impairment, no dementia (VCIND). Resting-state functional magnetic resonance images (fMRIs) were acquired from 16 patients with subcortical ischemic vascular disease (SIVD) who fulfilled the criteria for VCIND, as well as 18 age- and sex-matched subjects with SIVD with no cognitive impairment (control group). Posterior cingulate cortex connectivity was gathered by investigating synchronic low-frequency fMRI signal fluctuations with a temporal correlation method. Compared with the control group, the patients showed FC decrease in the left middle temporal gyrus, the left anterior cingulate/left middle frontal gyrus, the right caudate, the right middle frontal gyrus, and the left medial frontal gyrus/paracentral lobule. There were also some regions that showed increased connectivity. These regions included the right inferior temporal gyrus, the left middle temporal gyrus, the left precentral gyrus, and the left superior parietal lobule. Our findings revealed the change in resting-state patterns of neuronal activity in patients with VCIND. This change may be caused by subcortical white matter lesions that destroyed direct and indirect fiber tract connectivity across the cerebral white matter and influenced the cortical FC and hypoperfusion resulted from small vascular disease. The results of the increased connectivity may be evoked by the compensatory recruitment and plasticity mechanism. Our findings suggest that the simplicity and noninvasiveness of this method makes it a potential tool to help thoroughly understand the pathogenesis of VCIND.

1. Introduction

In developing countries, the incidence of dementia has been predicted to increase at an alarming rate in the near future [1]. Vascular cognitive impairment (VCI) has been defined as cognitive impairment evoked by or associated with vascular causes [2]. It has been classified into three subtypes: vascular dementia (VaD), Alzheimer's disease (AD) with a vascular component, and vascular cognitive impairment, no dementia (VCIND) [3]. O'Brien et al. [4] proposed that people with VCI have a specific cognitive profile: memory is preserved and executive function is impaired, which is different from AD. The pathophysiology of VCI continues to be investigated; subcortical ischemic vascular disease (SIVD), a more homogeneous subtype of cerebral vascular disease, is considered one of the major causes of VCI [5]. Considering its common occurrence, cost, and possible preventability, VCI remains of interest to clinicians and researchers [6].

Neuroimaging in VCIND shows a pattern of vascular lesions similar to, but less severe than the changes observed in VaD [7]. Pathology includes evidence of leukoaraiosis and white matter infarction [8,9], with mild hippocampal and entorhinal cortex atrophy relative to the level seen in mild cognitive impairment or AD [7]. Previous studies tried to find some special manifestation to aid early detection, to discriminate the neuropathology, to estimate the prognosis, and to monitor disease progression or treatment response in patients with VCI and VCIND, but research is hampered by the clinical and pathological heterogeneity of VCI and the presence of pathology. Several imaging techniques have been used to investigate the structural and functional change in the brains of patients with VCI and/or VCIND. These techniques include magnetic resonance imaging (MRI) [10,7,11], magnetic resonance spectroscopy (MRS) [12], diffusion-weighted imaging [13], and diffusion tensor imaging (DTI) [14–16]. The techniques search for specific MRI abnormalities, such as the distribution and severity of the white matter hyperintensities and the clinical significance of the parameters derived from MRS and DTI [10,7,11–16].

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The default-mode network (DMN) has been extensively used in the study of psychiatric and neurological disorders in recent years. A number of resting-state functional MRI (fMRI) studies on psychiatric and neurological disorders have applied functional connectivity (FC) as an analytical approach [17,18]. FC refers to interregional cooperation that can be represented by a synchrony of low-frequency fluctuations in signal at cerebral blood oxygen level-dependent (BOLD) fMRI. A number of studies suggest that the posterior cingulate cortex (PCC) plays an essential role in spatial orientation, self-appraisal, and internal monitoring, as well as memory processing [19]. In addition, PCC is commonly identified as a critical node in the traditional DMN [20]. Given that the PCC is the seed region most commonly used in studies of the default network, the PCC was used as the region of interest (ROI) to study its altered connections with other brain regions.

The DMN could be affected by neuropsychiatric disorders [17,18], and some researchers suggested that the cause of the small vessel disease-related cognitive decline may lie in a disruption and disconnection of the frontal–subcortical pathways [21]. Furthermore, vascular disease can reduce cerebral blood flow (CBF) [22], which may influence the BOLD fMRI signal. So we hypothesize that FC will dissociate within the default networks associated with the PCC in the VCIND patients, and the difference may contribute to the understanding of the pathogenesis of VCIND.

