Int J Clin Exp Med 2018;11(3):1984-1993
www.ijcem.com /ISSN:1940-5901/IJCEM0058354

Original Article

Aberrant default mode network in patients with vascular cognitive impairment, no dementia

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Received February 10, 2017; Accepted November 26, 2017; Epub March 15, 2018; Published March 30, 2018

Abstract: This study investigated changes in the default mode network (DMN) in patients with vascular cognitive impairment, no dementia (VCIND) using resting state functional magnetic resonance imaging (rsfMRI). Imaging data were collected for 14 patients with VCIND and 15 healthy controls matched by age, sex, and educational level. Whole brain voxelwise amplitude low frequency fluctuation (ALFF) and functional connectivity (FC) between posterior cingulum and other brain gray voxels were computed and compared between patients and controls. Our results indicated that VCIND patients had aberrant ALFF and FC measures in the DMN, providing functional imaging evidence for the clinical diagnosis of VCIND.

Keywords: Vascular cognitive impairment no dementia, resting state functional magnetic imaging, default mode network, amplitude low frequency fluctuation, functional connectivity

Introduction

The incidence of dementia is increasing as the population aging accelerating worldwide. Vascular brain injury, the second most common cause of dementia, has changed the clinical manifestations of Alzheimer's disease (AD) [1, 2]. VCIND refers to mild cognitive impairment even not reaching to the diagnostic Criteria For dementia (DSM-V) which is caused by the risk factors of cerebrovascular disease (such as hypertension, diabetes and hyperlipidemia, etc.), dominant (such as cerebral infarction and cerebral hemorrhage, etc.) or non-dominant cerebrovascular disease (such as white matter osteoporosis, and chronic cerebral ischemia). Subcortical ischemic cerebrovascular disease, caused by cerebral small vascular disease due to lacunar cerebral infarction and white matter damage, is the most common type of vascular cognitive impairment (VCI) [3]. Detection of early pathological physiological changes and early diagnosis of VCIND may help delay the disease progression. Non-invasive neuroimaging techniques may help achieve early diagnosis of VCIND [3].

Resting state resting state functional magnetic resonance imaging (rsfMRI) provides an effective noninvasive imaging technology for investigating intrinsic functional brain connectivity of the human brain when it is not engaged in any outside tasks [4]. Based on the rsfMRI data, amplitude low-frequency fluctuation (ALFF) and functional connectivity (FC) can be computed to measure functional information of the brain [5-7]. Particularly, ALFF reflects the level of spontaneous. A larger ALFF value indicates a higher brain excitability while a low ALFF indicates that neurons are inhibited and activity is decreased, which is vital for the understanding of the functioning of human brain tissue [5-7]. FC, measured by correlation between functional signals of two brain regions, has been widely adopted to investigate functional networks [8].

In the present study, we focused on the differences in the default mode network (DMN) between VCIND patients and matched healthy controls by adopting ALFF and FC. The DMN is consist of the posterior cingulate cortex (PCC), the bilateral ventromedial prefrontal cortex and its related regions, namely the hippocampus, the posterior thalamus, the inferior parietal lobe, the precuneus (PCu), and the lateral inferior temporal cortex [9]. The DMN is most commonly shown to be active when the brain is at wakeful rest but not involved in a task, and is

involved in memory, self-monitoring, social cognitive function [10, 11]. The DMN has been shown affected by neuropsychiatric conditions [12, 13], such as schizophrenia, Alzheimer's disease (AD), depression, Parkinson's disease (PD), and MCI [14-16].

Materials and methods

Subjects

The present study recruited 14 VCIND patients and 15 healthy normal controls (NC) matched by age, sex, and educational level between March 2012 and March 2014 at the neurology department in the Second Affiliated Hospital of Shanxi Medical University. All participants had signed informed consent before any data was acquired. All participants were assessed for collecting full socio-demographic and clinical data, including cognition, behavior, neurological function, and physical examination by two or more trained professional neurologists with at least a secondary senior position. Data of medical history was provided for all patients by their spouses. All patients underwent laboratory tests and conventional MRI scans for dementia.

