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Epileptic network of hypothalamic hamartoma: An EEG-fMRI study

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ABSTRACT

Objective: To investigate the brain networks involved in epileptogenesis/encephalopathy associated with hypothalamic hamartoma (HH) by EEG with functional MRI (EEG-fMRI), and evaluate its efficacy in locating the HH interface in comparison with subtraction ictal SPECT coregistered to MRI (SISCOM).
Methods: Eight HH patients underwent EEG-fMRI. All had gelastic seizures (GS) and 7 developed other seizure types. Using a general linear model, spike-related activation/deactivation was analyzed individually by applying a hemodynamic response function before, at, and after spike onset (time-shift model = −8–+4 s). Group analysis was also performed. The sensitivity of EEG-fMRI in identifying the HH interface was compared with SISCOM in HH patients having unilateral hypothalamic attachment.
Results: EEG-fMRI revealed activation and/or deactivation in subcortical structures and neocortices in all patients. 6/8 patients showed activation in or around the hypothalamus with the HH interface with time-shift model before spike onset. Group analysis showed common activation in the ipsilateral hypothalamus, brainstem tegmentum, and contralateral cerebellum. Deactivation occurred in the default mode network (DMN) and bilateral hippocampi. Among 5 patients with unilateral hypothalamic attachment, activation in or around the ipsilateral hypothalamus was seen in 3 using EEG-fMRI, whereas hyperperfusion was seen in 1 by SISCOM.
Significance: Group analysis of this preliminary study may suggest that the commonly activated subcortical network is related to generation of GS and that frequent spikes lead to deactivation of the DMN and hippocampi, and eventually to a form of epileptic encephalopathy. Inter-individual variance in neocortex activation explains various seizure types among patients. EEG-fMRI enhances sensitivity in detecting the HH interface compared with SISCOM.

1. Introduction

Hypothalamic hamartoma (HH) is a rare developmental malformation that has provided important insight about epileptology (Berkovic et al., 1988; Mullatti et al., 2003; Striano et al., 2012). HH is characterized by gelastic seizures (GS) which occur in almost all patients. Such patients often develop other seizure types, i.e., partial and generalized seizures, and cognitive/behavioral problems including memory deficits and mental retardation. Previous studies showed that HH per se accounts for the generation of these seizures (Kahane et al., 2003; Kameyama et al., 2010, 2009;

Abbreviations: HH, hypothalamic hamartoma; EEG-fMRI, EEG with functional MRI; GS, gelastic seizure; SISCOM, SPECT coregistered to MRI; DMN, default mode network.

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Table 1
Clinical profiles of patients.

Patient No., Age/gender	Hamartoma			Gelastic Sz	Other types of Sz	Complication	AED
	Attachment side	Delalande classification	Maximum diameter (mm)				
1. 15/M	L	III	20	+	GTC	PP	VPA, CBZ
2. 8/M	L	III	16	+	GTC, TC, CPS	PP, BD, MR	CZP, CLB, LTG
3. 3/M	R	II	7	+	–	BD	VPA, LTG
4. 27/M	R	II	8	+	GTC, SPS	–	CBZ
5. 1/F	R	II	10	+	GTC	–	ZNS, LEV
6. 19/F	Bilateral	I	13	+	AT	PP, MR	VPA, CBZ, GBP, TPM
7. 13/M	Bilateral	III	30	+	TC, CPS	PP, BD, MR	CBZ, TPM, SL
8. 23/F	Bilateral	I	16	+	GTC, CPS	PP, BD	VPA

Abbreviations: Sz = Seizure, GTC = generalized tonic clonic Sz, TC = tonic Sz, CPS = complex partial Sz, SPS = simple partial Sz, AT = atonic Sz, PP = precocious puberty, BD = behavioral disorder, MR = mental retardation, AED = antiepileptic drug.

Kuzniecky, 2004; Munari et al., 1995; Striano et al., 2012; Wethe et al., 2013). Therefore, the unique spectrum of symptoms in HH has been regarded as the model of subcortical epilepsy and epileptic encephalopathy (Kameyama et al., 2010; Striano et al., 2012). However, it remains unknown how the epileptic activity propagates, and how cognitive/behavioral dysfunction develops. For example, the networks associated with GS remain elusive, although the mammillo-thalamo-cingulate tract from HH or the pathway from the HH to the brainstem and cerebellum has been postulated (Kahane et al., 2003; Kameyama et al., 2010). Therapeutically, stereotactic radiofrequency thermocoagulation (SRT) has become one of the most useful surgical interventions. SRT of the HH interface has yielded better outcomes for seizure freedom and fewer surgical complications than a direct approach (Kameyama et al., 2010, 2009). Subtraction ictal SPECT coregistered to MRI (SISCOM) has been used for locating the HH interface (Kameyama et al., 2010), however, it is time-consuming and the likelihood of detecting the HH interface individually is not high.