2. Materials and methods

2.1. Subjects

Patients with SIVD were recruited from a stroke or transient ischemic attack (TIA) clinic. SIVD is defined as subcortical white matter hyperintensity on T2-weighted images on MRI with at least one lacunar infarct. All participants received baseline evaluation, including complete sociodemographic and clinical (cognitive, behavioral, neurological, functional, and physical) data collection. Patient histories were collected from knowledgeable informants, usually from their spouses. All patients underwent laboratory examinations and conventional MRI for routine investigation of dementia. The exclusion criteria were cerebral hemorrhages, cortical and/or corticosubcortical non-lacunar territorial infarcts and watershed infarcts, specific causes of white matter lesions (e.g., multiple sclerosis, sarcoidosis, and brain irradiation), neurodegenerative diseases (including AD and Parkinson's disease), and signs of normal pressure hydrocephalus or alcoholic encephalopathy. Patients with low education level (<6 years), severe depression [Hamilton Depression Rating Scale (HDRS) $\geq$ 18], other psychiatric comorbidities or severe cognitive impairment (inability to perform neuropsychological tests), severe claustrophobia, and contraindications to MRI (e.g., pacemaker, metallic foreign bodies) were also excluded. All the participants had lacunar infarcts, small white matter hyperintensities, and slight atrophy. In order to avoid the impact of brain atrophy on functional connectivity result, participants with obvious atrophy were excluded. Finally, the 36 patients recruited were subdivided based on cognitive status into the subcortical vascular disease with no cognitive impairment group (n = 18) and the VCIND group (n = 18). All the participants were right-handed.

The current study was approved by the Research Ethics Committee of the Ren Ji Hospital. All subjects gave their informed, written consent. All procedures were in accordance with institutional guidelines.

2.2. Neuropsychological assessment

Neuropsychological assessments were performed within 2 weeks of the MRI. All subjects did not suffer a new clinical stroke or TIA between the MRI and assessment. A comprehensive battery of neuropsychological tests was designed based on a review of relevant published reports. The tests were as follows: Trail-Making Tests A and B, Stroop color–word test, verbal fluency (category) test, auditory verbal learning test (short and long delayed free recall), Rey–Osterrieth Complex Figure Test (delayed recall), Boston Naming Test (30 words), Rey–Osterrieth Complex Figure Test (copy), Lawton and Brody's Activities of Daily Living (ADL) Scale Test, Barthel Index (BI), HDRS, and the Neuropsychiatric Inventory.

To assess the cognitive status of subjects, the scores for each measure of normal-aged patients in Shanghai, China, were used as the normal baseline (norms). Cognitive dysfunction was defined as −1.5 SD in at least one neuropsychological test. VCIND diagnosis was based on the following criteria: (1) normal ADL, (2) does not meet criteria for dementia, and (3) mild quantifiable cognitive impairment within one or more domains (i.e., attention, executive function, memory, language, and visuospatial function). Functional ability was assessed using BI and Lawton and Brody's ADL scales. However, because most patients with cognitive impairment due to cerebrovascular disease have some degree of disability, the study carefully excluded those with disability due to cognitive damage and motor sequelae using cognitive impairment history and clinical judgment. The patients were diagnosed with subcortical vascular disease with no cognitive impairment if their scores in all neuropsychological tests were within the normal range (<−1.5 SD).

To allow direct comparison of the different tests, Z-scores were generated for the neuropsychological measures. A Z-score defines where a score falls in the normal distribution of scores; a Z-score of +1.0 corresponds to a score 1 SD above the mean score. Direct comparison of the performance between tests was possible because Z-scores for all tests were based on an identical control population. Raw scores for each of the neuropsychological tests were Z-transformed. Thereafter, the Z-score of each domain was generated by averaging the Z-scores of the respective tests. Finally, the composite Z-scores, which represent general intellect, were computed by averaging the Z-scores of individual cognitive domains.

The present study focused on finding the difference in DMN between VCIND and subjects with subcortical vascular disease with no cognitive impairment (control group).

