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Epileptic discharges specifically affect intrinsic connectivity networks during absence seizures

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ABSTRACT

Intrinsic connectivity network (ICN) technique provides a feasible way for evaluating cognitive impairments in epilepsy. This EEG–fMRI study aims to comprehensively assess the alterations of ICNs affected by generalized spike-and-wave discharge (GSWD) during absence seizure (AS). Twelve fMRI sessions with GSWD, and individually paired non-GSWD sessions were acquired from 16 patients with AS. Ten ICNs corresponding to seizure origination and cognitive processes were extracted using independent component analysis. Intra- and inter-network connectivity alterations of the ICNs were observed through comparisons between GSWD and non-GSWD sessions. Sequential correlation analysis between GSWD and the ICN time courses addressed the immediate effects of GSWD on ICNs during AS. GSWD-related increase of intra-network connectivity was found only in the thalamus, and extensive decreases were found in the ICNs corresponding to higher-order cognitive processes including the default-mode network, dorsal attention network, central executive network and salience network. The perceptive networks and motor network were less affected by GSWD. Sequential correlation analysis further demonstrated different responses of the ICNs to GSWD. In addition to GSWD-related functional excitation in the thalamus and functional suspension in the default-mode network, this study revealed extensive inhibitions in the other ICNs corresponding to higher-order cognitive processes, and spared perceptive and motor processes in AS. GSWD elevated synchronization of brain network activity and sequentially affected the ICNs.

1. Introduction

Typical absence epilepsy is a common type of idiopathic generalized epilepsy in childhood; it is featured by sudden, brief impairment of consciousness, accompanied by a 2.5–4 Hz generalized spike and wave discharges (GSWD). It has been proposed that the cognitive processes underlying consciousness are selectively affected by GSWD during absence seizure (AS) [1]. Using general-linear-model (GLM) and time-series analyses, simultaneous electroencephalography (EEG) and fMRI have depicted the spatial and temporal properties of brain activation during AS. GSWD-related activation in the thalamus and deactivation in the medial frontal and posterior cingulate cortices are typically reported in EEG–fMRI studies [2–4]. These brain structures have been linked to seizure generation and deficits in the default-mode of brain function [2–4], respectively. In addition, distributed deactivation in the frontal and parietal regions has been suggested impaired attention and spared motion processes in AS [5,6]. Moreover, these brain regions presented different temporal patterns responding to GSWD during the evolution course of seizures. The accumulating imaging evidence may support the proposal that multiple cognitive processes are specifically involved in AS [7,8]. However, the precise alterations of brain processes associated with GSWD and the relationship among them have yet to be thoroughly assessed.

Cognitive impairments in epilepsy have been recently related to the alteration of intrinsic connectivity networks (ICNs) [9–11]. By measuring the correlation of spontaneous hemodynamic fluctuations, resting-state fMRI has been used to link ICNs to specific cognitive processes, such as self-awareness, attention, control and perceptions [12–14].

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Thus measuring connectivity within and across ICNs may permit examining the integrity of brain circuits related to consciousness [15–17]. This study investigated the intra- and inter-network alterations of extensive ICNs in AS, and addressed temporal evolutions of GSWD effect on the ICNs using sequential correlation analysis, which was expected to contribute to a better understanding of the neural correlates of consciousness impairments in absence epilepsy.

2. Methods

2.1. Patients

Sixteen patients with childhood absence epilepsy were recruited in this study (detailed in Table 1). They met the following criteria: (*i*) clinical diagnosis of childhood absence epilepsy based on International League Against Epilepsy criteria [18]; (*ii*) EEG with typical 2.5–4 Hz bilateral ictal GSWD and normal background activity; (*iii*) no additional seizure types, such as myoclonic, tonic–clonic, or partial seizures; (*iv*) no known structural brain abnormality in routine MRI and other neurological disorders. All patients had informed consent signed by their legal guardians, and all human study procedures were approved by the institutional review boards at Jinling Hospital, Nanjing University School of Medicine.

2.2. Simultaneous EEG and fMRI data acquisitions

All patients successfully underwent simultaneous EEG and fMRI data acquisitions on a 32 channels MRI-compatible EEG (Brain Product, Munich, Germany) and a 3 T MRI scanner (Siemens Trio, Erlangen, Germany). The patients were instructed to keep rest and not fall in sleep. Foam pads were used to help secure the EEG leads, minimize motion, and improve patient comfort.

For EEG recordings, the electrode FCz was set as the reference and electrocardiography was recorded using an electrode placed on the back. Data were transmitted via an optic fiber cable from the amplifier placed inside the scanner room to a computer outside the scanner room. For MRI data scanning, the functional data were acquired using a T2*-weighted single-shot echo planar imaging sequence (TR/TE = 2000 ms/40 ms, FA = 90°, matrix = 64 × 64, FOV = 24 × 24 cm, thickness/gap = 4.0 mm/0.4 mm, 2 sessions with each consisting of 500 volumes each, collected after five dummy volumes). Three-dimensional magnetization prepared rapid acquisition gradient-echo T1 anatomical images (TR/TE = 2300 ms/2.98 ms, FA = 9°, matrix = 256 × 256, FOV = 256 × 256 mm^2, and slice thickness = 1 mm) were obtained as a structural reference.