Here, we performed EEG with fMRI (EEG-fMRI) on eight patients with HH. EEG-fMRI can detect blood-oxygen-level dependent (BOLD) changes that are related to interictal discharges identified from scalp EEG (Lemieux et al., 2001; Warach et al., 1996). It was reported to be clinically useful for localizing the epileptic focus and investigating epileptic network even in the deep brain structures (Gotman and Pittau, 2011; Vulliemoz et al., 2010). In addition, it possibly predicts postsurgical outcome non-invasively although its clinical utility in comparison with other techniques, e.g. ictal SPECT, has been not determined (Chaudhary et al., 2013). With these in mind, we expected EEG-fMRI to clarify the common brain networks associated with subcortical epileptogenesis/encephalopathy in HH patients. Furthermore, we evaluated the clinical usefulness of EEG-fMRI in locating the HH interface in comparison with SISCOM (Kameyama et al., 2010). We thought EEG-fMRI would be an option for presurgical investigation, because it could provide us with the interictal epileptic network that could complement the findings of SISCOM in a relatively less time-consuming fashion.

2. Methods

2.1. Patients

Subjects were eight patients (pts.) with HH (age 1–27 years) (Table 1) who were examined at the Kyoto University Hospital from August 2011 to June 2013. Subjects included three patients who had received surgical intervention for HH in the past (pt. 2 as partial resection; pt. 6 as partial resection and SRT; pt. 7 as partial resection followed by infarction of the left hemisphere and gamma-knife surgery) with persisting seizures. Hamartomas were classified by the Delalande classification, which is based on the plane of insertion on the hypothalamus to help choose the best surgical route (Type I: horizontal implantation plane, Type II: vertical insertion plane and intraventricular location, Type III: combination of Types I and II. Type IV: all giant hamartomas for which no specific surgical procedures can be recommended) (Delalande and Fohlen, 2003). All the patients or parents of patients who were not capable of consent gave written informed consent. The protocol was approved by the Ethics Committee of our institute (IRB#E217).

2.2. EEG-fMRI acquisition

EEG was obtained during fMRI, using a custom-made MR-compatible cap with 19 (for pt. 5) or 23 (for other patients) Ag/AgCl scalp electrodes based on the 10–20 System, including Fp1, Fp2, F7, F3, F4, F8, T7, C3, C4, T8, TP9, P7, P3, P4, P8, TP10, O1, and O2 referenced to Cz (T1, T2, Fz, and Pz were added optionally) (EASY-CAP, EASYCAP GmbH, Herrsching, Germany). Electrocardiogram was also recorded. All the signals were transmitted from an MR-compatible amplifier (BrainAmp MR plus, Brain Products GmbH, Munch, Germany: sampled at 5 kHz) through an optic cable to a computer outside the MR scanner room and stored on the computer. The EEG system was synchronized with the MRI scanner clock.

A 3 Tesla MR scanner was used (Trio, Siemens, Erlangen, Germany). The MRI sequence for the echo planar imaging (EPI), i.e., blood oxygenation-level dependent (BOLD) fMRI (repetition time [TR] = 3000 ms; echo time [TE] = 30 ms; flip angle [FA] = 90°; field of view [FOV] = 192 × 192 mm; voxel size = 3 × 3 × 3 mm) was acquired with a one-channel bird-cage head coil. The initial two scans were discarded to ascertain the steady-state of the magnetization. Motion artifacts were minimized as much as possible by stabilizing patients' heads with a pillow filled with foam microspheres. Special care was taken to ensure the patients' comfort. Scans lasted 30–90 min in several runs per patient. T1-weighted, magnetization-prepared, rapid acquisition with gradient echo (MPRAGE) images (TR = 2000 ms; TE = 4.38 ms; FA = 8°; FOV = 176 × 192 mm; voxel size = 1 × 1 × 1 mm) were also acquired with an eight-channel phased-array head coil for coregistration of the fMRI results. By using this coil we expected to acquire a clearer anatomical image than one-channel coil does.

In all patients, SpO_2 was monitored in preparation for hypoxemia by a pulse oximeter under constant observation by a medical doctor in the scanner room. In order to perform the scan safely with minimal motion artifacts, trichrofos, midazolam, or pentobarbital were used to sedate patients, though pentobarbital was mainly used (Table 1).

2.3. EEG-fMRI pre-processing

First, MR and ballistocardiogram artifacts were removed in an offline manner according to a previously established method (Allen