The inclusion criteria for all subjects were: 1) aged 60 or older; 2) any gender; 3) level of education junior high school or above; 4) married; and 5) right-handed. The exclusion criteria were [7]: 1) cortical and/or subcortical non-lacunar infarction or watershed infarcts; 2) white matter lesions with certain causes, such as multiple sclerosis, sarcoidosis, radiation encephalopathy, and others; 3) neurodegenerative diseases, including AD and PD; 4) cognitive disorders due to other causes, such as tumor, epilepsy, cerebral trauma, mental disease, systemic disease (e.g., hypothyroidism, severe anemia, HIV, or syphilis infection), alcohol or drug addiction; 5) symptomatic normal-pressure hydrocephalus or alcohol encephalopathy; 6) years of education less than 6; 7) severe depression (HDRS $\geq$ 18); and 8) routine MRI scans showing obvious brain atrophy.

Neuropsychological assessment

The mini-mental state examination (MMSE) was used to assess the patients' status in cognitive function in orientation, memory, attention, computation, and language competence. The Montreal Cognitive Assessment Beijing Version (MoCA) scale was used to assess overall intelligence in visual space, executive function, naming, attention, language, abstract, delayed recall, and directional force.

Diagnosis criteria for VCIND were: 1) there exist risk factors for cerebrovascular disease or cerebral vascular disease, such as hypertension, diabetes mellitus, and hyperlipemia; 2) complain of patients themselves or their families for a decline in performance in cognition, with symptoms of cognitive decline lasting for at least 6 months and a course of fluctuating progress; 3) memory is preserved or only mildly damaged; 4) damage to cognitive function and risk factors for cerebrovascular disease are directly related to cerebrovascular disease; 5) activity of daily living is normal or near normal, Activity of Daily Living Scale (ADL) < 26; 6) overall cognitive function is normal, MMSE $\geq$ 24; 7) MoCA score < 26; 8) Hachinski ischemic scale (HIS) $\geq$ 7; 9) Clock Drawing Task (CDT) = 4; 10) clinical dementia rating scale (CDR) = 0.5; and 11) impairment of cognitive function has not yet reached the standard of the diagnosis of dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

Acceptance criteria of healthy controls with normal cognition were: 1) overall cognitive function is normal, MMSE > 26; 2) MoCA > 26; 3) CDR = 0; 4) ADL < 26; and 5) no abnormal signals on conventional MRI scans.

MRI acquisition

All subjects had a routine MRI 1.5-T scan collected with a whole-body MRI scanner (General Electric Medical Systems, GE) using a common head coil and phased array. Data scanning started after participants were familiar with the environment. Participants did not need to perform any tasks and were asked to take a supine resting posture, keeping their eyes closed and breathing quietly when rsfMRI data were being scanned. At the same time, the subjects were asked not to think actively and not to sleep. The rsfMRI scans were obtained using gradient echo sequence (GRE) and single-shot echo planar imaging (echo planar, EPI) techniques with TR = 2500 ms; TE = 40 ms; FA = 90°; number of slices = 28; slice thickness = 4 mm; gap = 1 mm; data matrix = 64 × 64; and FOV = 25.6 × 25.6. Scan time lasted 640 s.

Table 1. All subjects' general clinical data

	NC (n = 15)	VCIND (n =14)	χ^2/t	*P*-value
Male/female	7/8	8/6	0.318	0.572
Age	65.8±7.9	67.9±8.7	-0.681	0.502
Years of education	11.95±3.95	10.05±3.85	1.310	0.201
ADL score	14.5±1.1	15.2±2.5	-0.988	0.332
MMSE score	28.51±0.28	26.87±0.32	14.714	< 0.0001
MoCA score	26.33±2.98	20.32±3.72	4.818	< 0.0001
Visual space and executive function	4.17±0.37	2.73±0.32	11.173	< 0.0001
Naming	2.45±0.15	2.31±0.64	0.824	0.417
Attention	5.84±0.2	4.03±0.3	19.242	< 0.0001
Language	2.91±0.33	1.99±0.27	8.181	< 0.0001
Abstract	1.21±0.21	1.08±0.18	1.783	0.086
Delayed recall	3.67±0.28	2.52±0.25	11.635	< 0.0001
Orientation	5.87±0.36	4.34±0.61	8.295	< 0.0001

Note: VCIND = vascular cognitive impairment, no dementia, ADL = Lawton and Brody's activities of daily living, MMSE = Mini Mental State Examination.

