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Cognition in patients with benign epilepsy with centrotemporal spikes: A study with long-term VEEG and RS-fMRI☆

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ABSTRACT

Objective: The purpose of this study was to investigate the relationship between alterations of functional brain network and cognition in patients with benign epilepsy with centrotemporal spikes (BECTS) as a function of spike-wave index (SWI) during slow wave sleep.
Methods: Resting-state functional magnetic resonance imaging (RS-fMRI) data and Intelligence Quotient (IQ) were collected from two groups of patients with BECTS, including a SWI < 50% group (5 cases) and a SWI ≥ 50% group (7 cases). The SWI was calculated from the long-term video-electroencephalogram monitoring (one sleep cycle was included at least). The RS-fMRI data were analyzed by regional homogeneity (ReHo) method.
Results: There were three main findings. Firstly, Full Intelligence Quotient (FIQ), Verbal Intelligence Quotient (VIQ), and Performance Intelligence Quotient (PIQ) of the SWI ≥ 50% group were significantly lower than SWI < 50% group ($p < 0.05$). Secondly, there was a negative correlation between the FIQ, VIQ, PIQ, and SWI ($p < 0.05$), and the FIQ, VIQ, and PIQ were not dependent on age, age of onset, disease course, years of education, and total number of seizures ($p > 0.05$). Finally, compared with the SWI < 50% group, the SWI ≥ 50% group showed increased ReHo in the bilateral precentral gyrus, bilateral premotor area, bilateral subcortical structure, right temporal lobe, and bilateral insular lobe, while they showed decreased ReHo in the posterior cingulate cortex and posterior of right inferior temporal lobe.
Conclusions: The alterations of functional brain network caused by the frequent discharges during slow wave sleep could affect cognition in patients with BECTS.

1. Introduction

Benign epilepsy with centrotemporal spikes (BECTS) is the most frequent epilepsy syndrome of childhood, corresponding to an incidence of approximately 15–24% [1], and the etiology is unknown or undetermined. Typically, onset occurs between 3 and 13 years (peak 9–10 years) [2]. Benign epilepsy with centrotemporal spikes had been considered 'benign' mainly because spontaneous remissions occur in the late childhood or adolescence with expectations of a relatively healthy life [3]. However, accumulative evidence has indicated that there are significant individual differences in cognition, such as language, execution, visuospatial orientation, attention, and learning ability [4–6], and factors which influenced cognition were also reported, such as interictal discharges (IEDs), age at onset, duration of disease, number of seizures, and antiepileptic drugs [7–9]. However, the underlying mechanism of these cognitive impairments remains to be elucidated. Recent studies using diffusion tensor imaging (DTI) examinations have revealed widespread gray matter changes in BECTS, and these structural aberrances have been associated with cognitive impairments [10–12]. In addition, many studies have also found functional changes specifically involving language networks using task-positive functional magnetic resonance imaging (fMRI) [4,13]. Recently, resting-state fMRI (RS-fMRI) technique has been used extensively to study brain functional activity in various types of epilepsy, free of specifically designed tasks [14,15], and it can identify abnormal brain activity that cannot be found by task activation, and so it is particularly well-suited to childhood. Regional homogeneity (ReHo), as one of the RS-fMRI analysis methods, can measure the functional coherence of the low-frequency fluctuations in neighboring

Abbreviations: AED, Antiepileptic drug; BECTS, Benign epilepsy with centrotemporal spikes; DMN, Default mode network; DTI, Diffusion tensor imaging; FIQ, Full Intelligence Quotient; IEDs, Interictal discharges; NREM, Nonrapid eye movement sleep; PCC, Posterior cingulate cortex; PIQ, Performance Intelligence Quotient; ReHo, Regional homogeneity; RS-fMRI, Resting-state function magnetic resonance imaging; SWI, Spike–wave index; VEEG, Video-electroencephalogram; VIQ, Verbal Intelligence Quotient; WAIS-CR, The Wechsler Adult Intelligence Scale China Revised; WISC-CR, The Wechsler Intelligence Scale for Children China Revised.

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voxels [16]. This regional synchronization has neurobiological relevance that is likely determined by anatomical, developmental, and neurocognitive factors [17]. The abnormal ReHo has been used to depict aberrant spontaneous brain temporal synchrony in epilepsy and may be a clue to disrupted local functionality. Thus, ReHo could serve as a neuroimaging marker to investigate brain function [18]. This method has been suggested to investigate the neuropsychological changes in patients with various types of epilepsy in the resting state [19–21]. Little is known, however, about the changes of local synchronization of spontaneous neuronal activities in BECTS. The objective of this study was to investigate and correlate the alterations in functional brain network and cognition in a group with spike-wave index (SWI) ≥50% group and a group with SWI < 50%. Furthermore, we discuss these alterations of functional brain network in relation to cognitive development in children with BECTS.