2.3. MRI acquisition

The MRI was performed on a 3 T magnetic resonance scanner (3 T Achieva, Philips, Netherlands). A standard head coil was used with foam padding to restrict head motion. During the resting-state fMRI, the subjects were instructed to keep their eyes closed, to remain motionless, and not to think of anything in particular. A gradient-echo echo-planar sequence was used to acquire functional images (repetition time = 2000 ms, echo time = 30 ms, field of view = 230 mm × 230 mm, matrix = 64 × 64, thickness = 4 mm, gap = 0). Each fMRI scan lasted 440 s.

2.4. Data analyses

For demographic differences and neuropsychological scores between the two groups, F-test (two-way ANOVA) was used to compare continuous variables and χ^2-test was applied for comparing categorical variables. A two-tailed p-value of 0.05 was considered statistically significant for all analyses.

fMRI preprocessing was carried out using Data Processing Assistant for Resting-State fMRI (DPARSFV 2.0, by YAN Chao-Gan, http://www.restfmri.net), which is based on MRIcroN (by Chris Rorden, http://www.mricro.com), statistical parametric mapping (SPM5; Wellcome Department of Imaging Neuroscience, London, UK), and Resting-State fMRI Data Analysis Toolkit (REST, by SONG Xiao-Wei et al., http://www.restfmri.net). Given the instability of initial MRI signal and adaptation of participants to the circumstance, the first 10 volumes of each functional time series were discarded. The data from each fMRI scan contained 220 time points. The remaining 210 images were preprocessed. Then, the images were corrected for slice timing and realigned to the first image for rigid-body head movement correction (patient data with movement greater than 1 mm maximum translation in x, y, or z or 1° of maximum rotation about the three axes were discarded). Two patients with VCIND were excluded. Afterward, the functional images were normalized into standard stereotaxic anatomical Montreal Neurological Institute (MNI) space. The normalized volumes were resampled to a voxel size of 3 mm × 3 mm × 3 mm. Then, the echo-planar images were spatially smoothed using an isotropic Gaussian filter of 4 mm full width at half maximum. The gray matter and cerebrospinal fluid were segmented to eliminate the aliasing effect of cerebrospinal fluid before normalization.

Before FC analysis, all image data were simply filtered using a phase-insensitive band-pass filter (passband, 0.01–0.08 Hz) to reduce the effect of low-frequency drift and high-frequency physiologic noise. The voxel intensities were scaled by dividing the value of each time point by the mean value of the whole-brain image at that time point to minimize the effect of global drift. Then, we selected the PCC template as the ROI, which consists of Brodmann's area 29, 30, 23, and 31, using the WFU-Pick Atlas software [23,24]. Finally, to perform the ROI-based correlation analysis, the mean PCC signal intensity was calculated by averaging the time series of all voxels in the selected ROI. The resulting time course was used to perform a Pearson linear correlation analysis with all voxels of the brain data, and the mask images were acquired with a threshold of correlation coefficients [25]. A Fisher z-transform was applied to normalize the correlation coefficients [26]. The individual Z-scores were entered into SPM5 for random-effects one-sample t-test to determine brain regions with significant connectivity to the PCC within each group. These individual scores were also entered into SPM5 for random-effects analyses and two-sample t-tests to identify regions with significant differences in connectivity to the PCC between two groups. Regions with statistical significance were masked on MNI brain templates.

3. Results

3.1. Demography and neuropsychological test

Demographic characteristics and main neuropsychological information are showed in Table 1. No significant differences in age, gender, and education were found between the two groups. Com-

Table 1
Demographic and clinical information for VCIND and NCI subjects.

	Control $N = 18$	VCIND $N = 16$	p
Age	66.2 ± 7.7	69.1 ± 7.8	0.31
Males (N)	16/2	14/2	0.89
Educations (Years)	11.6 ± 2.9	10.2 ± 3.3	0.23
HDRS	3.5 ± 5.1	4.5 ± 3.9	0.57
ADL	14.1 ± 0.5	15.3 ± 3.1	0.23
MMSE	28.9 ± 1.3	28.1 ± 1.4	0.08
Z-scores	0.4 ± 0.56	−0.6 ± 0.75	<0.001

VCIND = vascular cognitive impairment, no dementia, HDRS = Hamilton depression rating scale, ADL = Lawton and Brody's activities of daily living, ADL = Lawton and Brody's activities of daily living, MMSE = mini-mental state examination.

pared with the control group, Z-scores were significantly lower in the VCIND group.

