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Regional homogeneity abnormalities in patients with transient ischaemic attack: A resting-state fMRI study

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HIGHLIGHTS

- The regional homogeneity (ReHo) method was employed to investigate transient ischaemic attack (TIA)-related modulations of neural activity in the resting state.
- Altered regional spontaneous activities in dorsolateral prefrontal cortex (dlPFC) and inferior prefrontal cortex (iPFC) were found in TIAs, which were positively correlated with cognitive function in these patients.
- ReHo could be regarded as a promising tool to better our understanding of the neurobiological consequences of TIA.

ABSTRACT

Objective: To investigate regional activity abnormalities in the resting state in patients with transient ischaemic attack (TIA) using a regional homogeneity (ReHo) method combined with functional magnetic resonance imaging (fMRI) and to examine the relationship between regional activity abnormalities and clinical variables.
Methods: Resting-state fMRI was conducted in 21 patients with right-sided TIA and in 21 healthy volunteers. The ReHo was calculated to assess the strength of the local signal synchrony and was compared between the two groups.
Results: Compared with the controls, the TIA patients exhibited a decreased ReHo in the right dorsolateral prefrontal cortex (dlPFC), the right inferior prefrontal cortex (iPFC), the right ventral anterior cingulate cortex (vACC) and the right dorsal posterior cingulate cortex (dPCC). In addition, the mean ReHo values in the right dlPFC and the right iPFC were significantly correlated with the Montreal Cognitive Assessment (MoCA) in TIA patients.
Conclusions: Neural activities in the resting state are changed in TIA patients even without visible ischaemic lesions on conventional MRI. The positive correlation between the ReHo of resting-state fMRI and cognition suggests that ReHo could be a promising tool to observe the neurobiological consequences of TIA.
Significance: The present study revealed abnormal local synchronisation of spontaneous neural activities in patients with TIA.

1. Introduction

Transient ischaemic attack (TIA) is defined as an episode of reversible neurological deficit caused by temporary focal cerebral nervous system hypoperfusion, of which the clinical symptoms can be resolved within 24 h (Albers et al., 2002). Although the brain is traditionally regarded as healthy, various studies have provided supporting evidence that patients who have suffered from a TIA may exhibit different degrees of neuropsychological impairment. Many risk factors of TIA, such as hypertension, carotid stenosis and diabetes, are associated with cognitive impairment, especially difficulties with temporal orientation and verbal recall (Johnston

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et al., 2004; Prencipe et al., 2003). In addition, TIA patients have been reported to have significant cognitive impairment compared with controls in recent studies (Guyomard et al., 2011). However, the mechanism of such neurocognitive dysfunction is unclear.

As resting-state functional magnetic resonance imaging (fMRI) has improved, the investigation of baseline brain activity associated with neurological function has become increasingly more sensitive. It can be applied to detect low-frequency fluctuation (LFF) in various cerebral areas based on resting-state blood oxygen level dependence (BOLD) signals. Therefore, fMRI reflects the spontaneous neuronal activity of certain brain regions (Biswal et al., 1995). Resting-state fMRI signals have been suggested to be functionally meaningful and reflect the 'intrinsic' functional organisation of the human brain (Raichle, 2010). Unique changes in resting-state fMRI have been reported in patients with various pathological states, such as epilepsy and Alzheimer's disease (Aghakhani et al., 2006; Liu et al., 2012). Recent studies have even demonstrated altered resting-state effective connectivity and corresponding neurological deficits in stroke patients (Park et al., 2011). However, though with similar pathophysiology, the baseline brain activity of patients with TIA has been rarely explored using resting-state fMRI.

Regional homogeneity (ReHo) is a newly developed resting-state fMRI approach that analyses the similarities or coherence of intraregional spontaneous low-frequency (<0.08 Hz) BOLD signal fluctuations using voxel-wise analysis across the whole brain (Zang et al., 2004). It is assumed that the brain activity occurs more likely as clusters rather than as a single voxel, and such activity changes with different diseases (Zang et al., 2004). Since the BOLD signal of resting-state fMRI can reflect spontaneous neuronal activity, ReHo can be used to measure the regional synchrony of brain activity recorded by resting-state fMRI (Yuan et al., 2008). ReHo has been successfully used to detect local abnormalities in subjects with various neurological diseases such as neuromyelitis optica and Parkinson's disease (Liang et al., 2011; Wu et al., 2009) and has been shown to be helpful in exploring the neurobiological consequences of these diseases. Therefore, we hypothesised that ReHo may also be a useful tool to reveal the neurobiological consequences of TIA.

