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Research article

Decreased functional connectivity within the default-mode network in acute brainstem ischemic stroke

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ABSTRACT

Purpose: Ischemic stroke within the brainstem is associated with an increased risk of cognitive dysfunction. This study aimed to explore the integrity of a default-mode network (DMN) and its relationship with clinical variables in patients with acute ischemic brainstem stroke using an independent component analysis (ICA) approach.
Materials and methods: Twenty-one patients with acute ischemic brainstem stroke and 25 well-matched healthy subjects were enrolled in this study and underwent resting-state functional magnetic resonance imaging. The ICA was adopted to extract the DMN, including its anterior and posterior components. Pearson correlation analyses were performed to investigate the relationship between DMN connectivity and clinical variables.
Results: Compared with healthy controls, patients with acute ischemic stroke showed significantly decreased functional connectivity in the right medial prefrontal cortex (mPFC) and right precuneus within the anterior and posterior DMN, respectively. After correcting for age, sex, and education, hypoconnectivity in the right mPFC and right precuneus was negatively correlated with higher homocysteine in patients with stroke ($r = -0.592$, $p = 0.010$ and $r = -0.491$, $p = 0.039$, respectively).
Conclusion: The finding of decreased functional connectivity within the DMN of patients with acute brainstem stroke provides novel insight into the neural mechanisms that underlie cognitive impairment following ischemic insult to this brain region.

1. Introduction

As a special type of stroke, brainstem ischemic stroke can destroy the cortico-ponto-cerebellar circuit and limbic system, which are extensively and reciprocally linked via neurotransmitter projection pathways [1], Such destruction can cause stroke related cognitive impairment (e.g., decline in memory and visuospatial skills), as well as executive dysfunction and attention deficits [2]. The abnormal production and delivery of neurotransmitters, such as dopamine, glutamate and acetylcholine, may lead to the functional dysconnectivity of remote brain regions [1]. It has been proposed that cognitive impairment after brainstem stroke is generated in the cerebral nervous system by a variety of mechanisms, such as decreased spontaneous activity, decreased neural synchrony, altered tonotopy, and aberrant neural connectivity to structures within the cerebral networks [2].

Recently, an increasing number of studies have reported significant insights on the structural and functional changes in the post-stroke brain [3,4], which suggest the potential for neuroimaging to understand the neuropathological mechanism of brainstem ischemic stroke. A single-photon-emission computed tomographic study by Hoffmann et al. suggested that brainstem stroke may cause significant cognitive impairment (best delineated by formal neuropsychological evaluation), and that the functional neuroimaging technique may be more sensitive than structural neuroimaging techniques to assess stroke-related damage [5]. Resting-state functional magnetic resonance imaging has enabled researchers to evaluate brain functional architecture on the basis of blood oxygenation level-dependent signal, which represents baseline spontaneous neuronal activity [6]. Resting-state networks (RSNs), namely intrinsic connectivity networks, are defined as brain regions with highly correlated time courses of low-frequency (< 0.1 Hz) blood oxygenation level-dependent signal fluctuations during the baseline state [7]. Among these RSNs, the default-mode network (DMN), consisting of the medial prefrontal cortex (mPFC), precuneus, anterior cingulate cortex, and posterior cingulate cortex

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(PCC) [8], has been suggested to be associated with cognitive impairment in a number of disorders, such as Alzheimer's disease [9] and mild cognitive impairment [10]. Reduction of functional connectivity within the DMN has been observed in patients with chronic subcortical stroke using a seed-based functional connectivity analysis [4]. However, no studies have revealed alterations within the DMN in acute brainstem ischemic stroke.

As a multiple-regression analysis method, the independent component analysis (ICA) has been increasingly applied to resting-state functional magnetic resonance imaging data [11]. This robust technique, which is based on blind source separation, captures the essential components of multivariate resting-state functional magnetic resonance imaging signals containing physiological noise [11]. Compared to the seed-based method, ICA has been proven to avoid a-priori seed selection as well as to reduce heterogeneity of the DMN pattern, thus allowing for unbiased exploration of the association between the DMN and cognitive function [12]. ICA also helps to separate signal fluctuations in RSNs from each other, and automatically captures the entire DMN as a single major component [13]. Moreover, the ICA-captured DMN exhibits a pattern which is consistent with that displayed by the task-based negative activation network [13].

On the basis of prior work and theoretical considerations, we aimed to apply the ICA method to identify the DMN and explore its connectivity in patients with acute brainstem ischemic stroke to test the hypotheses that (1) these patients would show reduced intrinsic connectivity within the DMN relative to healthy controls, and (2) that disrupted functional connectivity within the DMN would be correlated with specific clinical variables.

2. Materials and methods

2.1. Subjects and clinical data

All subjects provided written informed consent before their participation in the study protocol, which was approved by the Research Ethics Committee of our university.

