Aberrant Functional Connectivity of Resting State Networks in Transient Ischemic Attack

Rong Li[1][9], Shanshan Wang[1][9], Ling Zhu[1], Jian Guo[2], Ling Zeng[1], Qiyong Gong[3], Li He[2]*, Huafu Chen[1]*

1 Key Laboratory for Neuroinformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, PR China, **2** Department of Neurology, West China Hospital of Sichuan University, Chengdu, PR China, **3** Huaxi MR Research Center, Department of Radiology, West China Hospital of Sichuan University, Chengdu, PR China

Abstract

Background: Transient ischemic attack (TIA) is usually defined as a neurologic ischemic disorder without permanent cerebral infarction. Studies have showed that patients with TIA can have lasting cognitive functional impairment. Inherent brain activity in the resting state is spatially organized in a set of specific coherent patterns named resting state networks (RSNs), which epitomize the functional architecture of memory, language, attention, visual, auditory and somato-motor networks. Here, we aimed to detect differences in RSNs between TIA patients and healthy controls (HCs).

Methods: Twenty one TIA patients suffered an ischemic event and 21 matched HCs were enrolled in the study. All subjects were investigated using cognitive tests, psychiatric tests and functional magnetic resonance imaging (fMRI). Independent component analysis (ICA) was adopted to acquire the eight brain RSNs. Then one-sample t-tests were calculated in each group to gather the spatial maps of each RSNs, followed by second level analysis to investigate statistical differences on RSNs between twenty one TIA patients and 21 controls. Furthermore, a correlation analysis was performed to explore the relationship between functional connectivity (FC) and cognitive and psychiatric scales in TIA group.

Results: Compared with the controls, TIA patients exhibited both decreased and increased functional connectivity in default mode network (DMN) and self-referential network (SRN), and decreased functional connectivity in dorsal attention network (DAN), central-executive network (CEN), core network (CN), somato-motor network (SMN), visual network (VN) and auditory network (AN). There was no correlation between neuropsychological scores and functional connectivity in regions of RSNs.

Conclusions: We observed selective impairments of RSN intrinsic FC in TIA patients, whose all eight RSNs had aberrant functional connectivity. These changes indicate that TIA is a disease with widely abnormal brain networks. Our results might put forward a novel way to look into neuro-pathophysiological mechanisms in TIA patients.

* E-mail: heli2003new@126.com (LH); chenhf@uestc.edu.cn (HC)

[9] These authors contributed equally to this work.

Introduction

Transient ischemic attack (TIA) is usually defined as a neurologic ischemic disorder without permanent cerebral infarction and lasting neurological deficits [1]. Yet, several evidences have demonstrated that patients suffered a TIA can have lasting cognitive impairment, despite the recovery of focal neurological deficits [2]. In a meta-analysis of the risk of cerebral angiography in patients with TIA or stroke, the risk of transient neurological deficit was 3.0% and the risk of permanent neurological deficit was 0.7% [3]. There was a study reported that the deficits in executive function, information processing speed, visual memory, abstraction, and visuoconstruction were found in these patients, which may result from the disturbance of frontal functions [4]. And another research also found that TIA patients with carotid artery occlusion may develop persisting impairment in execution and reaction [5]. However, all these studies have been used the neuropsychological test scores to evaluate the cognitive abnormalities in TIA patients, which may relatively be insensitive to mild cognitive impairment and can not provide any information about the mechanism of such cognitive decline.

Recent neuroimaging studies suggested that widespread resting state brain networks were altered in many neurological and psychiatric disorders [6,7]. Functional connectivity in resting state has became a prevalent technique to study the brain networks without specifically designed behavioral tasks. Functional connectivity represents the temporal synchronization of neuronal activities between different brain regions within a network, and can be used to reflect the normal or abnormal state of the corresponding functions [8,9]. Besides, several related studies have

demonstrated that inherent brain activity in the resting state is spatially organized in a set of specific coherent patterns [10,11]. These patterns were named resting state networks (RSNs), which epitomize the functional architecture of memory networks, language, attention, visual, auditory and somato-motor [12]. Despite that there is not a consensus yet, a number of consistent RSNs, as detected by independent component analysis (ICA), could be jointly reported in the same study [10].

So far, it is unclear about the changes in the functional architecture of RSNs in TIA during resting state. Some prior studies found cognitive impairment in TIA patients on attention, memory, reaction and execution compared to healthy controls [4,5]. It could be explained just in the light of abnormal regional responses, but they may also reflect normal responses within a dysfunctional network. In this case, researches on RSNs in TIA patients would provide useful data to confirm the network impairment hypothesis. In the present study, we evaluated the topological differences of the RSNs between TIA patients and healthy controls, using the method of ICA on fMRI data of resting state. We mainly aim to verify 1) whether the functional connectivity of any RSNs may be altered in TIA patients and 2) if so, whether these changes are related to the measured clinical scales. The results of this research may employ a new manner to investigate the neurological and neurophysiological mechanisms of TIA.

Methods

Subjects

The study protocol was approved by the institutional ethics committee at Sichuan University. Written informed consent was obtained before each subject's participation in the trial. 21 TIAs suffered an ischemic event were enrolled in the study. A TIA was defined according to the World Health Organization recommendations as any syndrome of focal neurologic dysfunction ascribable to a vascular territory and lasted for less than 24 hours [13]. Those with brain lesions on fluid attenuated inversion recovery (FLAIR) images or T2-weighted images, leukoaraiosis or psychiatric diseases were excluded. The control subjects were healthy volunteers matched for age, sex, years of education, and with no history of stroke/TIA or other neurological disorders. All subjects had a complete blood count and metabolic profile testing, an ultrasonic cardiogram, a Holter monitor and a carotid duplex ultrasound examination.

