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QUANTIFY NEUROMAGNETIC NETWORK CHANGES FROM PRE-ICTAL TO ICTAL ACTIVITIES IN ABSENCE SEIZURES

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Abstract—*Objective:* The cortico–thalamo–cortical network plays a key role in childhood absence epilepsy (CAE). However, the exact interaction between the cortex and the thalamus remains incompletely understood. This study aimed to investigate the dynamic changes of frequency-dependent neural networks during the initialization of absence seizures.

***Methods:* Magnetoencephalography data from 14 patients with CAE were recorded during and between seizures at a sampling rate of 6000 Hz and analyzed in seven frequency bands. Neuromagnetic sources were volumetrically scanned with accumulated source imaging. Effective connectivity networks of the entire brain, including the cortico–thalamo–cortical network, were evaluated at the source level through Granger causality analysis.**

***Results:* The low-frequency (1–80 Hz) activities showed significant frontal cortical and parieto–occipito–temporal junction source localization around seizures. The high-frequency (80–250 Hz) oscillations showed predominant activities consistently localized in deep brain areas and medial frontal cortex. The increased cortico–thalamic effective connectivity was observed around seizures in both low- and high-frequency ranges. The direction was predominantly from the cortex to the thalamus at the early time, although the cortex that drove connectivity varied among subjects.**

***Conclusions:* The cerebral cortex plays a key role in driving the cortico–thalamic connections at the early portion of the initialization of absence seizures. The oscillatory activities in the thalamus could be triggered by networks from various regions in the cortex.**

***Significance:* The dynamic changes of neural network provide evidences that absence seizures are probably resulted from cortical initialized cortico–thalamic network.**

Key words: childhood absence epilepsy, magnetoencephalography, effective connectivity, cortico–thalamo–cortical network, high-frequency oscillations.

INTRODUCTION

Childhood absence epilepsy (CAE) is a common neurological disease characterized by frequent, brief, and typical absence attacks, which mostly occur in children aged 4–12 years with a female preponderance. The electroencephalography (EEG) of CAE patients shows characteristic 3 Hz bilateral and synchronous symmetric spike-wave discharges (SWDs) on normal background activity (Tenney and Glauser, 2013). CAE is considered as primary generalized epilepsy, but growing evidence supports the notion that SWDs have a focal origin, especially within the cortico–thalamo–cortical system (Meeren et al., 2005; Luttjohann and van Luijtelaar, 2012). However, the relative contribution of various brain structures to SWD generation and maintenance has aroused a new controversy and the relevant network interaction responsible for this phenomenon remains contentious.

Several imaging techniques, such as functional magnetic resonance imaging (fMRI), EEG and magnetoencephalography (MEG), have been used to investigate the generation of SWD in animal models and patients (Moeller et al., 2008; Masterton et al., 2013; Carney and Jackson, 2014). Studies with fMRI have identified a common network of structures involved in absence seizure, including anterior and posterior cortices, especially the default mode network (DMN), thalamus, caudate nuclei, cerebellum and the reticular structures of the pons (Moeller et al., 2008; Masterton et al., 2013; Carney and Jackson, 2014). However, fMRI detects indirect signals from the brain and would be less useful to determine the particular rapid sequence of the underlying electrophysiological course because of its inherent low temporal resolution.

EEG and MEG have high temporal resolutions for assessing the dynamics of absence seizures. Invasive intra-cranial EEG applied in animal models has revealed the dynamics of cortico–thalamo–cortical interactions

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Abbreviations: CAE, childhood absence epilepsy; DMN, default mode network; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; SWDs, symmetric spike-wave discharges.

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from the pre-SWD to SWD and SWD to post-SWD transition periods ((Meeren et al., 2002; Luttjohann and van Luijtelaar, 2012; Sysoeva et al., 2016)). The cortex reportedly guides the thalamus in the majority of SWDs around the first cortico–thalamic spike for several hundred milliseconds, before the coupling direction is alternated (Meeren et al., 2002; Luttjohann and van Luijtelaar, 2012). In CAE patients, the benign nature precludes invasive investigation of these processes. Non-invasive scalp-EEG and MEG have confirmed the pre-ictal localized cortical activity, which strongly indicates the existence of a cortical epileptic focus (Holmes et al., 2004; Westmijse et al., 2009; Tenney et al., 2013). However, a directed connectivity analysis along the time-course of a pre-SWD to SWD transition period remains lacking.