Data analyses

Image preprocessing. All MRI data were preprocessed using Statistic Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm), MRIcroN (by Chris Rorden, http://www.mricro.com), and Resting-State fMRI (DPARSFV 2.0, by YAN Chao-Gan, http://www.restfmri.net). Particularly, the first 10 volumes were discarded to allow magnetization equilibration. The remaining images were slice-time corrected and realigned to the first volume for head motion correction. All subjects' fMRI data were within the defined motion thresholds (i.e., translational or rotational motion parameters less than 3 mm or 3°). Then, temporal band-pass filtering (0.01 < f < 0.08 Hz) was performed to reduce the effects of low-frequency drift and high-frequency noise. The time series in the white matter and cerebrospinal fluid and 6 affine motion parameters were also regressed out of the data. Finally, individual subject images were spatially normalized to a EPI cerebral template and then normalized to the Montreal Neurological Institute (MNI) space with an affine transformation, resampled to 3 mm × 3 mm × 3 mm voxels, and smoothed with a Gaussian kernel with a full-width at half-maximum (FWHM) of 6 mm.

ALFF calculation. ALFF values were calculated using the REST software (http://www.restfmri.net). In particular, each voxel's time sequence was converted into the frequency domain using the fast Fourier transform. The area of the power spectrum under the peak was interpreted as the energy of the signal, and then the square root of the power spectrum was calculated, the results of which represented the strength of the BOLD signal change. The average of signal amplitude in 0.01-0.08 Hz was thus the ALFF value of each voxel. To eliminate the differences in ALFF per individual in the overall level, each voxel of ALFF value was divided by the average ALFF in the gray matter.

FC calculation. The posterior cingulate cortex (PCC) was selected as seed region based on Anatomical Automatic Labeling atlas, and then we calculated the mean PCC signal intensity by averaging the time series of all voxels in the PCC. The resulting time course was used to perform a Pearson linear correlation analysis with all voxels of gray matter in the brain.

Statistical analysis. SPSS 19.0 statistical software was used to compare demographic and neuropsychological characteristics. A two-sample t test was adopted to compare education levels, ADL scores, and neuropsychological scale scores between NCs and VCIND patients. The chi-square test was used to compare the gender difference between groups. The difference was statistically significant, $P < 0.05$.

All statistical analyses of rsfMRI data were based on the SPM8 and Resting-State fMRI Data Analysis Toolkit. A one-sample t-test was used to compute group level maps of ALFF and FC. A two-sample t-test was used to evaluate the difference in ALFF and FC between VCIND

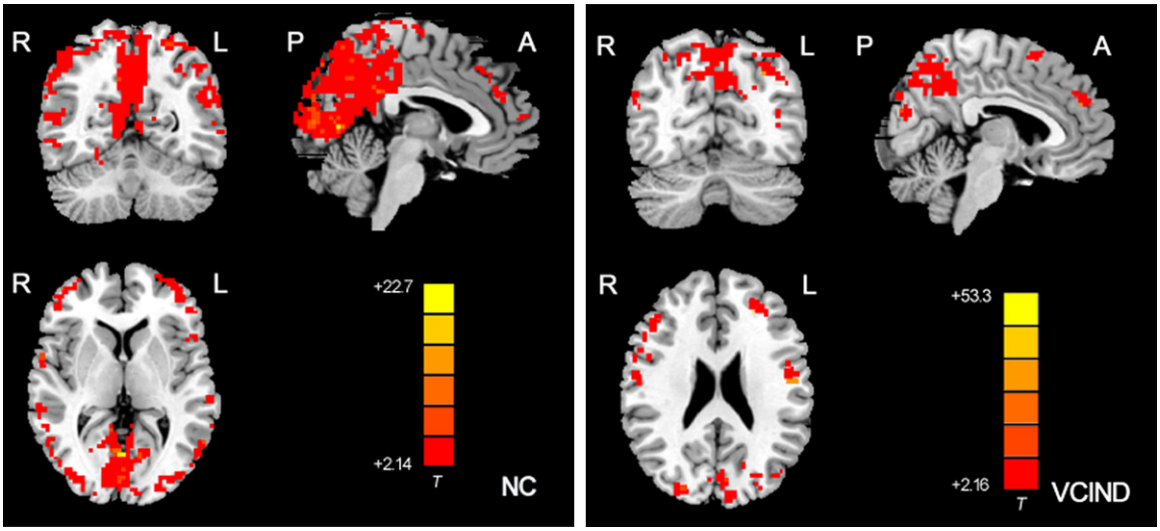

Figure 1. Group level ALFF maps of the NC (left) and VCIND (right) groups. High ALFF values were observed in posterior cingulum, adjacent PCu, inferior parietal lobule, frontal, occipital, and temporal in both groups ($P < 0.05$ for individual voxel and cluster size > 1458 mm^3, corresponding to a AlphaSim corrected $P < 0.05$). L, left; R, right; P, posterior; A, anterior.