3.2. PCC connectivity: within-group analysis

Within-group analysis was performed with the SPM5 random-effects one-sample t-test. With a p-value < 0.01 [false discovery rate (FDR)–corrected] and an extent threshold of 54 voxels, the PCC connectivity maps in both groups included the ventral medial prefrontal cortex (MPFC), the inferior temporal cortex (ITL), the precuneus, and the inferior parietal cortex on both sides (Fig. 1A and B). These regions coincide with the nodes underlying the DMN [27].

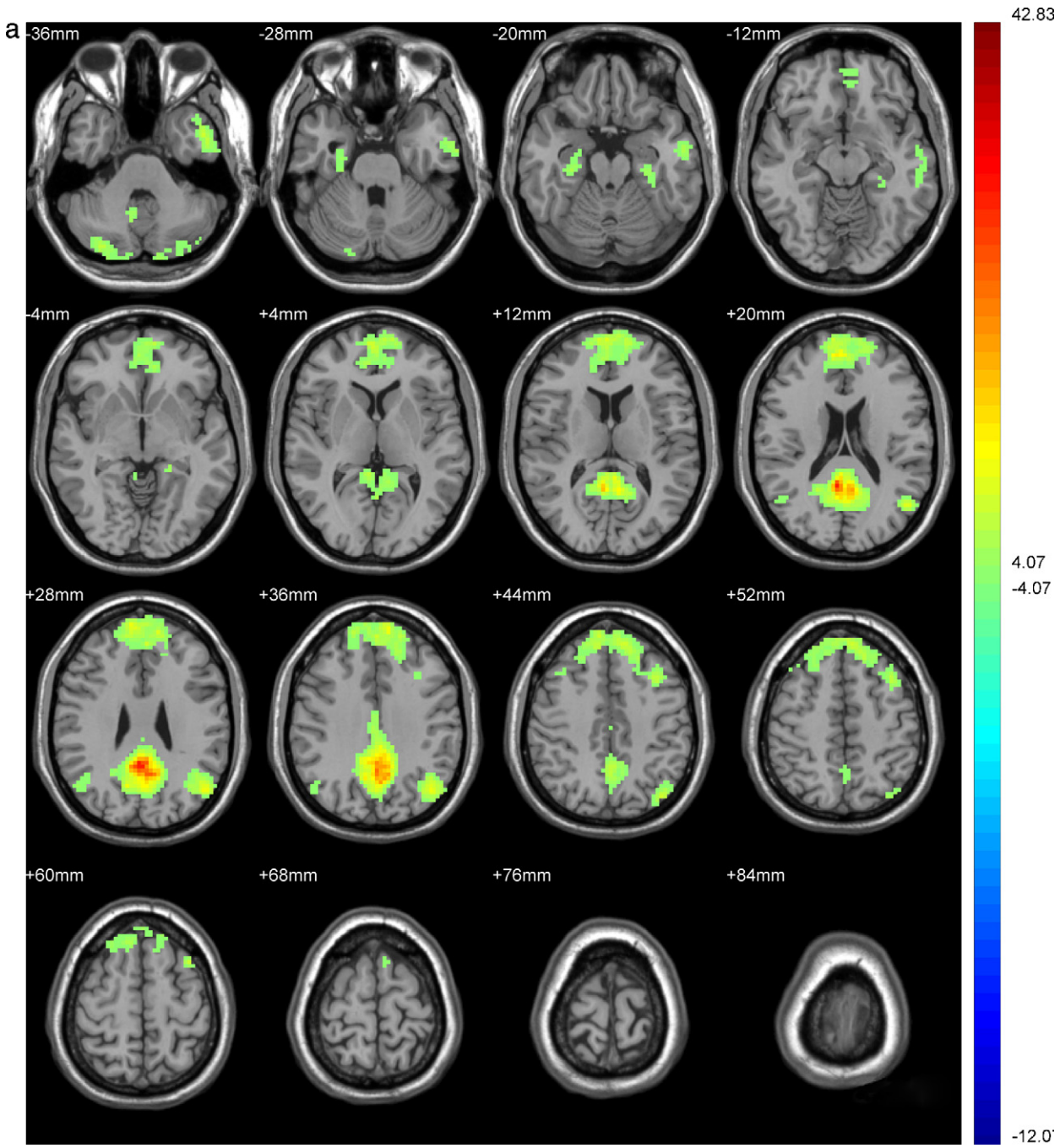

Fig. 1. Intragroup maps of connectivity to the PCC of the resting-state networks. (A) Control group; (B) VCIND group. Significant connectivity regions are overlaid on the MNI template (one-sample t-test, $p < 0.01$, FDR-corrected, voxel size > 54). Note: The left part of the figure represents the patient's right side. VCIND = vascular cognitive impairment, no dementia.