In the present study, we performed a group analysis of the MEG data from 14 CAE patients to investigate the spatiotemporal properties of generalized low-frequency (including SWDs) and high-frequency brain activities, especially the interaction between cortical and thalamic networks during the pre-ictal to ictal period in CAE. MEG data were obtained with whole brain MEG systems, and the significant source localization and predominant effective connectivity (EC) network were analyzed to reveal the dynamic neuronal network responsible for SWD.

EXPERIMENTAL PROCEDURES

Subjects

Children (5–11 years old) with newly diagnosed CAE were recruited from Nanjing Brain Hospital and the Neurology Division at Nanjing Children's Hospital from February 2013 to July 2015. A total of 30 CAE patients were screened, but only 14 met the inclusion criteria and were included in this research. The clinical details of the patients are shown in Table 1. This research protocol was approved by the medical ethics committees of Nanjing Medical University, Nanjing Brain Hospital, and Nanjing Children's Hospital. Informed consent was obtained from all children and their parents.

Similar to our previous research (Miao et al., 2014b; Tang et al., 2015), inclusion criteria were as follows: a diagnosis of typical CAE without automatisms, eye rolling or blinking, and consistent with the International League Against Epilepsy Proposal for Revised Classification of Epilepsies and Epileptic Syndromes; normal development; normal neurological examination; normal brain magnetic resonance imaging (MRI); bilaterally synchronous 3–4 Hz SWDs on a normal background with at least one electroclinical seizure lasting 4 s or more; and less than 5-mm head movement during MEG recordings. Exclusion criteria were as follows: a history of seizures other than absence seizures or other clinically significant diseases, current intake of an antiepileptic medication, or presence of metal implants, such as cochlear devices and pacemakers that would strongly interfere with MEG data. To test the reliability of technologies and methods used in this study, we obtained MEG data from 20 healthy children (age range: 6–17 years, mean and standard deviation: 12.3 ± 2.7 years, 10 girls and 10 boys). The detailed information about the subjects and the inclusion/exclusion criteria have been described in previous publications (Leiken et al., 2014).

MEG recordings

MEG data were recorded in a magnetically shielded room with a whole-head CTF MEG system with 275 channels (VSM Medical Technology Company, Canada) at the MEG Center at Nanjing Brain Hospital. All subjects were instructed to stay up late at night and wake up early in the morning before MEG recordings to increase the chance of seizures during MEG recordings. Before data acquisition, three coils were attached to the left and right pre-auricular points and nasion of each subject, and a head localization procedure was performed before and after each acquisition to locate the patient's head relative to the coordinate system fixed to the MEG

Table 1. Demographic of 14 patients in this study

Patients	Sex (F/M)	Age (years)	Duration of epilepsy (months)	Seizure frequency (times/day)	Seizure analyzed (times)	Ictal duration (s)
1	F	5.8	2	12.5	4	11.0
2	M	7.5	4	12.5	2	13.6
3	M	8.2	4	7.5	2	10.7
4	F	5.6	5	2	2	25.0
5	F	8.7	3	13	3	5.2
6	F	10.1	10	4.5	2	33.3
7	F	9.5	12	5.5	2	23.0
8	F	11.0	22	5.5	1	10.1
9	F	10.3	36	7.5	2	34.8
10	M	5.3	3	7.5	1	14.6
11	F	7.2	7	7.5	2	30.0
12	M	7.5	4	20	3	11.1
13	F	9.7	1	5.5	2	30.0
14	M	6.7	0.5	17.5	3	11.9
Total (Mean)	5 M, 9F	8.1	8	9.2	32	18.9

F = female; M = male.

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