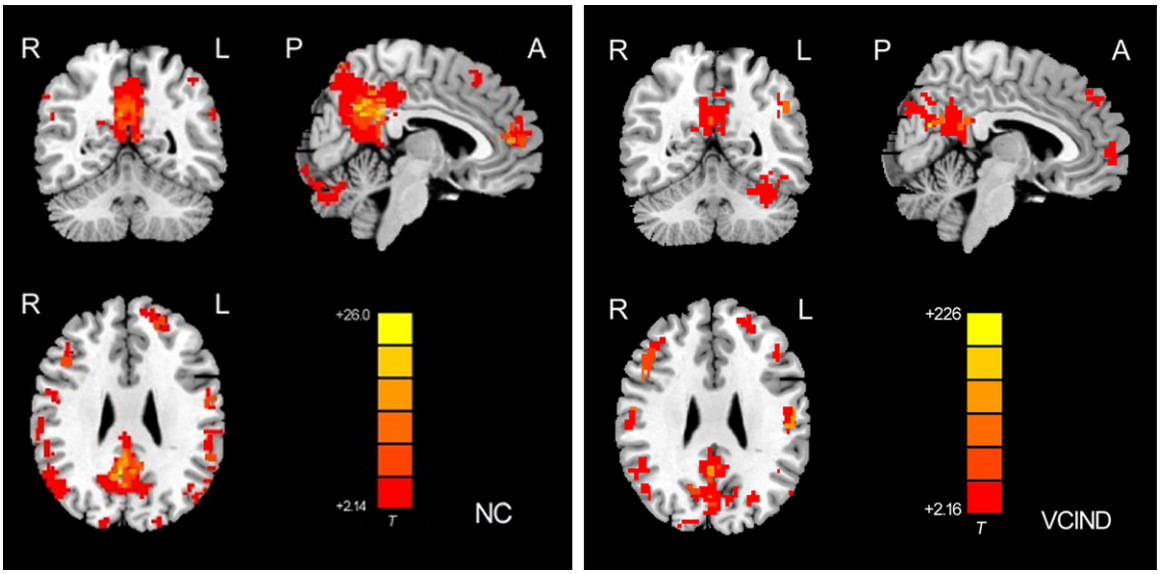

Figure 2. Group level FC maps of the NC (left) and VCIND (right) groups. High FC values were observed in posterior cingulum and adjacent PCu ($P < 0.05$ for individual voxel and cluster size > 1458 mm^3, corresponding to a AlphaSim corrected $P < 0.05$). L, left; R, right; P, posterior; A, anterior.

patients and HC subjects. A threshold $P < 0.05$ for individual voxel and cluster size > 1458 mm^3, corresponding to an AlphaSim corrected $P < 0.05$, were used to correct multiple comparison problems. XjView-REST 1.8 was used to identify significantly different brain regions with the MNI coordination information, and Slice viewer-REST 1.8 was used to present the results.

Results

Demographic information and neuropsychological test

Demographic characteristics and the main neuropsychological tests (**Table 1**) showed that there were no statistically significant differences in age, gender, level of education, ADL, nam-

