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Source localization of epileptiform discharges in juvenile myoclonic epilepsy (JME) using magnetoencephalography (MEG)

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ABSTRACT

Objective: The purpose of this study is to localize the sources of epileptiform discharges (EDs), in juvenile myoclonic epilepsy (JME) using Magnetoencephalography (MEG), at three different time instances and analyze the propagation of EDs, from onset to offset, for inferring the cortical and subcortical region of involvement.
Methods: Twenty patients (age 23.5 ± 6.3 years old) with JME were recruited in this prospective study. MEG source analysis was performed on the independently collected EDs of each patient. The distributed source model was employed for source localization using low resolution electromagnetic brain tomography (LORETA). In each EDs, the onset (leading edge of the spike from baseline), peak and offset (trailing edge of the spike), with time window of 8 ms, were subjected for source localization in order to study the propagation of the EDs. The obtained source location coordinates, from each individual MRI, were transformed in Talairach space and the distribution of region of source involvement was analysed.
Results: The frequency pattern of lobar distribution at onset, peak and offset respectively suggest that discharges most commonly localized at onset from sublobar region, at peak from frontal lobe and at offset from the sublobar region. It was observed that the maximum involvement of sources from the sublobar, limbic and frontal lobes at different time instances. It indicates that the restricted cortical-subcortical involvement during the generation and propagation of EDs in JME.
Significance: This MEG study supported the cortical-subcortical region of involvement and provided further insights in our understanding the network involvement in generation and propagation of EDs in JME.

1. Introduction

Seizures in epilepsy have been classified broadly into generalized, where both hemispheres are involved at the onset and focal seizures involving one hemisphere at the onset and later spreading to other regions of the brain. Idiopathic Generalized epilepsies (IGEs) constitute about 1/3rd of all epilepsies. Juvenile Myoclonic epilepsy (JME) is common among IGEs, well-defined and considered as the prototype of IGE (Fisher et al., 2014).

The question of 'generalized versus focal' onset of IGE was posed way back in 1941 by Jasper and Kershman (Jasper and Kershman, 1941) where they proposed that the absence seizures had a subcortical origin. The thalamic stimulation model in cats was the first experimental model for spike-wave pattern (Morison and Dempsey, 1942; Jasper and Drooglever-Fortuyn, 1946). Penfield (Penfield, 1952) introduced the term centrencephalic integrating system for the diffuse neural system projecting to both hemispheres, which was thought to be located in the brainstem and diencephalon. Gibbs et al. (Gibbs and Gibbs, 1952) suggested that spike-wave discharges are generated in the cortex, which was supported by other authors using experiment in cats (Bennett, 1953;

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Gloor, 1969). Hence, it was suggested that seizures originate in the frontal cortex, which rapidly propagates over the entire cortex through corticocortical pathways. Lüders et al. (Lüders et al., 1984) and Niedermeyer (Niedermeyer, 1972) suggested that IGE is the expression of a cortical abnormality and thalamus participates in the physiologic thalamocortical interactions. Currently, the corticoreticular theory still seems to be the most widely accepted among all absence theories, although the relative contributions of cortex and thalamus and the exact mechanisms continue to be matter of debate. Various authors, based on animal experiments, invasive human studies and now non-invasive tests (f-MRI, fMRI-EEG, MEG) have suggested varying areas of origin or source localization of epileptic activity from various cortical and/or subcortical structures suggesting focal or network involvement in IGEs.

Holmes et al. (Holmes et al., 2010) studied various regions of cerebral cortex activated during the onset and propagation of dense array EEG epileptiform discharges in patients with JME and showed that discharges localized to orbitofrontal cortex, medial frontopolar cortex and basal–medial temporal lobe. Liu et al. (Liu et al., 2007) found Blood oxygenation level-dependent (BOLD) signals getting activated in cuneus, insula, mesial midfrontal region, midline and bilateral cerebellum and thalamus. Agakhani et al. (Aghakhani et al., 2004) evaluated the hemo-dynamic response of the cerebral cortex and thalamus during generalized spike and wave or polyspike and wave (GSW) bursts in patients with idiopathic generalized epilepsy (IGE) using EEG-fMRI in 15 patients. The cortical changes as a result of this were present in 14 patients (93%). Bilateral thalamic changes were found in 12 patients (80%).