Table 1
Demographic and clinical information of involved patients.

Sex/Nos.	Age, y	Onset age, y	Medication	Nos. and durations of GSWD (in s) in AS
F1	12	9	None	2 (75)
F2	6	4	SV, LTG, LEV	2 (17)
F3	5	4	None	3 (16)
F4	11	9	None	1 (14)
M1	7	5	SV, LTG, LEV	2 (15)
M2	10	9	SV	3 (33)
F5	7	7	SV	8 (73)
F6	8	6	SV	1 (12)
M3	9	6	None	1 (9)
F7	18	10	SV	1 (16)
M4	7	8	SV	2 (39)
F8	10	3	SV, LTG	1 (16)
Mean ± *Std*	9.1 ± 3.5	6.7 ± 2.3	/	2.2 ± 1.9 (28.8 ± 22.8)

Abbreviations: F: Female, M: male; SV: Sodium Valproate; LTG: Lamotrigine; LEV: levetriacetam; AS: Absence seizure; GSWD: Generalized spike-wave discharge.

2.3. Data preprocessing

The EEG data was offline-processed to remove gradient and ballisto-cardiogram artifacts using the Brain Vision Analyzer 2.0 software. The GSWDs were marked on artifact-removed EEG by an experienced neurologists (Yang) and an electroencephalographer (Tian). The fMRI data preprocessing was performed using a software package SPM8 (http://www.fil.ion.ucl.ac.uk/spm). After slice-timing adjustment and realignment for head-motion correction, data were realigned to the corresponding anatomical images, warped into the anatomical MNI152 space using a 12-parameter affine linear transformation, resliced at a resolution of 3 × 3 × 3 mm^3, and spatially smoothed using an isotropic Gaussian kernel (8 mm full width at half maximum).

In order to match data segments with and without GSWD in each individual, we divided the full amount of fMRI data into four sub-sessions comprising 250 volumes. Accordingly, we selected pairs of data segments from 12 patients who presented seizures during scanning. Each pair consisted of a GSWD sub-session and a matched non-GSWD sub-session. The following criteria were used for data selection: (*i*) Each GSWD sub-session contained seizure events. Seizure event was defined to occur if the GSWD was longer than 6 s [19,20] and the events had the same duration and morphology as clinically confirmed events on the routine EEG using the International League Against Epilepsy guidelines[4]. A total of 32 events of GSWD were included. The GSWD durations across events are 11.6 ± 8.9 s, and across sub-session are 29.6 ± 22.6 s. (*ii*) For the non-GSWD sub-sessions, no discharge occurred 18 s before or after the selected data segment. (*iii*) The sub-sessions containing large motion (more than 1.5 mm or 1.5°) or the ones that could not be matched in the same subject were excluded (see Supplementary Fig. 1). There were no significant differences of head motion between the two data groups (Paired *t*-test, $t = -0.6$, $p = 0.52$ for translation and $t = -0.8$, $p = 0.48$ for rotation).

2.4. Data analysis

2.4.1. Sequential HRF generation and dynamic GLM framework

In line with previous studies [21,22], we first generated a sequence of hemodynamic response functions (HRFs) to model the dynamic BOLD changes induced by GSWD. Sequential HRFs consisted of 49 successive gamma functions of FWHM of 5.2 s, peak = 5.4 s, centered at 0 s and spaced 1 s between one another. At the individual level, we convolved a boxcar function expressing the timing of seizure events with sequential HRFs shifted between 24 s before to 24 s after the GSWD (HRF-24 to HRF + 24), to generate a series of regressors that modeled the BOLD responses. Then, we performed separate *t*-tests within a general-linear-model (GLM) framework for each regressor with specific HRF, thereby producing 49 *t*-maps representing GSWD-related BOLD activation modeled with different HRFs. The dynamic GLM framework allows us to observe the dynamic BOLD changes before and after seizure onset [22].

For group-analysis, we used one-sample *t*-tests ($p < 0.05$, AlphaSim correction) to determine regions showing significant GSWDs-related BOLD changes. Sequential-HRF based dynamic GLM framework was mainly used as a reference for the subsequent ICA analysis.

2.4.2. Group comparison analysis for intra- and inter-network connectivity of ICNs

Subsequently, we performed group independent component analysis (ICA) to examine ICNs in the patients. We used the GIFT software (version 2.0d; http://icatb.sourceforge.net/) to both fMRI sub-sessions related to GSWD and non-GSWD. Forty-four spatially independent components were decomposed after component number estimation using the minimum description length criteria [23]. The decomposition produced a set of components, each with a spatial map of intensities and a representative time course. The spatial maps were converted to *z*-scores, which reflect the degree to which synchronous activity occurs