Cognitive and Psychiatric Assessment

Cognitive and psychiatric assessments of these subjects were conducted by two independent neuropsychologists. The Montreal Cognitive Assessment (MoCA) was used for assessing the general condition of cognitive function, which is a useful brief tool to assess cognition in TIA patients with mild cognitive impairment(MCI) [14]. The Auditory Verbal Memory Test (AVMT, Chinese version based on California Verbal Learning test) was for the verbal memory and the backward Digital Span Test (DST-backward) was for working memory. The Hamilton Anxiety (HARS) and Depression (HDRS) Rating Scales were also administered to rate the psychiatric characteristics in all subjects.

MRI Acquisition

All TIA patients experienced symptoms with acute onset of paralysis or numbness which less than 1 month before the MRI examination. And the median duration of symptoms in TIA patients was 48 min (ranging from 15 min to 1.5 h).Imaging was performed on a 3 Tesla Trio scanner (Siemens AG). The resting-

state fMRI was obtained by using an echo planar imaging sequence with following protocols: TR = 2000 ms, TE = 30 ms, field of view, 240×240 mm^2, acquisition matrix, 64×64, and slice thickness, 5 mm, voxel size = $3.75 \times 3.75 \times 5$ mm. This acquisition sequence generated 190 volumes in 6 min and 24 s. During the fMRI scanning, all subjects were informed to keep still with their eyes closed, to think of nothing in particular and remain awake. A 3D time-of-flight MR angiography (MRA) was performed to visualize the cerebral vasculature of the subjects and 3D high-resolution T1-, T2-weighted. High-resolution anatomical images of the whole brain were acquired with a volumetric three-dimensional spoiled gradient recall sequence to detect clinically silent lesions. (TR = 1900 ms, TE = 2.28 ms, 240×240 mm^2, matrix, 256×256,whole head: 176 sagittal slice, slice thickness, 1.0 mm with no gap, voxel size = $0.9 \times 0.9 \times 1$ mm).

Data Processing and Statistical Analysis

Data preprocessing. Data preprocessing was carried out by using the SPM8 package (http://www.fil.ion.ucl.ac.uk/spm). The first ten volumes were discarded because of instability of the initial MRI signal. The remaining 180 volumes were first carried out slice timing correction and slice realignment for head motion correction. No subject's translational or rotational parameters in a data set exceeded ± 1 mm or $\pm 1°$. Therefore, no datasets were excluded from the analysis. The functional images were realigned with the corresponding T1-volume and warped into a standard stereotaxic space at a resolution of $3 \times 3 \times 3$ mm^3, using the Montreal Neurological Institute (MNI) echo-planar imaging template in SPM8. Then, they were spatially smoothed by convolution with an isotropic Gaussian kernel (FWHM = 8 mm).

ICA and identification of RSNs. Group spatial ICA was performed using the GIFT software (http://icatb.sourceforge.net/, version 1.3e) [15]. For the specific process, please see Methods S1.

Second-level analysis of the RSNs. The ICs in line with eight RSNs were extracted from all subjects. One-sample t-tests were then calculated in each group to gather the spatial maps of each RSNs. Thresholds were set at p<0.001 (FDR corrected) [16]. To compare the changes of the RSNs between TIA and HC, two-sample t-tests were calculated (p<0.001, FDR corrected). The group comparisons were masked to the voxels within corresponding RSNs. The mask was created by combining the regions of corresponding RSNs in both TIA and HC, which were obtained from one-sample t-tests results (p<0.001, FDR corrected) [17].

Correlation analyses. A Pearson correlation analysis was performed to explore the relationship between Z values in network maps and neuropsychological scores. The voxels in corresponding RSNs showing significantly different Z values between TIA and HC groups were extracted as a mask, which consists of several regions of interest (ROIs). These ROIs were applied to all subjects. The mean Z values of each individual within these ROIs were correlated to the neuropsychological scores and then thresholded at a significance level of p<0.05.

Results

Subjects' Characteristics

Demographic profiles and risk factors of both groups are presented in Table 1. Patients with TIA showed only significant differences compared with normal controls in carotid artery stenosis (P = 0.006). The results of the cognitive and psychiatric tests are summarized in Table 2. The TIA patients tended to have poorer scores in MoCA, AVMT, and DST-backward but without statistical significant difference. There were no significant differences in HARS and HDRS between two groups.

Table 1. Demographic characteristics and risk factors of participants.

Characteristics	TIA Patients (n = 21)	HC (n = 21)	P value
Age, mean (SD)	50.1(6.5)	48.2(7.9)	0.39
Sex, males (%)	15(0.71)	13(0.62)	0.51
Education, mean years (SD)	10.4(2.1)	10.5(2.8)	0.95
Risk factors (%)			
Hypertension	8(0.38)	5(0.24)	0.32
Diabetes	3(0.14)	1(0.05)	0.29
Hyperlipidemia	7(0.33)	6(0.28)	0.74
Atrial Fibrillation	0	0	
Previous stroke	0	0	
Smoking	5(0.24)	2(0.09)	0.21
Carotid artery stenosis	11(0.52)	2(0.09)	**0.006**
Intracranial arteries stenosis	2(0.09)	0(0)	0.49

Abbreviations: TIA, Transient ischemic attack; HC, Healthy controls; SD, standard deviation.
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Spatial Pattern of RSNs in each Group

The one-sample t-tests revealed a typically spatial pattern in each RSN in both TIA and HC group. Our results for IC classification and spatial pattern were consistent with the results of previous studies [10,18], which are illustrated in Fig. 1.