We recruited 21 patients with brainstem ischemic stroke (15 males and 6 females, 65.10 ± 11.28 years) from the neurological department of our hospital from January 2017 to June 2017. Eleven out of the 21 patients had infarct lesions on the left side of the brainstem, while 10 had lesions on the right side of the brainstem. Stroke severity was based on National Institutes of Health Stroke Severity (NIHSS) score [14]. The inclusion criteria for patients were as follows: (1) between 40 and 80 years of age, (2) right-handedness before stroke; (3) first-onset brainstem ischemic stroke, and (4) 24 h after acute stroke onset. The exclusion criteria were as follows: (1) any neuropsychiatric comorbidity, such as depression based on the Hamilton Depression Rating Scale score > 7, (2) any clinically significant or unstable major medical disorder that could affect cognitive function (e.g., anemia, thyroid dysfunction and cancer), (3) severe white matter hyperintensity manifesting as a Fazekas scale score > 1, (4) any serious movement disorders (whole extremity Fugl-Meyer Assessment > 90 and Barthel Index > 90), (5) any criteria for mild cognitive impairment as described by Petersen [15], and (6) any contraindication for magnetic resonance imaging (MRI). In addition, 25 age-, sex-, and education-matched healthy subjects (18 males and 7 females; 66.68 ± 7.16 years) were recruited as controls.

The blood pressure was measured just before the fMRI scan. Clinical data, including cardiovascular disease risk factors (hypertension, dyslipidemia, hyperglycemia, smoking and alcohol intake), Fugl-Meyer Assessment scores, and Barthel Index values were obtained from questionnaires and medical records. Homocysteine was also measured, as it has been reported as a risk factor for cognitive impairment in patients with acute stroke [16].

2.2. MRI acquisition

MRI data were acquired at 24 h after stroke onset using a 3.0 Tesla MRI scanner (Ingenia, Philips Medical Systems, Netherlands) with an 8-channel receiver array head coil. Head motion and scanner noise were reduced using foam padding and earplugs. Subjects were instructed to lie quietly with their eyes closed and without falling asleep, to not think about anything in particular, and to avoid any head motion during the scan. Functional images were obtained axially using a gradient echo-planar imaging sequence, as follows: repetition time = 2000 ms; echo time = 30 ms; slices = 36; thickness = 4 mm; gap = 0 mm; field of view = 240 mm × 240 mm; acquisition matrix = 64 × 64; and flip angle = 90°. The fMRI sequence took 8 min and 8 s to complete. Structural images were acquired with a three-dimensional turbo fast echo T1WI sequence with high resolution, as follows: repetition/echo time = 8.2/3.8 ms; slices = 170; thickness = 1 mm; gap = 0 mm; flip angle = 8°; acquisition matrix = 256 × 256; field of view = 256 mm × 256 mm. The structural sequence took 5 min and 29 s to complete.

2.3. Data preprocessing and independent component analysis

fMRI data preprocessing was carried out using the software tool, Data Processing Assistant for Resting-State fMRI (http://www.restfmri.net/forum/DPARSF), based on statistical parametric mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm). The first 20 volumes were removed from each time series to account for the time it took participants to adapt to the scanning environment. Slice timing and realignment for head-motion correction were then performed for the remaining 230 images. Participant data exhibiting head motion > 2.0 mm translation or > 2.0° rotation were excluded from analysis. The remaining dataset was spatially normalized to the Montreal Neurological Institute template (resampling voxel size = 3 × 3 × 3 mm^3), after which spatial smoothing with a Gaussian kernel of 6 mm was sequentially performed.

RSNs were selected using the Group ICA of fMRI Toolbox software (Medical Image Analysis Lab, University of New Mexico, Albuquerque, NM, USA; http://icatb.sourceforge.net/). The ICA analysis was performed in three stages: (a) data reduction, (b) application of the ICA algorithm, and (c) back-reconstruction for each individual subject. The validation analyses were performed with the number of components from 50 to 40, then to 30. The data reduction was followed by a group spatial ICA, performed on the participants' aggregate data, resulting in the final estimation of our independent components (ICs) [17]. To achieve robust and accurate results, the number of independent components was set at 40 and the run times of the Group ICA of fMRI Toolbox were chosen as 100. The intensity values of connectivity within each independent component were converted to z-scores to reflect the degree to which the time series of a given voxel correlated with the mean time series of its corresponding component. The DMN component was identified by visual inspection as previously described [13] with the distinct peak of power spectrum at low-frequency (< 0.1 Hz) range, and spatial pattern and periodic temporal fluctuation.

2.4. Statistical analysis

Differences in demographic and clinical characteristics between patients with stroke and healthy controls were assessed using an independent two-sample *t*-test for continuous variables and a χ^2 test for proportions by the SPSS 19.0 software package (SPSS, Inc., Chicago, IL, USA). Statistical significance was set to $p < 0.05$.

For within-group analyses, one-sample *t*-tests were performed on the DMN spatial maps for each group using the SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The threshold was set to $p < 0.001$ and corrected using the false discovery rate (FDR) criterion. This strong p value, alongside the relatively conservative multiple comparison correction method, helped to obtain the most significant results that accurately