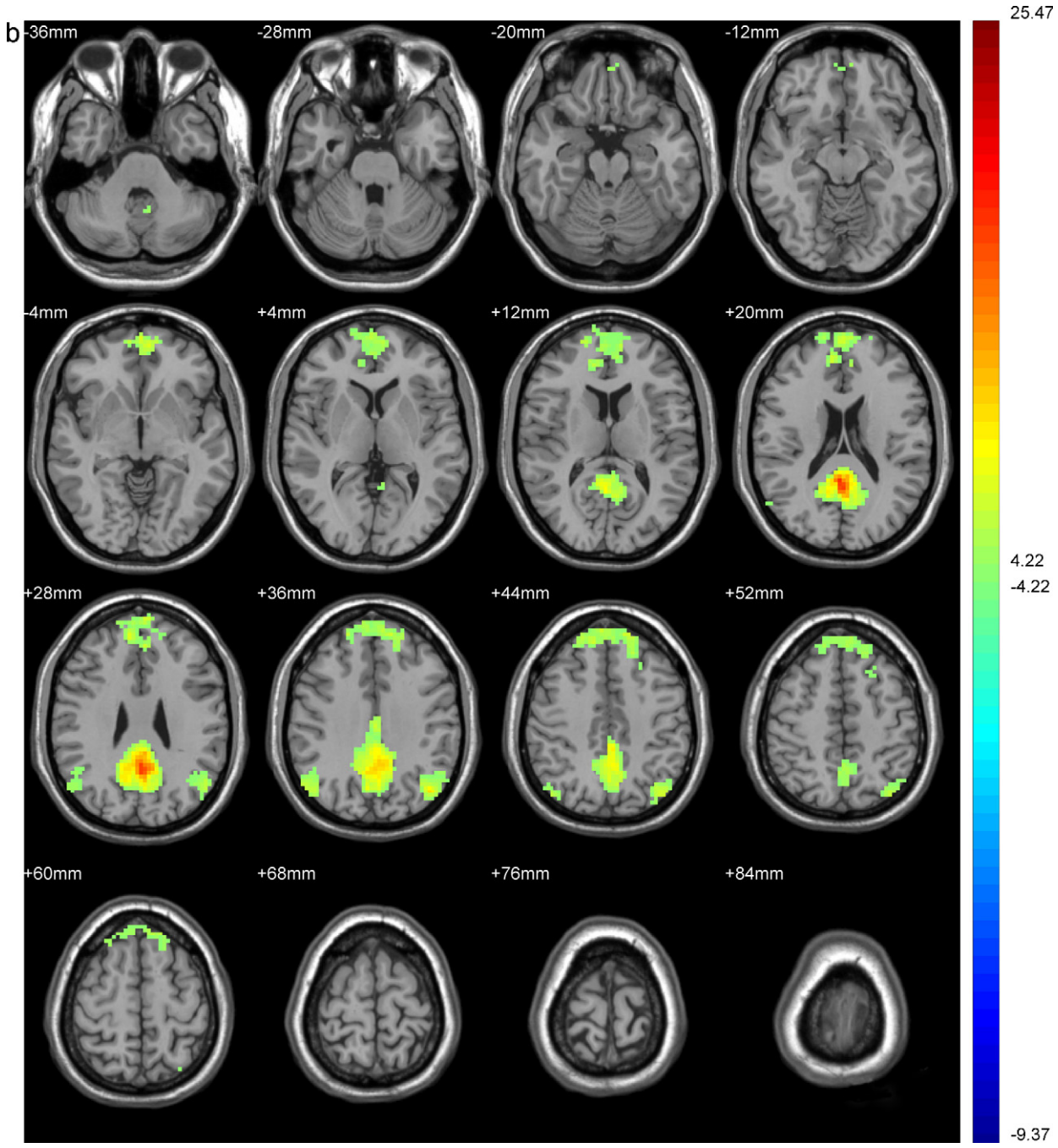

Fig. 1. (*Continued*).

Both sides of the hippocampus were shown in the control group but not in the VCIND group.