Aberrant RSNs in Patients with TIA

The two-sample t-tests revealed the differences in functional connectivity between the two groups (Fig. 2; Table 3). Compared to HC, TIA patients illustrated both increased and decreased (p<0.001, FDR corrected) functional connectivity in the DMN and SRN, and TIA patients exhibited specifically decreased (p<0.001, FDR corrected) functional connectivity in the DAN, CEN, CN, SMN, VN and the AN(clustering extent threshold, 15 voxels). Table 3 summarizes for the abnormal functional connectivity brain regions of each RSN.

However, no significant correlation was found between brain regions with aberrant functional connectivity and neuropsychological scores.

Table 2. Cognitive and psychiatric tests of participants.

	TIA Patients (n = 21)	Controls (n = 21)	P value
MoCA, mean (SD)	24.5(3.5)	26.2(1.6)	0.053
AVMT, mean (SD)	47.9(15.8)	55.7(19.8)	0.065
DST-backward, mean (SD)	5.1(1.9)	5.7(3.4)	0.060
HARS, mean (SD)	9.3(2.7)	8.3(2.3)	0.224
HDRS, mean (SD)	6.5(2.1)	5.6(1.7)	0.142

Abbreviations: MoCA, Montreal Cognitive Assessment; AVMT, Auditory Verbal Memory Test; DST-backward, Backward Digital Span Test; HARS, Hamilton Anxiety Rating Scales; HDRS, Hamilton Depression Rating Scales; SD, standard deviation.
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Discussion

In the present study, we mainly focused on the confirmation of whether the intrinsic functional connectivity of RSNs was altered or not in patients with TIA and on detecting whether there was a link between these changes and the disease severity.

Previous studies have demonstrated that the most common cause of TIA is atherosclerosis, which usually occurs in one of the internal carotid arteries [19]. Meanwhile, some other studies have suggested that the occlusion of internal carotid arteries may be a major risk factor for cognitive impairment [20,21]. It's reported that individuals who experienced a TIA have some changes in cognitive functions, such as attention, working memory, and learning and memory, which rely on DAN, SRN, CN and DMN. We also chose other RSNs (including VN, AN, SMN and CEN) in our study. Different regions belonging to these networks have already showed abnormal brain activations in TIA patients as compared with HC. We found that functional connectivity was significantly different among eight RSNs. Both increased and decreased functional connectivity was found in the DMN and the SRN and decreased functional connectivity was found in all other networks in TIA patients. These results were similar to the literature on differential activations of specific cerebral regions in nondisabling transient ischemic attacks (TIA) and minor strokes patients as compared with healthy controls.

The default mode network (DMN) is engaged in maintaining the baseline brain activities associated with cognitions of pisodic memory, and environmental monitoring [22]. As we know, DMN exhibited high levels of activity during resting state and decreased the activity for processes of externally oriented mental activity, which was induced by a wide range of sensory and cognitive tasks [23]. Our findings indicated that the left middle temporal gyrus, inferior temporal gyrus and right superior frontal gyrus showed decreased functional connectivity in TIA patients as compared with HC. Previous functional neuroimaging studies have suggested that the middle temporal gyrus and inferior temporal gyrus are involved in several cognitive processes, including language and semantic memory processing, as well as visual perception [24,25]. Furthermore, the superior frontal gyrus (SFG) is thought to contribute to higher cognitive functions and particularly to working memory [26,27]. Together, these may suggest that the dysfunction of middle temporal gyrus and superior frontal gyrus could be resulted from long-term existence of various ischemic risks and was related to the impairment of cognitive function of TIA patients.

In the present study, the aberrant functional connectivity of DMN in TIA patients was also represented by the increased functional connectivity in the left medial frontal gyrus, left posterior cingulate/precuneus and right angular gyrus. Recent neuroimaging studies have shown that the posterior cingulate cortex (PCC), ventral medial prefrontal cortex (vmPFC) and the bilateral angular gyrus were more active during resting state than during cognitive tasks [28,29]. In addition, the angular gyrus and posterior cingulate/precuneus were significantly activated during memory retrieval [30]. What's more, the mPFC is supposed to provide information from prior experiences in the form of memories during the construction of self-relevant mental simulation. These findings have suggested that medial prefrontal cortex played an important role in the prominent cognitive behavioral models of TIA. It has been showed that DMN played a critical role in social cognition and particularly in the relationship between the self and the social environment in TIA patients.