2. Materials and methods

2.1. Participants

According to the diagnostic criteria for BECTS published by the International League Against Epilepsy [22], 12 right-handed patients were recruited (from May 2015 to November 2016) from epilepsy specialist outpatients of the Tianjin Medical University General Hospital, China. They ranged in age from 6 to 18 years (10.56 ± 3.9 years). The age of onset was 3 to 11 years (6.20 ± 2.32 years). The duration of epilepsy was 10 months to 12 years (55.17 ± 39.20 months). They all had Full Intelligence Quotient >70 scores (developmental delay was excluded) and attended regular schools. They had no neurologic diseases and no proven focal structural abnormality on MRI. The electroencephalogram (EEG) of each patient showed centrotemporal epileptiform activity against a normal background. Observed seizure types were sensorimotor hemifacial, hemiclonic, or bilaterally clonic, and seizures in some patients evolved to generalized seizure at sleep onset or just before awakening. They all took one antiepileptic drug (AED) except one patient who was not taking any drugs before being recruited (Table 1). The intelligence assessment and RS-fMRI examination were completed within 3 days. Written informed consent was obtained from the parents or guardians of all subjects, and the present study was approved by the local ethics committee of Tianjin Medical University General Hospital.

2.2. The video-EEG acquisition

All patients underwent digitalized VEEG (Nicolet of America). The 20Ag/AgCl electrodes (10/20 system) were attached to the scalp with conductive cream. Four electro-oculogram/electrocardiogram channels were simultaneously recorded. The monitoring time was 8 h or 24 h, including awake and sleep stages (one sleep cycle was included at least). Provocative tests such as intermittent photic stimulation and hyperventilation were also performed during the VEEG exam.

The non-rapid eye movement (NREM) sleep spike–wave index (SWI) was calculated counting the number of 1-second bins containing at least one spike over the total number of 1-second bins in NREM sleep.

2.3. Intelligence assessment

The patients between 6 and 16 years were administered the Wechsler Intelligence Scale for Children China Revised (WISC-CR) test, and those older than 16 years were administered the Wechsler Adult Intelligence Scale China Revised (WAIS-CR) test. The Intelligence assessment included Full Intelligence Quotient (FIQ), Verbal Intelligence Quotient (VIQ), and Performance Intelligence Quotient (PIQ). The VIQ assessment include information, similarities, arithmetic, vocabulary, comprehension, and digit span; and the PIQ assessment included picture completion, picture arrangement, block design, object assembly, coding, and mazes. Of note, the WAIS-CR had no mazes assessment. All scores were standardized for age. The level of FIQ was categorized as follows: mental retardation, FIQ < 70; borderline mental retardation, FIQ70–79; nearly normal, 80–89; and normal, FIQ ≥ 90.

2.4. RS-fMRI date acquisition and processing

Images were acquired using a 3.0-Tesla MRI scanner (Siemens Magnetom Trio Tim, Germany) and 32 head coils. The 3D T1-weighted anatomical images were acquired in a sagittal orientation using a magnetization-prepared rapid gradient-echo sequence covering the whole brain with the following parameters: repetition time/echo time 400/8.9 ms; flip angle = 70°, thickness/gap = 1.0/0.0 mm, FOV = 220 mm × 220 mm, matrix = 256 × 256, 176 slices. The resting-state functional data were acquired using a T2-weighted gradient-echo planar imaging sequence with the following parameters: repetition time/echo time 2000/30 ms, thickness/gap = 5.0/0.0 mm, FOV = 220 mm × 220 mm, matrix = 256 × 256, 300 slices; the total scan time was 1200 s. The first 10 time points of each subject's fMRI images were discarded because of the instability of the initial MRI signal. The remaining images were preprocessed using SPM8 software package (Wellcome Institute of Cognitive Neuroscience, London) on the MATLAB (2013a), which included reorientation, realignment, and normalization (voxel size [3, 3, 3]). The participants lay supine with their head snugly fixed by straps and foam pads to minimize head movement and reduce scanner noise. Subjects were instructed to keep as motionless as possible with eyes closed, not to think of anything in particular, and not to fall asleep during scanning. Any patients with head motion

Table 1
Clinical characteristics of individual patients with BECTS.

Patient no.	Gender	Onset age (y)	Disease duration (m)	Education (y)	SWI (%)	Total number of seizures	EEG epileptiform side	EEG epileptiform focus	Seizure types	AEDs
1	F	8.8	50	8	30	1	R	T-C	SPS	OXC
2	M	9.5	85	9	50	4	R	C-T–P	GTCS	OXC
3	M	7.7	10	2	20	8	R	T-C-P	SPS	OXC
4	F	4.2	34	1	80	20	B	C-T–P	sGTCS	OXC
5	M	5.3	66	6	30	6	B	T-C-F	GTCS	OXC
6	M	5.0	38	2	52	4	L	C-T–P	SPS	OXC
7	F	5.0	60	1	80	20	R	T-C-F	SPS	LEV
8	F	3.0	96	5	80	6	B	C-T–P	CPS	OXC
9	F	6.0	144	11	30	10	B	C-T–P	sGTCS	OXC
10	M	4.3	52	2	80	5	R	C-T–P	sGTCS	OXC
11	M	5.3	10	0	10	3	B	T-C	CPS	LEV
12	F	10.3	17	5	85	2	B	T-C-P	SPS	NONE

Abbreviations: M = male; F = female; y = years; m = month; L = left; R = right; B = bilateral; T = temporal; C = central; P = parietal; F = frontal. SPS = simple partial seizures; CPS = complex partial seizures; GTCS = generalized tonic–clonic seizures; sGTCS = secondarily generalized tonic–clonic seizures; AEDs = antiepileptic drugs; OXC = oxcarbazepine; LEV = levetiracetam; NONE = without any AEDs.