3.3. PCC connectivity: between-group analysis

Between-group analysis was performed with the SPM5 random-effects two-sample *t*-test. Compared with the controls, the patients showed FC decrease in the left middle temporal gyrus, left anterior cingulate/left middle frontal gyrus, right caudate, right middle frontal gyrus, and left medial frontal gyrus/paracentral lobule. There were also some regions that showed increased connectivity. These regions included the right inferior temporal gyrus, the left middle temporal gyrus, the left precentral gyrus, and the left superior parietal lobule (Table 2 and Fig. 2).

4. Discussion

SIVD, as a manifestation of cerebral small vessel disease, is related to progressive cognitive impairment and a considerable risk factor for developing dementia; it seems to contribute specifically to the deterioration of psychomotor speed, executive control, and global cognitive function [5,6]. The cause of the small vessel disease-related cognitive symptoms, including the psychomotor slowing and the executive deficits, may lie in a disruption and disconnection of the frontal–subcortical pathways [21]. The dorsolateral prefrontal circuit is involved mainly in executive function, which includes abilities to solve complex problems such as learning new information, planning ahead, activating remote memories, regulating actions according to the environmental stimuli, shift-

Table 2
Significant connectivity difference between-group contrasts with their location.

	Number of cluster voxels	Peak MNI coordinate			Peak MNI coordinate region	Peak *T* value
		x	*y*	*z*		
1	209	−42	12	−39	Left middle temporal gyrus	5.17
2	61	−3	42	−9	Left anterior cingulate/left middle frontal_gyrus	3.05
3	55	9	12	15	Right caudate	4.17
4	55	27	51	24	Right middle frontal gyrus	3.3
5	97	−3	−18	63	Left medial frontal gyrus/Left paracentral_Lobule	3.65
6	80	60	−45	−21	Right inferior temporal gyrus	−4.51
7	131	−57	−54	−3	Left middle temporal gyrus	−3.8
8	73	−48	−9	24	Left precentral Gyrus	−3.66
9	98	−36	0	27	Left precentral Gyrus	−4.2
10	219	−24	−75	45	Left superior parietal lobule	−4.67

($p < 0.01$,corrected with FDR, extent threshold = 54 voxel).
Note: $T > 0$ indicated decreased connectivity to the PCC in VCIND group *vs* control group. $T < 0$ indicated increased connectivity to the PCC in VCIND group *vs* control group.

ing behavioral sets appropriately, generating motor programs, and temporal ordering of recent events [28]. Executive dysfunction is one of the principal components of subcortical dementia. Patients with subcortical dementia are characterized by slowed information processing, mood and personality changes, retrieval-type memory deficits, and motor abnormalities. Similarly, lesions in the dorsolateral prefrontal cortex and caudate nucleus lead to poor recall with preserved recognition abilities. The orbitofrontal circuit connects the frontal monitoring systems to the limbic system. Dysfunction of the circuit is characterized by personality changes, including behavioral disinhibition and emotional lability. The anterior cingulate gyrus mediates motivated behavior, and dysfunction associated with lesions in this area reflects decreased motivation [29]. Cortical FC relies on direct and indirect fiber tract connectivities across the cerebral white matter. Subcortical white matter lesions would destroy this connectivity and influence the white matter microstructure of DMN connectivity [30].

The DMN concept comes from an emergent body of evidence demonstrating a consistent pattern of deactivation across a network of brain regions [31]. As demonstrated by fMRI and positron emission tomography studies of humans, the DMN is involved with the PCC, linking regions of the bilateral MPFC, hippocampus, posterior thalamus, inferior parietal cortex, precuneus, and inferior lateral temporal cortex [27,32]. Although the precise functions collectively subserved by the DMN remain largely unknown, the individual brain regions comprising DMN are involved in the integration of autobiographical, self-monitoring, and social cognitive functions [33]. The PCC is activated during tasks that involve autobiographical memory and self-referential processes [34]. The MPFC is associated with social cognitive processes related to self and others [35], whereas the middle temporal lobe is engaged in episodic memory [36]. The central role of the precuneus is the provision of a wide spectrum of highly integrated tasks, including visuospatial imagery, episodic memory retrieval, and self-processing operations. Furthermore, the precuneus and the surrounding posteromedial areas are among the brain structures displaying the highest resting metabolic rates and are characterized by transient decreases in tonic activity during engagement in non-self-referential goal-directed actions. The precuneus has been recently proposed to be involved in the interwoven network of the neural correlates of self-consciousness and engages in self-related mental representations during rest [37]. In some research, the anterior cingulate cortex (ACC) and the hippocampus [27] are included in the DMN.