The SRN has already shown special physiological characteristics with a high level of neural activity during resting conditions
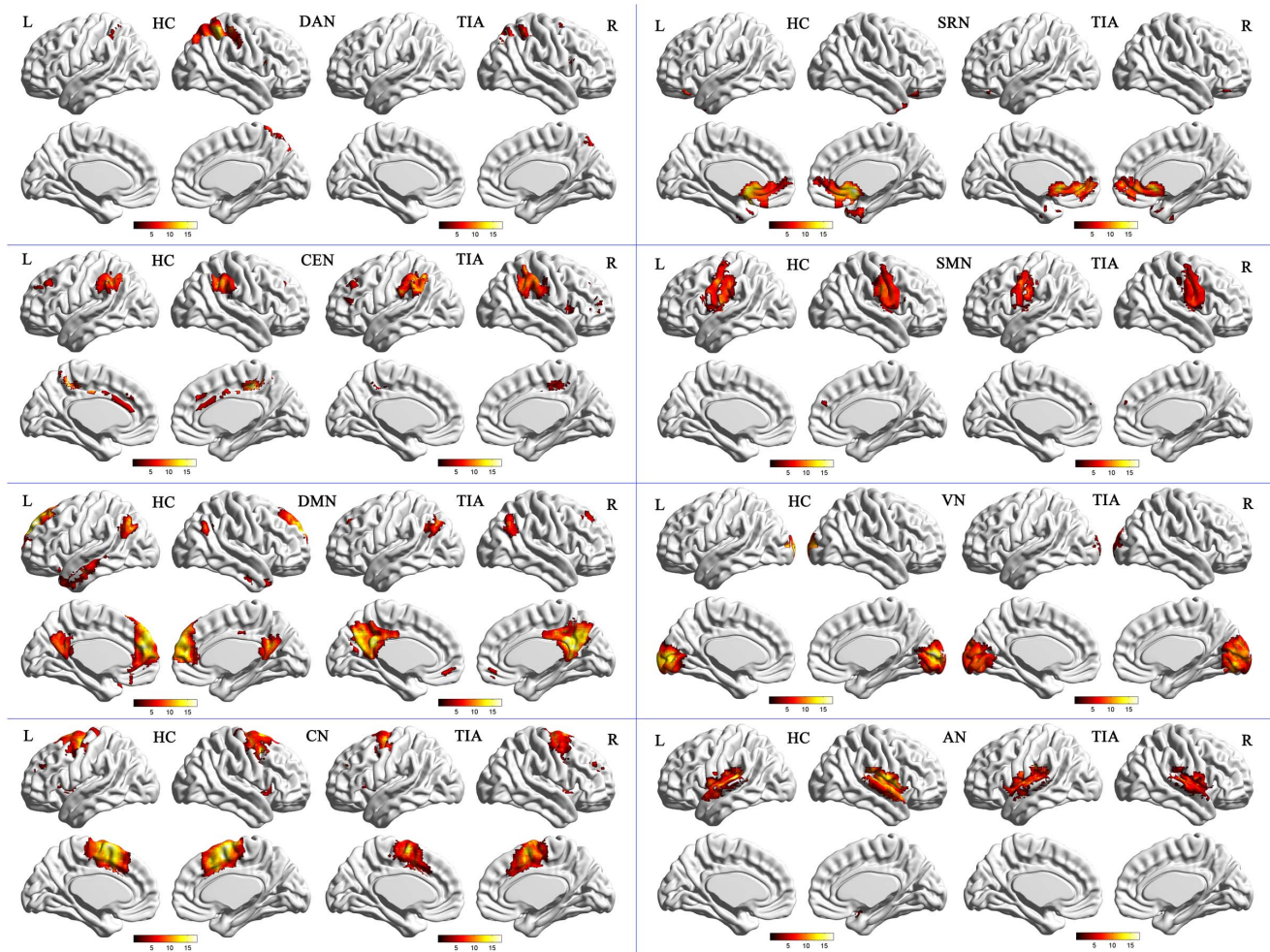
Figure 1. Cortical representation of the eight group-level RSNs in HC and in TIA groups. Lateral and medial views of left hemisphere and lateral and medial views of right hemisphere for each groups. The color scale represents T values in each RSN (maps thresholded at p<0.001, FDR corrected).
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[18,31]. In this study, patients with TIA showed significant decreased functional connectivity in left medial prefrontal cortex, and increased functional connectivity in left superior frontal gyrus in SRN compared to HC. There were several studies indicating that monitoring-related medial prefrontal cortex activity was served as a signal that was engaged regulatory processes in the lateral prefrontal cortex to implement performance adjustments [32]. Thus, it may hint that the reduction of functional connectivity of the medial prefrontal cortex in SRN may affect the self-related activity of TIA patients. In fMRI experiments, Goldberg et al. have found evidence that the superior frontal gyrus is involved in self-awareness, in coordination with the action of the sensory system [33]. According to the definition of TIA, the symptoms of a TIA are short-lived and usually last a few seconds to a few minutes and most symptoms disappear within 60 minutes [1]. This may indicate that the increase of functional connectivity of the superior frontal gyrus regulated the recovery process of TIA patients after onset of illness.

DAN is thought to mediate goal-directed top-down processing. It is also involved in many higher-order cognitive tasks [34]. Disruption of interhemispheric FC was reported to significantly correlate with abnormal detection of visual stimuli in the attention network in stroke patients [35], who share the similar pathophys-

iology with TIAs. We found that the right inferior parietal lobule (IPL) and left superior parietal lobule presented the decreased functional connectivity within DAN in TIA patients. We reviewed evidences which showed that the right IPL played an important role in two different aspects of attention: maintaining attentive control on current task goals [36,37] as well as responding to salient new information or alerting stimuli in the environment [38,39]. Therefore, damage to the right IPL may lead to deficits in both maintaining attention and responding to salient events in TIA patients. Previous study suggested that the superior parietal lobe was critical for sensorimotor integration by maintaining an internal representation of the body's state [40]. Our findings may reflect that the two brain regions within DAN play a role in cognitive regulation and functional maintenance in TIA patients.