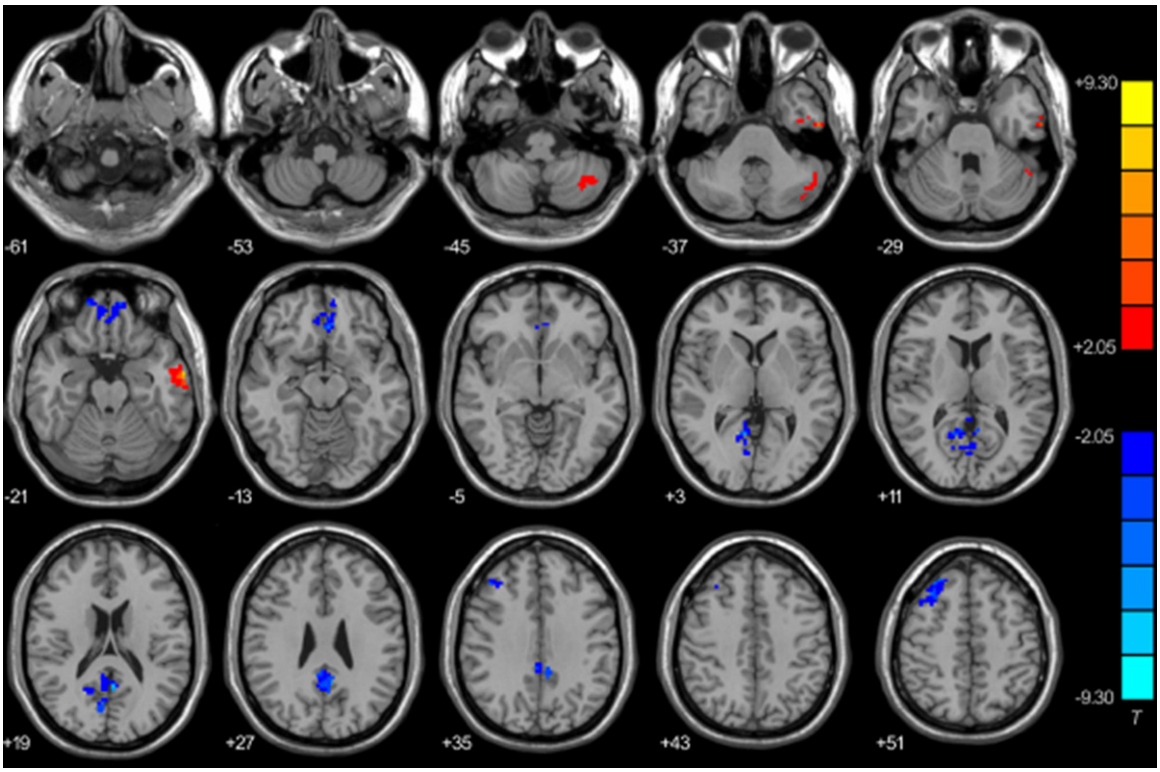

Figure 3. Between-group differences in ALFF. Compared with NCs, VCIND patients showed decreased ALFF in the posterior cingulate cortex, adjacent PCu, bilateral rectus, right middle frontal gyrus, right medial superior frontal gyrus, and left orbital medial frontal gyrus. VCIND patients also showed increased ALFF in left temporal gyrus and left cerebellum ($P < 0.05$ for individual voxel and cluster size > 1458 mm^3, corresponding to a AlphaSim corrected $P < 0.05$).

ing, and abstract thinking between the NCs and VCIND patients. However, significant differences were observed in the scores of MMSE and MoCA, as well as in visual space, executive function, attention, language, delayed recall, and orientation. All of these scores were lower in the VCIND group than the scores in the NC group.

Group maps of ALFF and FC

The group level maps of ALFF and FC for VCIND and NC groups are shown in **Figures 1** and **2**, respectively. High ALFF and FC were observed in posterior cingulate cortex (PCC), PCu, inferior parietal lobule, frontal lobe, occipital lobe, temporal lobe for both groups. Among those regions, the highest ALFF was in PCC and PCu (**Figure 1**).

Comparison of ALFF between two groups

Compared with the NC group, decreased ALFF was observed in the PCC, the PCu, the bilateral rectus, the right middle frontal gyrus, the right medial superior frontal gyrus, and the left media orbital frontal in the VCIND patients while increased ALFF was also found in the left middle temporal gyrus and left cerebellum (**Figure 3**; **Table 2**).

Comparison of FC between two groups

Compared with the NCs, decreased FC was observed in the PCC, the PCu, the right middle frontal gyrus, and the right occipital lobe in the VCIND patients. Moreover, increased FC was found in the left superior temporal gyrus, the middle temporal lobe, the inferior parietal lobe, and the right superior temporal lobe (**Figure 4**; **Table 2**).

