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Research article

Alterations in the functional connectivity of a verbal working memory-related brain network in patients with left temporal lobe epilepsy

Wenli Huang[a], Donghong Huang[a], Zirong Chen[a], Wei Ye[b], Zongxia Lv[a], Limei Diao[c], Jinou Zheng[a,*]

[a] Department of Neurology, the First Affiliated Hospital, Guangxi Medical University, Nanning 530021, China
[b] Department of Radiology, the First Affiliated Hospital, Guangxi Medical University, Nanning 530021, China
[c] Department of Neurology, the First Affiliated Hospital, Guangxi University of Chinese Medicine, Nanning 530023, China

HIGHLIGHTS

- We extracted the VWM network for controls with n-back task from fMRI.
- We evaluated the RSFC of VWM network in left TLE patients and controls.
- Left TLE presented a decreased FC in bilateral MFG, IFG, IPL at resting state.
- The alterations in FC may reflect the impairment of VWM-related network in left TLE.
- ACCmeanRT (2-back) were not correlated with the FC in VWM-related regions.

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ABSTRACT

The aim of this study was to investigate the alterations in a verbal working memory (VWM)-related network in left temporal lobe epilepsy (lTLE) at rest. We evaluated 14 patients with lTLE and 14 control subjects by resting-state functional connectivity (RSFC). The region of interest was defined by the voxel with the highest *Z*-score during a VWM task according to functional magnetic resonance imaging in 16 healthy volunteers. Our study revealed that the network of RSFC was similar to the task-induced network in the healthy volunteers. Moreover, the patients with lTLE exhibited significantly decreased RSFC in the bilateral middle frontal gyrus, the inferior frontal gyrus and the inferior parietal lobule at rest compared to the control subjects. We found no significant correlation between the mean reaction time of the accurate responses in a 2-back task and the mean z-values within the regions that exhibited significant differences in RSFC at the individual level. The alterations in FCs of VWM-related network in lTLE suggested that epileptiform discharges can damage the brain regions, both local focus and remote areas and that the alterations were not associated with VWM performance.

1. Introduction

Temporal lobe epilepsy (TLE) is among the most common types of refractory focal epilepsy and is characterized by seizures originating in the temporal lobe structure. TLE has multiple causes, among which hippocampal sclerosis (HS) is particularly notable [1]. Studies have shown that patients with TLE suffer from different degrees of cognitive dysfunction in the domains of intelligence, executive function, alertness and memory [2,3]. Working memory (WM) is a crucial system that provides temporary storage and manipulation of information [4] and is also considered to be the foundation of complex cognitive functions, such as learning,

Abbreviations: TLE, temporal lobe epilepsy; HS, hippocampal sclerosis; VWM, verbal working memory; RSFC, resting-state functional connectivity; fMRI, functional magnetic resonance imaging; ROI, region of interest; MFG, middle frontal gyrus; IPL, inferior parietal lobule; SPL, superior parietal lobule; IFG, inferior frontal gyrus; PCG, precentral gyrus; PC, precuneus; CPL, cerebellar posterior lobe; SMA, supplementary motor area; SFG, superior frontal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; PFC, prefrontal cortex.

* Corresponding author. Fax: +86 771 5352627.
E-mail address: jiozheng@163.com (J. Zheng).

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language comprehension and reasoning [4]. Based on different storage materials, WM is divided into verbal, spatial and object memories [5]. Verbal WM (VWM) depends on the phonological loop and the central executive system to process verbal information, including words, letters and other materials that are primarily linguistically coded [5]. This type of information processing plays a crucial role in daily life.

Recently, blood oxygen level-dependent functional magnetic resonance imaging (BOLD fMRI) has been used to observe the neural activity of the entire brain cortex and changes in this activity directly and noninvasively due to this method's high spatial and temporal resolutions and good repeatability. Resting-state functional connectivity (RSFC) is a type of fMRI analysis that is conducted to observe brain networks and is based on temporal correlations between BOLD intensities in remote brain regions. This measure can determine spontaneous low-frequency neural activity in a brain network. Since Biswal et al. [6] demonstrated the reliability of functional connectivity (FC) by examining the motor system at rest in 1995, numerous similar studies have been performed [7,8] Studies have reported the FCs of TLE at rest [8] and in a WM task [9,10]. Moreover, researchers have studied the changes in the brain networks with the RSFC and a WM task in healthy controls [11]. To date, the alteration in FC of the VWM-related network in TLE at resting state is poorly understood.

Numerous studies have demonstrated that impairments of WM exist in patients with TLE. Patients with unilateral TLE are impaired on both verbal and visuospatial WM tasks irrespective of the affected hemisphere [12]. Left TLE (lTLE) patients commit more intrusion errors than right TLE patients on verbal tasks, whereas right TLE patients exhibit an additional impairment for visuospatial WM when compared with lTLE patients [12]. Regarding cerebral functional lateralization, the brain network for VWM exhibit a left hemisphere dominance, whereas the network for spatial WM exhibits a lateralization to the right hemisphere[13]. These findings demonstrate that lTLE patients exhibit strong effects on VWM. However, the association between VWM performance and alteration in FC of the VWM-related network has not been evaluated in lTLE patients.