A central-executive network (CEN) is responsible for high-level cognitive functions [41]. The CEN plays a critical role in the active maintenance and manipulation of information in working memory, and in judgment and decision making in the context of goal directed behavior [42].We knew that TIA patients may develop persisting impairment in execution, visual attention function and working memory. However, the relation between brain regions belonging to CEN and behavioral expression of TIA patients need to be further studied. Besides, our study found the
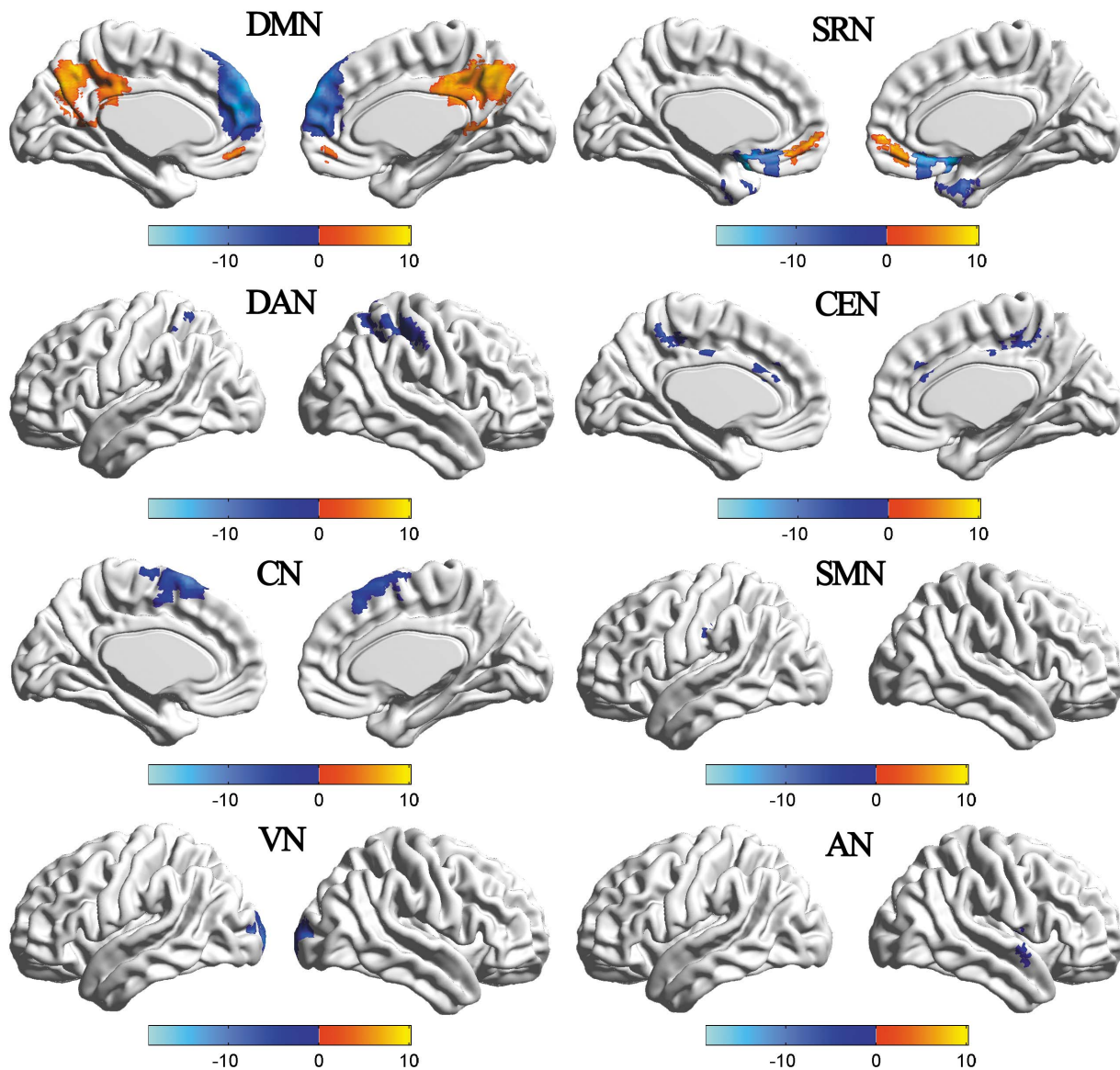
Figure 2. 3D renders of a two-sample t-test each RSNs in the TIA vs. HC (p<0.001, FDR corrected). The warm and cold colors indicate the brain regions with significantly increased and decreased functional connectivity in TIA, respectively.
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decreased functional connectivity of the anterior cingulate cortex in CEN in TIA patients compared with HC. It has been suggested that the top-down attention control is mediated by the anterior cingulate cortex (ACC) [43,44]. The ACC is connected with the prefrontal cortex and parietal cortex as well as the motor system and the frontal eye fields [45], which makes it a central station for processing top-down and bottom-up stimuli and assigning appropriate control to other areas in the brain [46]. To sum up, these findings may thus reflect the functional impairment of CEN in the cognitive control of TIA.

Some research found that core network (CN) was not only associated with task control function [47,48], but also involved in "salience" processing during resting state [49]. Another important role of CN is to switch between the DMN and task-related networks in cognitive control [50]. We found decreased functional connectivity in left superior frontal gyrus and right medial frontal gyrus. Previous researches have suggested that the superior frontal

gyrus and medial frontal gyrus may form part of an attention or executive control system [47,51], and TIA patients also have the impairment in these functions. This implied that these brain regions within CN played a significant role in cognitive control of TIA patients.

In general, the perceptual systems consisted of the visual, auditory and somato-motor networks, which can be considered at the lower-order of the cognitive processing hierarchy. Our results indicated that TIA patients presented a certain decreased functional connectivity among SMN (left postcentral gyrus), VN (bilateral middle occipital gyrus) and AN (right superior temporal gyrus) compared with HC. What's more, some previous researches have demonstrated the functions of these brain regions: the lateral postcentral gyrus was involved in somatosensory processing from the heterolateral side of the body [52,53]; the middle occipital gyrus was involved in visual function [54,55], memory [56,57], language [58,59] and some other functions [60,61]; the superior

Table 3. The differences in functional connectivity between the two groups.