Discussion

In the present study, we investigated VCIND changes in both ALFF and FC based on rsfMRI data. We found that VCIND patients had decreased ALFF in the PCC, the PCu, the bilat-

Table 2. Comparison of ALFF/FC between two groups

	MNI coordinate (X, Y, Z)			Number of cluster voxels	*t* value	*P*-value
Brain regions	X	Y	Z			
Decreased regions of ALFF in VCIND						
PCC	0	-50	23	132	-6.11	$P < 0.05$
PCu	-3	-55	19	82	-9.22	$P < 0.05$
Rectus, R	6	47	-25	97	-4.63	$P < 0.05$
Rectus, L	-4	48	-17	81	-4.63	$P < 0.05$
Frontal, Mid, R	29	33	51	77	-6.94	$P < 0.05$
Frontal, Sup, Medial, R	6	51	45	56	-9.01	$P < 0.05$
Frontal, Med, Orb, L	-3	36	-10	58	-5.61	$P < 0.05$
Increased regions of ALFF in VCIND						
Temporal, Mid, L	-62	-5	-22	77	8.94	$P < 0.05$
Cerebelum, L	-51	-63	-39	74	6.27	$P < 0.05$
Decreased regions of FC in VCIND						
PCC	3	-44	25	63	-3.75	$P < 0.05$
PCu	-1	-55	22	57	-3.67	$P < 0.05$
Frontal, Mid, R	37	24	45	89	-6.43	$P < 0.05$
Cerebelum, R	15	-88	-24	138	-3.592	$P < 0.05$
Increased regions of FC in VCIND						
Temporal, Mid, L	-53	-38	7	128	9.12	$P < 0.05$
Temporal, Sup, L	-51	-22	7	73	4.66	$P < 0.05$
Temporal, Sup, R	66	-15	5	67	4.30	$P < 0.05$
Parietal, Inf, L	-27	-57	44	98	4.31	$P < 0.05$

($P < 0.05$, corrected with AlphaSim, threshold of extent = 1458 mm^3). Note: $t < 0$ indicates decreased ALFF/functional connectivity to PCC in VCIND group vs. NC group; $t > 0$ indicates increased ALFF/functional connectivity to PCC in VCIND group vs. NC group.

eral rectus, the right middle frontal gyrus, the right medial superior frontal gyrus, and the left media orbital frontal cortex in DMN, while increased ALFF was observed in the left middle temporal gyrus and the left cerebellum compared with the NC group. We also found that VCIND patients had decreased FC in the PCC, the PCu, the right middle frontal gyrus, and the right occipital lobe and increased FC in the left superior temporal gyrus, the middle temporal lobe, the inferior parietal lobe, and the right superior temporal lobe.

The characteristics of cognitive function in VCIND

The MMSE is widely used in cognitive function measures. It emphasizes the detection of memory function. Its sensitivity is poor and the rate of missed diagnosis is high. Unlike the MMSE scale, the MoCA scale evaluates visual space and executive function, naming, attention, language, abstract, delayed recall, and directional force. It is more suitable for the evaluation of patients with VCI. In this study we found that some scores of the VCIND group were lower than those in the NC group in the MoCA scale of visual space, executive function, attention, language, delayed recall, and directional force. This indicates that VCIND patients had at least one aspect of cognitive dysfunction in visual, executive function, language, or attention, in accordance with previous studies [17].

Differences in ALFF between two groups

VCIND patients had decreased ALFF in some regions of DMN, including the posterior cingulate cortex, the PCu, the bilateral rectus, the right middle frontal gyrus, the right medial superior frontal gyrus, and the left media orbital frontal cortex and increased ALFF in the left middle temporal gyrus and the left cerebellum. This finding provides evidence that the DMN is altered in VCIND patients. The decreased ALFF in the ventromedial prefrontal cortex was in accordance with a previous study by PET, which showed that there was decreased metabolism