In this study, we investigated the VWM-related network in groups of lTLE patients and healthy controls by applying RSFC with a seed region of interest (ROI), which was defined during a VWM task according to task-related fMRI. We tested the hypothesis that lTLE leads to an alteration in the FC of the VWM-related network during resting state, and that this alteration is associated with VWM performance.

2. Materials and methods

2.1. Subjects

Sixteen healthy volunteers (right-handed, nine males and seven females, 26.94 ± 1.64 years old, averaged educational time 14.37 ± 1.75 years) were investigated to examine the VWM network as identified by activation during a verbal n-back task. The subjects of RSFC included 14 patients with lTLE (right-handed, six males and eight females, 25.21 ± 8.03 years old, averaged educational time 12.57 ± 2.79 years) and 14 healthy control subjects (right-handed, seven males and seven females, 27.71 ± 2.58 years old, averaged educational time 14.21 ± 1.93 years). These patients were recruited from the Outpatient Neurologic Clinic of the First Affiliated Hospital of Guangxi Medical University (China). The inclusion criteria for the patients were based on the epilepsy classification of the International League Against Epilepsy as follows: (1) a clinical onset of symptoms that indicated that the location of the epileptogenic zone was in the left temporal lobe; (2) MRI manifestation of left temporal lobe lesions or left HS; and (3) interictal or ictal electroencephalogram suggesting epileptic discharges in the left temporal lobe. The exclusion criteria were as follows: (1) age <16 years or age >60 years; (2) patients who take drugs that could impair cognition, such as cannabis users and others; and (3) history of mental illness or systemic disease. The subjects were informed in detail about the study and provided written consent to participate. This study was approved by the medical ethics committee of the First Affiliated Hospital of Guangxi Medical University.

2.2. Experimental paradigm

Sixteen healthy volunteers performed an n-back task and simultaneously underwent neuroimaging scanning. This task was practiced twice prior to the fMRI scanning to ensure that the subjects completely understood the task.

Typically, researchers use words or letters as stimuli in VWM tasks. However, in our study, single-digit numbers (1–9) were used. The processing of digital information can be divided into two types; i.e., verbal and nonverbal. A portion of digital processing belongs to the verbal type, including reading, listening and writing. The task with single-digit numbers as stimuli was designed in a previous study [14]. In this study, an n-back task was used to investigate the VWM network. The task was designed with E-prime_2.0 (Psychology Software Tools, Inc., n.d; Schneider, Eschmann, & Zuccolutto, 2002). The stimuli were presented at the centre of the screen as target cues using the SAMRTEC SA-9800 system. The task included two conditions; i.e., a 0-back and a 2-back condition. Before each condition began, a 2000-ms instruction indicating the condition to the participant was provided. Twenty random case stimuli were presented in each block, which included five targets. Each stimulus lasted for 1000 ms with an interval of 1000 ms. In the 0-back condition, the participants were required to identify the target "5". In the 2-back condition, the subjects were required to confirm whether each presented number was the same as that presented two stimuli previously. The 2-back condition was alternated with the 0-back control condition three times with a blank delay interval of 18 s. The subjects were instructed to identify the target by pressing the response button with their right index finger as quickly as possible. The n-back experiment lasted for 6 mins.

2.3. Neuropsychological test of VWM

To evaluate VWM ability, 14 lTLE patients and 14 healthy controls were required to perform a neuropsychological test of VWM that was identical to that used in the experimental paradigm. The mean reaction times of the accurate responses for the 0-back and the 2-back (ACCmeanRT (0-back) and ACCmeanRT (2-back)) were calculated (Table 1), and a two-way ANOVA was conducted ($P < 0.05$) with the factors of subjects (controls *vs*. lTLE; factor A) and conditions (0-back vs.2-back; factor B).

2.4. Data acquisition

The fMRI scanning was performed using an Achieva 3T MRI scanner (Philips, Netherlands). We initially scanned 16 healthy volunteers while they performed the n-back task. The SAMRTEC SA-9800 system (Sinorad, China) was used to generate the task stimuli. The subjects' heads were stabilized with foam pads to minimize head movement. The following parameters were used for axial T1 anatomical imaging: spin-echo sequence (T1 weighted); repetition time = 60 ms; echo time = 16 ms; slice thickness = 5 mm; gap = 1 mm; and field of view = 220 mm × 220 mm. The following parameters were used for axial functional imaging: gradient echo–echo planar imaging sequence (EPI sequence; T2); repetition time = 2000 ms; echo time = 30 ms; slice thickness = 5 mm;