RSNs	Brain areas	MNI			T values	Voxel size
		X	Y	Z		
DMN	L-Middle Temporal Gyrus	−63	−15	−18	−12.5921	30
	L-Inferior Temporal Gyrus	−48	3	−36	−8.0991	30
	R-Superior Frontal Gyrus	12	57	24	−18.8929	638
	L-Medial Frontal Gyrus	−3	51	−9	6.4498	27
	L-Cingulate Gyrus/Precuneus	−9	−69	36	10.2085	705
	R-Angular Gyrus	42	−63	51	5.7933	29
SRN	L-Medial Prefrontal Gyrus	−39	54	−9	−19.8424	86
	L-Superior Frontal Gyrus	0	51	−6	8.4107	34
DAN	R-Inferior Parietal Lobule	42	−36	60	−7.9824	91
	L-Superior Parietal Lobule	−36	−54	63	−6.3067	12
CEN	R-Precuneus	9	−24	39	−10.9888	89
	R-Anterior Cingulate	3	33	27	−6.6113	40
CN	L-Superior Frontal Gyrus	−3	15	63	−11.5482	356
	R-Medial Frontal Gyrus	−33	−15	51	−6.8303	36
SMN	L-Postcentral Gyrus	−48	−18	30	−6.4079	32
VN	R-Middle Occipital Gyrus	24	−96	−3	−10.6933	63
	L-Middle Occipital Gyrus	−3	−105	−3	−14.1585	46
AN	R-Superior Temporal Gyrus	51	−3	12	−6.2424	39

Abbreviations: RSNs, Resting state networks; L, Left; R, Right; FC, Functional connectivity; TIAs, Transient ischemic attack patients; HC, Healthy controls; MNI, Montreal Neurologic Institute; DMN, default mode network; SRN, self-referential network; DAN, dorsal attention network; CEN, central-executive network; CN, core network; SMN, somato-motor network; VN, visual network; AN, auditory network. All the coordinates are donated by Montreal Neurological Institute (MNI) space coordinates. T score represents the statistical value of peak voxel showing the differences in functional connectivity between the two groups. Positive and negative T values indicate increased and decreased functional connectivity in the TIA group, respectively.
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temporal gyrus was involved in auditory processing, but also has been implicated as a critical structure in social cognition [62]. Furthermore, known from clinical history and the previous studies, the most frequent symptoms of TIA patients include temporary loss of vision, difficulty speaking, weakness on one side of the body, and numbness or tingling, usually on one side of the body [63]. Therefore, the aberrant functional connectivity of SMN, VN and AN found in our study may be associated with perceptual impairments in TIA patients.

Unfortunately, the study failed to demonstrate significant correlation between RSNs and neuropsychological scores. The possible reason might be that the patients we recruited were young and only had a short disease history. Therefore, function alteration may not be significantly enough to be explored by traditional psychological scales used in our study. Actually, this was in line with the hypothesis that there was a long presymptomatic period in the development of cognitive impairment and psychiatric disturbances after the ischemic attack [64].

Several limitations of the current study are deserved to be mentioned. First, the sample size for TIA patients is small, with variations in the age and disease on-set time, which might affect the statistical analysis and results of this study. In addition, the ICA method is not able to provide information on the functional connectivity in all brain regions, for instance, the limbic system [65]. Furthermore, the neurophysiological meaning of the RSNs still remains unclear. Finally, although a lot of literature revealed that spontaneous brain activity [66] is organized into RSNs [18,67], so far, the RSNs hasn't provide a complete description of brain functional architecture.

Conclusions

In conclusion, we observed selective impairments of RSN intrinsic FC in TIA patients, whose all eight RSNs had aberrant functional connectivity. Both increased and decreased functional connectivity was found in the DMN and SRN, and decreased functional connectivity was exhibited in all other RSNs in TIA patients compared to HC. Our fMRI study might potentially put forward a novel way to understand the neuro-pathophysiological mechanism of cognition function changes in TIA.

Supporting Information

Methods S1   Supporting methods.
(DOC)

Author Contributions

Conceived and designed the experiments: JG LH QG RL HC. Performed the experiments: JG LH QG L. Zeng HC. Analyzed the data: RL SW L. Zhu HC. Contributed reagents/materials/analysis tools: RL SW L. Zhu HC. Wrote the paper: RL SW JG HC.

References

1. Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, et al. (2002) Transient ischemic attack–proposal for a new definition. N Engl J Med 347: 1713–1716.

2. Bakker FC, Klijn CJ, Jennekens-Schinkel A, Kappelle LJ (2000) Cognitive disorders in patients with occlusive disease of the carotid artery: a systematic review of the literature. J Neurol 247: 669–676.

3. Cloft HJ, Lynn MJ, Feldmann E, Chimowitz M (2011) Risk of cerebral angiography in patients with symptomatic intracranial atherosclerotic stenosis. Cerebrovasc Dis 31: 588–591.

4. Sachdev PS, Brodaty H, Valenzuela MJ, Lorentz L, Looi JC, et al. (2004) The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients. Neurology 62: 912–919.

5. Bakker FC, Klijn CJ, Jennekens-Schinkel A, van der Tweel I, Tulleken CA, et al. (2003) Cognitive impairment in patients with carotid artery occlusion and ipsilateral transient ischemic attacks. J Neurol 250: 1340–1347.

