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A resting-state functional connectivity study in patients at high risk for sudden unexpected death in epilepsy

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ABSTRACT

Objective: Seizure-related respiratory and cardiac dysfunctions were once thought to be the direct cause of sudden unexpected death in epilepsy (SUDEP), but both may be secondary to postictal cerebral inhibition. An important issue that has not been explored to date is the neural network basis of cerebral inhibition. Our aim was to investigate the features of neural networks in patients at high risk for SUDEP using a blood oxygen level-dependent (BOLD) resting-state functional connectivity (FC) approach.
Subjects and methods: Resting-state functional magnetic resonance imaging (Rs-fMRI) data were recorded from 13 patients at high risk for SUDEP and 12 patients at low risk for SUDEP. Thirteen cerebral regions that are closely related to cardiorespiratory activity were selected as regions of interest (ROIs). The ROI-wise resting-state FC analysis was compared between the two groups.
Results: Compared with patients at low risk for SUDEP, patients at high risk exhibited significant reductions in the resting-state FC between the pons and the right thalamus, the midbrain and the right thalamus, the bilateral anterior cingulate cortex (ACC) and the right thalamus, and the left thalamus and the right thalamus.
Conclusions: This investigation is the first to use neuroimaging methods in research on the mechanism of SUDEP and demonstrates the abnormally decreased resting-state FC in the ACC–thalamus–brainstem circuit in patients at high risk for SUDEP. These findings highlight the need to understand the fundamental neural network dysfunction in SUDEP, which may fill the missing link between seizure-related cardiorespiratory dysfunction and SUDEP, and provide a promising neuroimaging biomarker for risk prediction of SUDEP.

1. Introduction

Compared with the general population, patients with chronic epilepsy are at least 20 times more likely to experience sudden death [1–3]. Sudden unexpected death in epilepsy (SUDEP) has been defined as the sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death in patients with epilepsy, with or without evidence of seizure, with exclusion of documented status epilepticus, and when postmortem examination does not reveal a structural or toxicological cause of death [1,3,4]. The incidence of SUDEP varies widely within different source populations, ranging from approximately 0.09 per 1000 people to 9 per 1000 people [1–4]. Sudden unexpected death in epilepsy is the most common direct cause of death in people with epilepsy [1,3]. In our previous epidemiological research, probable SUDEP was the second most common putative cause of death in people with convulsive epilepsy in rural western China and accounted for 14.7% of all epilepsy-related deaths [5]. The physiological and psychological burden of SUDEP on patients with epilepsy and their families should not be underestimated [4].

Researchers have investigated the mechanism of SUDEP in the last few decades [1,2,4]. From a traditional point of view, cardiorespiratory failure may constitute the most likely potential mechanism of SUDEP [1,2,4]. However, Bird first reported a SUDEP case in which the cerebral electrical activity came to a full stop; meanwhile, the pulse artifact continued for an additional 120 s [6]. Bateman also noted that a diffuse cerebral electrical shutdown occurred before cardiorespiratory dysfunction in SUDEP cases [7]. Based on these prior observations, several scholars have postulated that cardiorespiratory failure, which directly

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leads to SUDEP, is actually secondary to postictal cerebral inhibition [1,4,8]. This speculation guided our reasoning that our future investigations on SUDEP mechanisms should focus on the pathophysiology by which cerebral inhibition could lead to cardiorespiratory arrest and consequent SUDEP.

Resting-state functional magnetic resonance imaging (Rs-fMRI) is a powerful technique for exploring cerebral activity and has been widely used to investigate the pathophysiology of many brain diseases [9,10]. There have been abundant studies of the pathophysiology of SUDEP, including studies in animal experiments and case reports on patients who experienced SUDEP or near-SUDEP, that have used electroencephalography (EEG), electrocardiography (ECG), or other diagnostic methods [1,4]. To date, no application of Rs-fMRI in the SUDEP mechanisms has been conducted on patients with epilepsy at high risk for SUDEP. Thus, to clarify the features of brain networks in the population susceptible to SUDEP, we compared the resting-state functional connectivity (FC) in patients with epilepsy at high risk and those at low risk for SUDEP using specific regions of interest (ROIs) known to be involved in cardiorespiratory regulation. We hypothesized that differences in brain network characteristics in patients with epilepsy at high risk for SUDEP may explain the missing link between the seizure-related cardiorespiratory dysfunction and SUDEP. We hope that the results will promote an innovative recognition of the mechanisms behind SUDEP and provide a promising neuroimaging biomarker for patients susceptible to SUDEP.

2. Subjects and methods

2.1. Participants

A total of 27 patients with epilepsy were recruited from the outpatient Department of Neurology at the West China Hospital of Sichuan University, China. Every patient underwent detailed clinical interviews and physical examinations performed by two experienced neurologists. All patients fulfilled the following inclusion criteria: 1) clinical diagnosis of epilepsy based on the ILAE criteria [11] and 2) absence of visible conventional MRI lesions and the following exclusion criteria: 1) <16 years or >65 years of age, 2) with other serious systemic diseases or psychological diseases, 3) pregnant and nursing women, and 4) had experienced seizures within 15 days prior to fMRI scan.

