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Alteration of functional connectivity within visuospatial working memory-related brain network in patients with right temporal lobe epilepsy: A resting-state fMRI study

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ABSTRACT

Purpose: This study aimed to investigate the resting-state brain network related to visuospatial working memory (VSWM) in patients with right temporal lobe epilepsy (rTLE). The functional mechanism underlying the cognitive impairment in VSWM was also determined.
Method: Fifteen patients with rTLE and 16 healthy controls matched for age, gender, and handedness underwent a 6-min resting-state functional MRI session and a neuropsychological test using VSWM_Nback. The VSWM-related brain network at rest was extracted using multiple independent component analysis; the spatial distribution and the functional connectivity (FC) parameters of the cerebral network were compared between groups. Behavioral data were subsequently correlated with the mean Z-value in voxels showing significant FC difference during intergroup comparison.
Results: The distribution of the VSWM-related resting-state network (RSN) in the group with rTLE was virtually consistent with that in the healthy controls. The distribution involved the dorsolateral prefrontal lobe and parietal lobe in the right hemisphere and the partial inferior parietal lobe and posterior lobe of the cerebellum in the left hemisphere ($p < 0.05$, AlphaSim corrected). Between-group differences suggest that the group with rTLE had a decreased FC within the right superior frontal lobe (BA8), right middle frontal lobe, and right ventromedial prefrontal lobe compared with the controls ($p < 0.05$, AlphaSim corrected). The regions of increased FC in rTLE were localized within the right superior frontal lobe (BA11), right superior parietal lobe, and left posterior lobe of the cerebellum ($p < 0.05$, AlphaSim corrected). Moreover, patients with rTLE performed worse than controls in the VSWM_Nback test, and there were negative correlations between ACCmeanRT (2-back) and the mean Z-value in the voxels showing decreased or increased FC in rTLE ($p < 0.05$).
Conclusion: The results suggest that the alteration of the VSWM-related RSN might underpin the VSWM impairment in patients with rTLE and possibly implies a functional compensation by enlarging the FC within the ipsilateral cerebral network.

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1. Introduction

Epilepsy is a chronic disease manifested by seizures, which are caused by highly synchronized abnormal neuronal discharges. Temporal lobe epilepsy (TLE) is the most prevalent form of localization-related epilepsy in humans [1]. Numerous studies have observed that patients with TLE, to a variable extent, suffer from cognitive impairment affecting memory [2], attention, alertness [3], language, and executive control function, with memory dysfunction being the most susceptible. As a type of memory function, working memory (WM) is a fundamental element for high-order cognitive functions and refers to the process of encoding and maintaining the information of material, followed by its retrieval. As proposed by Baddeley and his colleagues in their studies, the most common model of WM is composed of different subsystems, including the phonological loop, visuospatial sketchpad, episodic buffer system, and central executive machine [4]. Depending on the variable materials to be operated on, WM can be categorized into different types, two of which [i.e., verbal and visuospatial WM (VSWM)] are frequently investigated. Visuospatial working memory refers to the storage and transient manipulation of the visual information and spatial location of the object, followed by its retrieval [5]. This type of cognitive process is important for its use in everyday life.

Numerous studies have demonstrated that the VSWM in humans exhibits a right hemispheric laterality [6]. Its impairment is primarily linked to alterations in structure or function in the right side of the brain. Migliaccio et al. [7] explored the visuospatial memory performance in patients with PCA and the water diffusional parameters of the whole

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brain fibers, and their results suggested that the mnemonic deficits on the visuospatial field are associated specifically with the damage of fiber networks in the right hemisphere. A recent task functional MRI (fMRI) study concerning the VSWM in TLE revealed that the patients' performance score is lower and accompanied by weaker brain activation in the right superior parietal lobe (rSPL) compared with the healthy controls [8]. These evidences may help confirm the material-specific hypothesis of hemispheric function for memory, with right hemisphere specializing in VSWM.

Researchers have devoted a considerable amount of time into measuring the activation pattern associated with certain cognitive functions using the technique of task-based fMRI. This type of research is relevant towards the cognition studied and requires a priori information, optimized experimental paradigm, and the ability to execute in the tests, which is unavailable in cases with motor dysfunction. However, these demands are beyond consideration when it comes to rest. Resting-state fMRI (rs-fMRI) measures the spontaneous neural activities among separated and functionally connected brain regions in a relaxed subject, eyes closed but in the awake state. Since Biswal discovered in 1995 [9] that low frequency fluctuations between bilateral motor areas exhibit good temporal correlation, the exploration of the resting-state network (RSN) has become prevalent.

Many rs-fMRI studies have suggested the existence of an array of cerebral networks working persistently even when our brain is not involved in any cognitive tasks. These cerebral networks include primary networks of motion, vision, and audition and other superior cognitive networks, such as default mode, language, executive control, and WM networks [10]. A recent rs-fMRI study of healthy subjects that applied the ICA method by Filippi [11] extracted two lateralized frontal–parietal networks and named them left and right WM networks. The range of activity for the right-lateralized network mainly comprises the right prefrontal and intraparietal cortex. The regions involved within the network have a large extent of overlaps with previous findings regarding the cognitive function of VSWM in task-based fMRI [12]. For the lateralized distribution characteristic of the right WM network, right dominant hemisphere of VSWM and its organizational architecture in the WM system, we hypothesized that the right frontal–parietal network, or the right WM network displayed at rest, mainly represents the VSWM and can be used to help evaluate this cognitive function, especially in patients with an ipsilateral pathological lesion in the right cerebrum.