6. Mohammadi B, Kollewe K, Samii A, Krampfl K, Dengler R, et al. (2009) Changes of resting state brain networks in amyotrophic lateral sclerosis. Exp Neurol 217: 147–153.

7. Liao W, Chen H, Feng Y, Mantini D, Gentili C, et al. (2010) Selective aberrant functional connectivity of resting state networks in social anxiety disorder. NeuroImage 52: 1549–1558.

8. Calhoun VD, Kiehl KA, Pearlson GD (2008) Modulation of temporally coherent brain networks estimated using ICA at rest and during cognitive tasks. Hum Brain Mapp 29: 828–838.

9. Zhang Z, Lu G, Zhong Y, Tan Q, Yang Z, et al. (2009) Impaired attention network in temporal lobe epilepsy: a resting FMRI study. Neurosci Lett 458: 97–101.

10. Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, et al. (2006) Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 103: 13848–13853.

11. Jafri MJ, Pearlson GD, Stevens M, Calhoun VD (2008) A method for functional network connectivity among spatially independent resting-state components in schizophrenia. NeuroImage 39: 1666–1681.

12. Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME (2006) Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc Natl Acad Sci U S A 103: 10046–10051.

13. Bejot Y, Rouaud O, Benatru I, Durier J, Caillier M, et al. (2007) Trends in the incidence of transient ischemic attacks, premorbid risk factors and the use of preventive treatments in the population of Dijon, France from 1985 to 2004. Cerebrovasc Dis 23: 126–131.

14. Pendlebury ST, Markwick A, de Jager CA, Zamboni G, Wilcock GK, et al. (2012) Differences in cognitive profile between TIA, stroke and elderly memory research subjects: a comparison of the MMSE and MoCA. Cerebrovasc Dis 34: 48–54.

15. Calhoun VD, Adali T, Pearlson GD, Pekar JJ (2001) A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp 14: 140–151.

16. Genovese CR, Lazar NA, Nichols T (2002) Thresholding of statistical maps in functional neuroimaging using the false discovery rate. NeuroImage 15: 870–878.

17. Sorg C, Riedl V, Muhlau M, Calhoun VD, Eichele T, et al. (2007) Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proc Natl Acad Sci U S A 104: 18760–18765.

18. Mantini D, Perrucci MG, Del Gratta C, Romani GL, Corbetta M (2007) Electrophysiological signatures of resting state networks in the human brain. Proc Natl Acad Sci U S A 104: 13170–13175.

19. Kasner SE, Gorelick PB (2004) Prevention and treatment of ischemic stroke. Blue Books of Practical Neurology 29.

20. Johnston SC, O'Meara ES, Manolio TA, Lefkowitz D, O'Leary DH, et al. (2004) Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. Ann Intern Med 140: 237–247.

21. Charoenkitkarn V, Kasemkitwattana S, Therrien B, Thosingha O, Voraponsathorn T (2009) Cognitive Performance after a Transient Ischemic Attack: Attention, Working Memory, and Learning and Memory. Thai Journal of Nursing Research 13: 199–215.

22. Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 1124: 1–38.

23. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, et al. (2009) Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci Biobehav Rev 33: 279–296.

24. Cabeza R, Nyberg L (2000) Imaging cognition II: An empirical review of 275 PET and fMRI studies. J Cogn Neurosci 12: 1–47.

25. Herath P, Kinomura S, Roland PE (2001) Visual recognition: evidence for two distinctive mechanisms from a PET study. Hum Brain Mapp 12: 110–119.

26. du Boisgueheneuc F, Levy R, Volle E, Seassau M, Duffau H, et al. (2006) Functions of the left superior frontal gyrus in humans: a lesion study. Brain 129: 3315–3328.

27. Shaywitz SE, Shaywitz BA, Pugh KR, Fulbright RK, Skudlarski P, et al. (1999) Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks. JAMA 281: 1197–1202.

28. Kennedy DP, Redcay E, Courchesne E (2006) Failing to deactivate: resting functional abnormalities in autism. Proc Natl Acad Sci U S A 103: 8275–8280.

29. Shulman G, Fiez J, Corbetta M, Buckner R, Miezin F, et al. (1997) Common Blood Flow Changes across Visual Tasks: II. Decreases in Cerebral Cortex. Journal of Cognitive Neuroscience 9: 648–663.

30. Sestieri C, Corbetta M, Romani GL, Shulman GL (2011) Episodic memory retrieval, parietal cortex, and the default mode network: functional and topographic analyses. J Neurosci 31: 4407–4420.

31. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, et al. (2001) A default mode of brain function. Proc Natl Acad Sci U S A 98: 676–682.

32. Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004) The role of the medial frontal cortex in cognitive control. Science 306: 443–447.

33. Goldberg, II, Harel M, Malach R (2006) When the brain loses its self: prefrontal inactivation during sensorimotor processing. Neuron 50: 329–339.

34. Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3: 201–215.

35. Carter AR, Astafiev SV, Lang CE, Connor LT, Rengachary J, et al. (2010) Resting interhemispheric functional magnetic resonance imaging connectivity predicts performance after stroke. Ann Neurol 67: 365–375.

36. Adler CM, Sax KW, Holland SK, Schmithorst V, Rosenberg L, et al. (2001) Changes in neuronal activation with increasing attention demand in healthy volunteers: an fMRI study. Synapse 42: 266–272.

37. Hager F, Volz HP, Gaser C, Mentzel HJ, Kaiser WA, et al. (1998) Challenging the anterior attentional system with a continuous performance task: a functional magnetic resonance imaging approach. Eur Arch Psychiatry Clin Neurosci 248: 161–170.