In this study, we employed ReHo to investigate whether the synchrony of regional spontaneous activity in resting-state fMRI is altered in TIA. Moreover, we examined whether ReHo is associated with clinical parameters in this disease.

2. Materials and methods

2.1. 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 study. From June 2010 to September 2011, 21 TIA patients who had suffered from an ischaemic event in the right hemisphere were enroled in the study. According to the WHO recommendations, TIA was defined as any syndrome of focal neurological dysfunction ascribable to a vascular territory and lasting <24 h (Bejot et al., 2007). TIA was diagnosed by two senior stroke neurologists and confirmed by consensus at clinical team meetings. The study's exclusion criteria were as follows: (1) patients younger than 40 years or older than 65 years of age; (2) posterior circulation or left-hemisphere localisation; (3) symptoms most likely related to a non-ischaemic diagnosis such as a psychiatric disorder, seizure or migraine; (4) patients with leukoaraiosis or brain lesions on fluid attenuated inversion recovery (FLAIR) images or T2-weighted images and (5) patients with pre-existing cognitive impairment or psychiatric diseases before TIA. The controls were healthy volunteers matched for age, sex and years of education with no history of stroke/TIA or other neurological disorders. All subjects underwent complete blood count and metabolic profile testing, and a carotid duplex ultrasound examination. The degree of carotid stenosis was calculated according to Grant's method (Grant et al., 2003) by a consensus of two readers blinded to the clinical data using carotid duplex ultrasound or magnetic resonance angiography (MRA). To detect potential cardiac sources of emboli (including atrial fibrillation and valve diseases), 12-lead electrocardiogram, Holter monitor and transthoracic echocardiography or trans-oesophageal echocardiography were used.

2.2. Cognitive assessment

Cognitive assessments of these subjects were made by two independent neuropsychologists. The Montreal Cognitive Assessment (MoCA), which assesses the general condition of cognitive function; the Auditory Verbal Memory Test (AVMT, Chinese version based on the California Verbal Learning Test), which analyses verbal memory; and the backward Digital Span Test (DST-backward), which evaluates working memory, were conducted in all subjects.

2.3. Data acquisition

Imaging was performed on a 3-tesla Trio scanner (Siemens AG, Erlangen, Germany) by using an eight-channel birdcage head coil. Each subject lay supine with the head snugly fixed by a belt and foam pads. The resting-state fMRIs were obtained by using an echo-planar imaging sequence with the following protocols: TR/TE, 2000/30; field of view, $240 \times 240\ mm^2$; acquisition matrix, 64×64; and slice thickness, 5 mm with no gap. This acquisition sequence generated 190 volumes in 6 min and 20 s. During the resting-state fMRI scanning, all subjects were informed to keep still with their eyes closed, think of nothing in particular and remain awake. A 3D time-of-flight MRA was performed to visualise the cerebral vasculature of the subjects, and 3D high-resolution T1- and T2-weighted and FLAIR images were also acquired to detect clinically silent lesions.

2.4. Data analysis

Demographic data as well as cognitive characteristics were analysed using SPSS (version 15.0). The differences in these variables between the TIA patients and the controls were calculated by the two-sample *t*-test and Pearson's χ^2-test.

Pre-processing of the resting-state fMRI data was conducted using data processing assistant for resting-state fMRI (DPARSF, http://www.restfmri.net/forum/DPARSF) v2.1 software as previously described (Chao-Gan and Yu-Feng, 2010). In brief, the first 10 volumes of each functional time series were discarded for participant adaptation to the scanning. The remaining 180 images were slice-time-corrected, realigned, normalised to the East Asian brain template provided by statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and resampled to $3 \times 3 \times 3\ mm^3$. Several sources of spurious variance, including estimated motion parameters, linear drift and average BOLD signals in ventricular and white matter regions, were removed from the data through linear regression. Then a temporal filter (0.01–0.08 Hz) was used to reduce the low-frequency drift and physiological high-frequency noise.

Anatomical data were processed to separate the grey matter (GM) from the 3D T1-weighted structural images using voxel-based morphometry toolbox (VBM8, http://dbm.neuro.uni-jena.de/vbm.html). Briefly, images were bias corrected, tissue