In the current study, we sought to determine how the DMN map changes in patients with VCIND and whether there is increased connectivity in the VCIND-affected brain. The most conspicuous areas showing connectivity deficits were regions of the left middle temporal gyrus, left anterior cingulate/left middle frontal gyrus, right caudate, right middle frontal gyrus, and left medial frontal gyrus/paracentral lobule. There were also some regions that showed increased connectivity. These regions included the right inferior temporal gyrus, the left middle temporal gyrus, the left precentral gyrus, and the left superior parietal lobule.

Regions such as the ACC, the middle frontal gyrus, and the inferior temporal gyrus are the important components of the DMN. Although the hippocampus was not detected as a significant difference between the two groups, we inferred it might have mild abnormal function because it was not detected in the in-group analysis of the VCIND group. Deactivation of key nodes of the DMN may in fact be a prerequisite for focused attention and successful memory encoding [38]. Conversely, there is evidence that failure to suppress activity in some of the core default mode areas is associated with failed encoding and poor performance in subsequent memory tests in cognitively normal young and elderly subjects [39].

The caudate plays a crucial role in relaying inputs from the prefrontal cortex in animals and thus maybe involved in processing higher executive cognitive functions associated with these regions [40]. The extensive interconnections of the human caudate nucleus with the prefrontal cortex, temporal gyri, frontal eye fields, cerebellum, and thalami have been demonstrated using diffusion tensor imaging [41]. Damage to such circuits may potentially disconnect and degrade cognition subserved by such circuits. A recent research revealed that smaller caudate nucleus volumes are associated with increased cognitive deficit severity [42].

Our data suggest that although deficits in connectivity occurred, enhanced connectivity to the PCC, mainly through the temporal–parietal cortex, simultaneously occurred. The enhanced spatiotemporal interaction with the PCC may be considered a compensatory adaptation for the loss due to its plasticity after damage of the original neural networks. Previous investigators [43,44] have found that the resting human brain is intrinsically organized into dynamic anticorrelated functional networks. When the activity in the DMN reduced, the activity of the opposing networks increased, and the balance between the reciprocal resting functional networks is broken [17]. This may explain the fact that although some cross-sectional evidence suggests that VCIND lies on a spectrum between normal cognition and VaD [45], VCIND does not always progress to dementia, and data from epidemiological and clinical series indicate that improvement in patients with VCIND is common [46].

Another reason of the DMN change would be the declined cerebral blood flow (CBF) resulted from SIVD. FMRI signal is dependent upon blood flow and blood oxygen level. CBF and perfusion studies, using a variety of techniques including xenon clearance and positron emission tomography, have shown reduced CBF in the white matter of patients with SIVD, particularly in leucoaraiosis [47] or clinical dementia is present [47,48]. Perfusion MRI studies have confirmed that reduced cerebral blood flow in not only T2W-