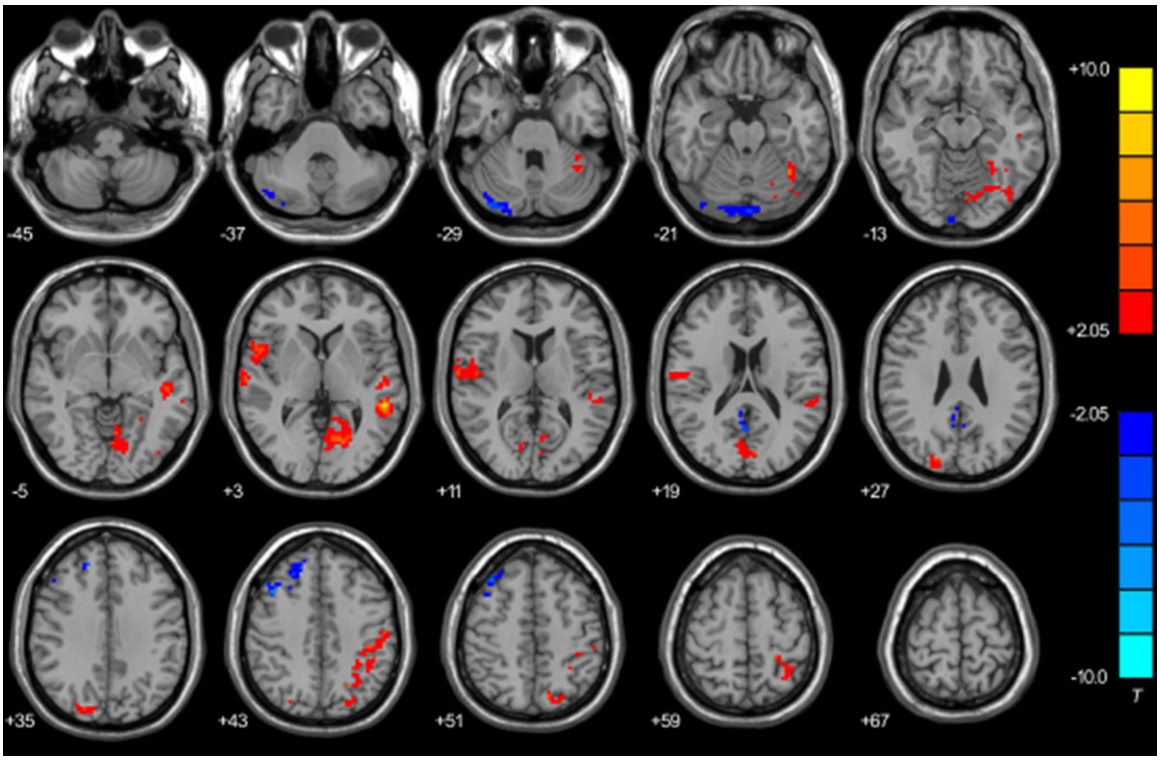

Figure 4. Between-group differences in functional connectivity. Compared with NCs, VCIND patients showed decreased FC in the posterior cingulum, adjacent PCu, right middle frontal lobe regions and right occipital lobe. VCIND patients also showed increased FC in left superior temporal gyrus, left middle temporal gyrus, right superior temporal gyrus, and left inferior parietal lobe ($P < 0.05$ for individual voxel and cluster size > 1458 mm^3, corresponding to a AlphaSim corrected $P < 0.05$).

in the frontal region in VCIND [10]. The ventromedial prefrontal cortex is associated with the executive function, regulation of emotions, and social cognitive process [18]. Van Dam found that differences in spontaneous low-frequency fluctuations at rest were correlated with differences in cognitive performance [19]. Therefore, there may be an association between cognitive dysfunction, neurobehavioral changes, and the attenuation of activity in the ventromedial prefrontal cortex in VCIND. The cerebellum may not only maintain the body's balance and movement but also participate in cognitive functions such as language, memory, learning, and calculation. In the present study, increased ALFF in the left cerebellum might indicate compensatory mechanism for cognitive disorder in VCIND.

Previous studies found that structural and functional damage of the hippocampus was associated with memory in the early stage of MCI [6, 10, 20]. Particularly, decreased ALFF was observed in MCI subjects in the hippocampus, parahippocampal gyrus, medial temporal cortex, and ventromedial prefrontal lobe, together with increased ALFF in the temporoparietal border area, inferior parietal lobe [7]. In our study, no change in the hippocampus was observed. However, increased ALFF was observed in the left temporal gyrus and the posterior lobe of the cerebellum in the VCIND patients, which supported our hypothesis that there would be differences in the pathophysiological mechanism between VD and AD, which to a certain extent may reflect a compensatory mechanism in the resting state of VCIND.

Changes in FC to PCC between two groups

Decreased FC was observed in VCIND patients in some DMN regions such as the PCC, the PCu, the right middle frontal gyrus, and the right occipital lobe. Moreover, increased FC was found in the left superior temporal gyrus, the middle temporal lobe, the inferior parietal lobe, and the right superior temporal lobe. Decreased FC may lead to progressive cognitive impairment, including impairment of men-

tal activity, executive function, and whole-brain cognitive decline.