Currently, the use of rs-fMRI to investigate VSWM-related networks in patients with ipsilateral TLE has not been reported. Therefore, this study focused on investigating the differences in VSWM-related networks between a group of patients with right TLE (rTLE) and healthy controls under the resting state. By applying multiple independent component analysis (MICA) onto the rs-fMRI data, we selected the right-lateralized network and compared the spatial distribution and functional connectivity (FC) alteration between groups. Moreover, a neuropsychological test of VSWM_Nback was administered to all subjects. The behavioral data are subsequently correlated with the mean Z-value in voxels showing significant FC difference during intergroup comparison. This study aimed to uncover, from the perspective of the resting-state brain network, the functional correlation of VSWM impairment in patients with rTLE, as well as the underlying mechanism of compensation.

2. Material and method

2.1. Participants

Seventeen patients (eight males and nine females; mean age: 26.7 ± 6.9, average years of education: 10.8 ± 1.6 years) recruited from the Epilepsy Clinic of the Department of Neurology of the First Affiliated Hospital of Guangxi Medical University were enrolled in this study. Patients were included when clinical data and MRI and electroencephalography (EEG) findings suggested unilateral TLE. The diagnosis of TLE was based on the diagnostic manual from the International League Against Epilepsy [13]. Patients with epilepsy who met any two of the following criteria were included as patients with rTLE: i) seizures with typical semiology suggesting epileptic focus in the temporal lobe, ii) moderate to severe atrophy or sclerosis of the right hippocampus or aberrations in the right temporal lobe based on brain MRI, and iii) ictal or interictal EEG traces suggesting epileptic discharges in the right temporal lobe. All patients were on regular antiepileptic drug treatment following the International League Against Epilepsy therapeutic guideline (2006) [14], with Mini-Mental State Examination score of more than 24. Except for TLE, the patients did not have other systemic, neurological, or psychiatric diseases. The characteristics of clinical seizures and MRI and EEG findings are shown in Table 1 and Fig. 1.

Seventeen healthy volunteers (eight males and nine females; mean age: 26.5 ± 3.5, average years of education: 11.0 ± 3.4 years), matched for age, sex, and education, were recruited as healthy controls for the study. All participants were right-handed and provided written informed consent approved by the Ethics Committee of Guangxi Medical University.

2.2. fMRI data acquisition

Magnetic resonance imaging data were obtained using an Achieva 3 T MRI scanner (Philips, Netherlands) with a 12-channel head coil. The following sequences of the brain were acquired from all subjects: a) T1-weighted spin-echo sequence (repetition time [TR] = 3000 ms; echo time [TE] = 10 ms; slice thickness = 5 mm; pitch = 1 mm); and b) T2 flair sequence (TR = 9000 ms; TE = 120 ms; slice thickness = 6 mm; pitch = 1 mm) to check for MRI lesions/abnormalities. Moreover, the parameters for standard gradient-echo echo-planar rs-fMRI were as follows: TR = 2000 ms; TE = 30 ms; 31 axial slices; slice thickness = 5 mm; spacing between slices = 1 mm; flip angle = 90°; matrix size 64 × 64; field of view = 220 mm × 220 mm; and spatial resolution = 3.44 × 3.44 × 6.00 mm, containing 180 blood oxygenated level-dependent volumes, which were scanned in 6 min. During scanning, individuals were instructed to remain motionless, close their eyes, and not think about anything in particular, with their head stabilized by a head movement-constraining headphone and cushion to minimize motion. All subjects reported that they had not fallen asleep during the imaging protocol.

2.3. fMRI data processing and statistical analysis

2.3.1. Data preprocessing

The rs-fMRI data were preprocessed by Statistical Parametric Mapping (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK: http://www.fil.ion.ucl.ac.uk/spm/) using the MATLAB 7.11.0 platform. The ten initial images were discarded to eliminate nonequilibrium effects of magnetization. Functional images were realigned to the first one of each session with a six-degree rigid-body transformation to correct for minor head movements. To exceed the criteria, the maximum cumulative translation should be <2 mm and the maximum rotation should be <2°. Two male patients with rTLE and one female healthy control were excluded from the analysis because of motion. Finally, 15 patients with rTLE and 16 controls remained for further analysis. Data were then normalized to the SPM8 default EPI template using a standard affine transformation through data resampling with a resolution of 3 × 3 × 3 mm^3 and smoothed using an isotropic 4 mm Gaussian kernel. The smoothed images were subsequently used for the next step of ICA analysis.

2.3.2. Network identification through MICA

After these preprocessing steps, group-level spatial ICA was implemented on the entire sample of participants using MICA (http://www.nitrc.org/projects/cogicat/), which comprised three main steps:

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