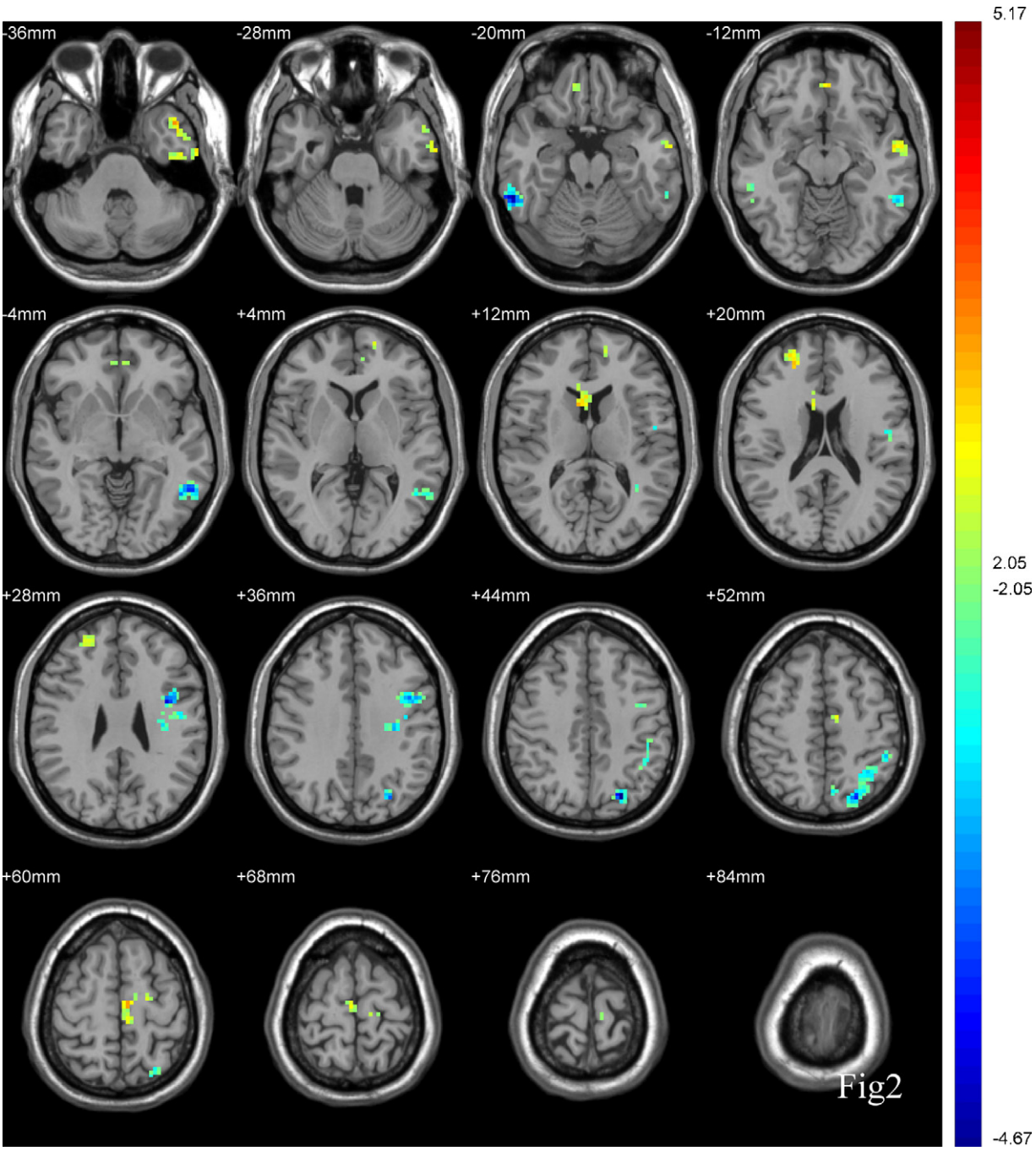

Fig. 2. Location of regions showing disrupted connectivity in VCIND *vs* controls (two-sample *t*-test, $p < 0.05$, FDR-corrected, voxel size > 54). The *t*-score bars are shown on the right. Hot and cold colors indicate FC decreases and increases in the VCIND group *vs* control group, respectively. Note: The left part of the figure represents the patient's right side. VCIND = vascular cognitive impairment, no dementia; FC = functional connectivity.

lesion but also in normal appearance white matter. This suggested that the white matter is particularly vulnerable to hypoperfusion [49]. Although they have not found hypoperfusion in gray matter, it would be a factor that influenced the change of FC in patients with VCIND.

The small sample size limits the current study and the overlap of early AD in our patients with VCIND could not be fully excluded. AD and vascular diseases are common in old age in that they unavoidably occur together. Therefore, our results are not surprisingly partly consistent with previous research regarding AD [50,51]. Second, all the patients had lacunar infarcts, small white matter hyperintensities, and slight atrophy, and because the lesions were very small (<1 cm) and distributed throughout the brain, removal of the lesions is difficult; hence, the data was processed as usual. Third, some researchers suggested [52] functional connectivity maybe partly affected by volume atrophy, although we excluded the participants with severe atrophy, slight atrophy especially in the PCC could have some impact on our results.

In summary, change in the resting-state patterns of neuronal activity was demonstrated in patients with VCIND. This change maybe caused by subcortical white matter lesions that destroy direct and indirect fiber tract connectivities across the cerebral white matter and influence cortical FC and hypoperfusion resulting from small vascular disease. The results of the increased connectivity may support the compensatory recruitment and plasticity mechanism. The simplicity and the noninvasiveness of this method

make it a potential tool to help thoroughly understand the pathogenesis of VCIND.

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