Neurology and the meta-analysis of neuroimaging studies showed that frontal areas are closely related to executive function. Thus damage to this region should lead to a decline in executive function [21]. Our results strongly support this argument. PET studies found decreased metabolism in the frontal cortical area in patients with subcortical vascular MCI (svMCI), which had supported that abnormal social behavior may attribute to the damage in the frontal-subcortical pathways in svMCI [10, 22]. It has been found that the DMN may be divided into three parts, from the front to the back. Therefore, changes in different parts remote from each other in space in the DMN may reflect a characteristic mechanism of pathological changes in svMCI [23]. Our results showed that a decrease in functional connectivity to PCC in the right frontal right middle frontal gyrus might be caused by certain damage in connective integrity between the first (the ventromedial prefrontal cortex) and second parts (cingulate) in the DMN among patients with VCIND [11]. Disorder in the executive function was correlated with the lesions in the frontal white matter [24]. Unlike MCI which was caused by neural degeneration, damages to the frontal and subcortical pathways were relatively heavy in VCIND [22]. A linear mixed model based study found that correlations existed between damage to the frontal-parietal pathways or the frontal-parietal-subcortical pathways and declines in executive function. However, there was no correlation between damage to frontal-subcortical pathways and changes in executive function in MCI [25]. Thus, the different pathological changes between the vascular factors and the neural degeneration can be distinguished. Nevertheless, we were unable to find specific FC changes in VCIND, which merits further research.

Recent studies have found occipital lobe atrophy both in subcortical vascular dementia and svMCI patients [26]. The atrophy of the gray matter of the occipital lobe may be a secondary result, since the occipital region was one of the most important original purpose fibers, and vascular injury may cause the destruction of long white matter fiber [27]. Occipital lobe white matter lesions were associated with visual space and memories, and white matter lesions were correlated with MoCA scores [24]. Our study revealed decreased FC in VCIND patients between the right occipital lobe and the posterior cingulate cortex, as well as visual space barriers, which were in accordance with previous studies [11].

Previous studies showed cortical atrophy both in the superior temporal gyrus and the inferior temporal gyrus in subcortical dementia svMCI [27]. The superior temporal gyrus played an important role in complex social activities as an important node of the social awareness system [28]. The damaged volume of the temporal lobe area and the hippocampal white matter is correlated with the MMSE score [24]. The inferior parietal lobule has important implications for the process of attention, particularly for nonspatial attention. The language barrier is associated with the damaged volume of parietal white matter and gray matter [24]. Fernandez et al. found damage to the brain network was related to the orientation in svMCI [29]. Posterior white matter, such as the parietal lobe and the postcentral gyrus, are more vulnerable in MCI caused by AD, compared with VCIND [25]. Our research showed that a compensatory mechanism was triggered to reach normal cognitive function: increased FC between the PCC and the left superior temporal gyrus, the middle temporal lobe, the inferior parietal lobe, and the right superior temporal lobe.

A large number of studies in the field of cognitive impairment, including normal aging, AD, anxiety, and depression are currently being carried out. However studies of VCIND based on the rsfMRI data have only just begun.

Conclusion

In the present study, we investigated changes in the DMN in VCIND patients. One pathophysiological mechanism of VCIND may be the reduction of functional activity and the loss of FC in specific regions of the brain. Due to the hypoperfusion of cortical and sub-cortical gray matter caused by cerebral small blood vessel diseases, the functional activity were reduced [30]. White matter lesions impact the connective fiber pathways directly or indirectly, and may weaken the strength of FC between cortical and sub-cortical neurons [31]. The enhancement of FC may be due to a compensatory mechanism and the plasticity of the body [11].

In our study, we observed differences in both ALFF and FC measures between VCIND and NC subjects, particularly in the DMN. Such aberrant ALFF and FC patterns of VCIND patients were different from those observed in MCI studies [32]. One limitation of our study was based on cross-sectional data. We do have longitudinal data of the VCIND patients and therefore are not able to characterize their longitudinal ALFF and FC changes. Furthermore, we do not have data of MCI subjects. A future study will compare MCI and VCIND patients with respect to their ALFF and FC patterns.

Acknowledgements

We specially thank Prof. Yong Fan of the institute of automation, Chinese academy of sciences for data processing.

Disclosure of conflict of interest

None.

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