38. Gur RC, Turetsky BI, Loughead J, Waxman J, Snyder W, et al. (2007) Hemodynamic responses in neural circuitries for detection of visual target and novelty: An event-related fMRI study. Hum Brain Mapp 28: 263–274.

39. Linden DE, Prvulovic D, Formisano E, Vollinger M, Zanella FE, et al. (1999) The functional neuroanatomy of target detection: an fMRI study of visual and auditory oddball tasks. Cereb Cortex 9: 815–823.

40. Wolpert DM, Goodbody SJ, Husain M (1998) Maintaining internal representations: the role of the human superior parietal lobe. Nat Neurosci 1: 529–533.

41. Bressler SL, Menon V (2010) Large-scale brain networks in cognition: emerging methods and principles. Trends Cogn Sci 14: 277–290.

42. Bunge SA, Ochsner KN, Desmond JE, Glover GH, Gabrieli JD (2001) Prefrontal regions involved in keeping information in and out of mind. Brain 124: 2074–2086.

43. Gitelman DR, Nobre AC, Parrish TB, LaBar KS, Kim YH, et al. (1999) A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive controls. Brain 122 (Pt 6): 1093–1106.

44. Marois R, Chun MM, Gore JC (2004) A common parieto-frontal network is recruited under both low visibility and high perceptual interference conditions. J Neurophysiol 92: 2985–2992.

45. Posner MI, DiGirolamo GJ, editors (1998) Executive attention: Conflict, target detection, and cognitive control. Parasuraman, R. ed. Cambridge, MA. 401–423 p.

46. Zhang WH, Lu JM (2009) The Practice of Affective Teaching: A View from Brain Science. International Journal of Psychological Studies 1: 35–41.

47. Dosenbach NU, Visscher KM, Palmer ED, Miezin FM, Wenger KK, et al. (2006) A core system for the implementation of task sets. Neuron 50: 799–812.

48. Mantini D, Corbetta M, Perrucci MG, Romani GL, Del Gratta C (2009) Large-scale brain networks account for sustained and transient activity during target detection. NeuroImage 44: 265–274.

49. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, et al. (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27: 2349–2356.

50. Sridharan D, Levitin DJ, Menon V (2008) A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci U S A 105: 12569–12574.

51. Dehaene S, Artiges E, Naccache L, Martelli C, Viard A, et al. (2003) Conscious and subliminal conflicts in normal subjects and patients with schizophrenia: the role of the anterior cingulate. Proc Natl Acad Sci U S A 100: 13722–13727.

52. Downar J, Crawley AP, Mikulis DJ, Davis KD (2000) A multimodal cortical network for the detection of changes in the sensory environment. Nat Neurosci 3: 277–283.

53. Georgiadis JR, Reinders AA, Paans AM, Renken R, Kortekaas R (2009) Men versus women on sexual brain function: prominent differences during tactile genital stimulation, but not during orgasm. Hum Brain Mapp 30: 3089–3101.

54. Waberski TD, Gobbele R, Lamberty K, Buchner H, Marshall JC, et al. (2008) Timing of visuo-spatial information processing: electrical source imaging related to line bisection judgements. Neuropsychologia 46: 1201–1210.

55. Larsson J, Landy MS, Heeger DJ (2006) Orientation-selective adaptation to first- and second-order patterns in human visual cortex. J Neurophysiol 95: 862–881.

56. Slotnick SD, Schacter DL (2006) The nature of memory related activity in early visual areas. Neuropsychologia 44: 2874–2886.

57. Leube DT, Erb M, Grodd W, Bartels M, Kircher TT (2001) Differential activation in parahippocampal and prefrontal cortex during word and face encoding tasks. Neuroreport 12: 2773–2777.

58. Vorobyev VA, Alho K, Medvedev SV, Pakhomov SV, Roudas MS, et al. (2004) Linguistic processing in visual and modality-nonspecific brain areas: PET recordings during selective attention. Brain Res Cogn Brain Res 20: 309–322.

59. Abrahams S, Goldstein LH, Simmons A, Brammer MJ, Williams SC, et al. (2003) Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. Hum Brain Mapp 20: 29–40.

60. Herholz K, Ehlen P, Kessler J, Strotmann T, Kalbe E, et al. (2001) Learning face-name associations and the effect of age and performance: a PET activation study. Neuropsychologia 39: 643–650.

61. Ushida T, Ikemoto T, Tanaka S, Shinozaki J, Taniguchi S, et al. (2008) Virtual needle pain stimuli activates cortical representation of emotions in normal volunteers. Neurosci Lett 439: 7–12.

62. Bigler ED, Mortensen S, Neeley ES, Ozonoff S, Krasny L, et al. (2007) Superior temporal gyrus, language function, and autism. Dev Neuropsychol 31: 217–238.

63. Crisostomo RA, Garcia MM, Tong DC (2003) Detection of diffusion-weighted MRI abnormalities in patients with transient ischemic attack: correlation with clinical characteristics. Stroke 34: 932–937.

64. den Heijer T, Geerlings MI, Hoebeek FE, Hofman A, Koudstaal PJ, et al. (2006) Use of hippocampal and amygdalar volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly people. Arch Gen Psychiatry 63: 57–62.

65. Damoiseaux JS, Beckmann CF, Arigita EJ, Barkhof F, Scheltens P, et al. (2008) Reduced resting-state brain activity in the "default network" in normal aging. Cereb Cortex 18: 1856–1864.

66. Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8: 700–711.

67. Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005) Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 360: 1001–1013.