This study had been approved by the local ethics committee at West China Hospital of Sichuan University. All patients gave written informed consent for their participation.

2.2. Classification criterion

The risk factors for SUDEP have been abundantly documented and include young age, male sex, early age at onset, generalized tonic–clonic seizure (GTCS), high seizure frequency, long duration of epilepsy, symptomatic etiology, antiepileptic drug (AED) polytherapy, poor compliance with AEDs, prescription of specific AEDs, structural brain lesions, mental retardation, alcohol abuse, stressful life events, and prone position [1–4]. However, the results from different studies are not always consistent because of different definitions of the factors and different methodologies [1–4]. To refine the identification of patients with epilepsy who are at high risk for SUDEP, the International League Against Epilepsy (ILAE) Commission on Epidemiology screened major studies of SUDEP to perform a combined analysis of risk factors for SUDEP. The results showed that people with early-onset intractable epilepsy with frequent GTCS and AED polytherapy are at a higher risk for SUDEP [3]. Therefore, we combined the high risk factors indicated in this research to form the classification criteria of patients susceptible to SUDEP. The criteria included the following: 1) age at onset: <16 years old, 2) duration of epilepsy: >15 years, 3) GTCS frequency: >3 times/year, and 4) AED polytherapy: >2 AEDs.

2.3. Data acquisition

All functional images were obtained using gradient-echo echo-planar imaging (EPI) sequences in a 3-T MRI scanner (EXCITE, GE, Milwaukee, USA) with an eight-channel phased array head coil: thickness = 5 mm (no gap), TR = 2000 ms, TE = 30 ms, FOV = 24 cm × 24 cm, flip angle = 90°, and matrix = 64 × 64. Two hundred volumes (30 slices per volume) were acquired. The T1-weighted images were obtained using a three-dimensional (3D) spoiled gradient-recalled (SPGR) sequence, generating 156 axial slices (thickness: 1 mm without gap, TR = 8.5 ms, TE = 3.4 ms, FOV = 24 cm × 24 cm, flip angle = 12°, and matrix = 512 × 512). During Rs-fMRI acquisition, all patients were instructed to keep their eyes closed and to not focus on any thoughts.

2.4. Data processing

Functional image preprocessing was performed using DPARSF software (http://resting-fmri.sourceforge.net) using the following steps: 1) convert the DICOM data to NIFTI images, 2) remove the first 5 time points from each patient's data, 3) correct slice timing, 4) realign to the middle image, 5) normalize space to the Montreal Neurological Institute (MNI) template, 6) resample each voxel to 3 × 3 × 3 mm^3, 7) smooth with a Gaussian filter of FWHM = 8 mm, 8) filter band pass (0.01–0.08 Hz), 9) remove linear trend, and 10) regress out nuisance covariates, comprising six rigid body motion parameters from head movements, the global signal, white matter signal, and cerebrospinal fluid (CSF) signal.

2.5. Connectivity analysis based on ROIs

Thirteen cerebral regions, which have been demonstrated to be closely related to respiratory and cardiovascular activity in previous studies [2,12–15], were picked as ROIs. The medulla, pons, and midbrain represent the basic center of cardiorespiratory activity. The bilateral hypothalamus, thalamus, and amygdala were selected as the subcortical regulation center. At the level of higher cortical control, the bilateral insula and the ACC were included. Five spheres, which were created with Marsbar (http://marsbar.sourceforge.net), in standard space based on the anatomy, were manually placed on the medulla, pons, midbrain, and bilateral hypothalamus by an experienced radiologist. The remaining four pairs of ROIs were constructed using the Automated Anatomical Labeling (AAL) atlas as implemented by Individual Brain Atlases using SPM (IBASPM) [16].

Region of interest-wise FC was calculated by performing a seed area analysis provided by REST (http://resting-fmri.sourceforge.net). The mean time course of each ROI was correlated with every other ROI to obtain a 13 × 13 matrix of correlation coefficients (r) in every participant. A Fisher's r-to-z transformation was applied to improve the normality of the r-value. Two-sample two-tailed t-tests were performed in SPM8 on all possible 78 ($C^2{}_{13}$) connections between the high-risk group and the low-risk group represented in the individual 13 × 13 Z-score matrices. The statistical significance level was set at $P < 0.05$.

3. Results

Resting-state functional magnetic resonance imaging data were recorded from 27 patients with epilepsy. Two patients were excluded because of excessive head motion. All subjects were right-handed. According to the classification described above, these 25 patients were divided into two groups. Thirteen patients (male/female: 8/5, average age: 23.9 ± 5.3 years) with early-onset intractable epilepsy with frequent GTCS and AED polytherapy formed the high-risk group. The remaining 12 patients (male/female: 5/7, average age: 21.8 ± 6.9 years) without any of the above classification criteria were placed into the low-risk group. The clinical and demographic information for these