MEG has an excellent temporal and spatial resolution and hence studying brain functions and abnormalities might help us to unravel the origin of discharges in this group. MEG being non-invasive and sensitive enough in detecting origin of epileptiform discharges from subcortical structures. There are limited studies using MEG in patients with JME. Stefan et al. (Stefan et al., 2009) investigated 7 patients with IGE using MEG and EEG. Patients with JME had source localizations mainly occurring in the central and premotor regions. Kotini et al. (Kotini et al., 2010), studied MEG in two patients with JME carried out with 122-channel magnetometer (Neuromag-122, Helsinki, Finland). In the first patient, vermis was source localized while in the second patient, cerebellar vermis and hemisphere was involved.

Hence, studying systematically patterns of MEG changes in patients with JME and source localization of MEG epileptiform discharges might unravel some of the unknown facts and certainly would improve the understanding.

2. Methods

This is a prospective, cross-sectional, hospital based study carried out at a MEG centre of a premier institute in south India. This study included 20 patients (age 23.5 ± 6.3 years, M: F = 10:10), diagnosed to have juvenile myoclonic epilepsy (JME) as per the ILAE definition with its characteristic clinical and EEG features. Non-cooperative patients, those with general contraindications for MEG, those without EEG changes, and those who did not consent for the study were excluded. Thirteen patients were drug naive (n = 13) while 7 were on anti-epileptic drugs (AEDs = 7) for a mean duration of 6.4 ± 5.1 years. This study was approved by the Institutional Ethical Committee and written informed consent was obtained from patients and/or guardians of the children. All the subjects underwent a structured evaluation, including a detailed clinical, family, treatment history, neurological examination, routine 21 channel digital EEG, and neuroimaging. All the EEG records showed epileptiform discharges and then they were subjected to MEG recording. Patients who were drug naïve were initiated on AEDs immediately after MEG recording, carried out on the same day of evaluation.

2.1. MRI of brain

For co-registration, T1-weighted MPRAGE sequence of brain MRI (TR = 650 ms, TE = 14 ms, acquisition time of 2.5 min, matrix of 256 × 256, field of view (FOV) – 230 mm, 1 mm slice thickness) was obtained on a 3T MRI scanner using 32 channels head coil. For accurate integration of MEG with MRI, three fiducial markers (vitamin E capsules) were placed in nasion, left and right pre-auricular points during MRI acquisition. The MR images were transferred to the brain electrical source analysis (BESA Research 6.0, BESA GmbH, Graefelfing, Germany) workstation and segmented in accordance with Talairach (one of the normalized brain map) for co-registration with MEG data.

2.2. MEG recording

All patients underwent MEG recordings either in comfortable supine or sitting position using a whole head 306-channel MEG system (ElektaNeuromag® TRIUX™, Helsinki) inside a magnetically shielded room (MSR). Simultaneous 23 channels EEG recording was carried out based on modified 10–20 international system. For monitoring and eliminating the artifacts contamination caused by ocular and cardiac activity, additional electrodes for electro-oculogram (EOG) and electrocardiogram (EKG) were attached. Five head position indicator (HPI) coils were placed on the scalp for determining the relative position of the head with respect to the MEG sensors during acquisition and later for head movement correction. Digitization of 3 fiducial points viz. nasion, left and right pre-auricular points, HPI coils, EEG electrodes and additional points on the scalp/surface of the head was performed using 3D Polhemeus digitizer to obtain the coordinates which used for transformation of MEG coordinates on to the MRI and for locating the head relative to the MEG system coordinate. The change in position of the head within the helmet, during acquisition, <5 mm was acceptable. Data was sampled at 2 kHz with band pass filter settings of DC to 660 Hz. Approximately 1 h continuous MEG-EEG recording, with 15 min time blocks repeated 4 times with measurement of head position before and after each block. The recorded data (raw data) was visually examined to identify bad channels and then pre-processed for head movement correction and artefact elimination using Elekta-*Maxfilter* software, which use temporal extension of signal space separation (tSSS) to eliminate the artifacts contained outside the spherical approximation of the head and constant/periodic artifacts.

2.3. MEG spikes and source analysis

The epileptiform discharges (EDs) in MEG were identified by looking at the EEG and MEG simultaneously and emphasis was given to amplitude, duration, sharpness, and emergence from the background activity. In each patient, five EDs were independently selected for source analysis irrespective of the number of discharges contained in the whole data. In few patients, less than five EDs were noted and in this case, all EDs were selected for source analysis. For 20 patients, totally 83 EDs were collected and were subjected to source localization. In this study, the first discernible prominent spike, in spike/polyspike-wave complex, were localized at three different instants, namely (*a*) onset (leading edge of the spike from the baseline at which the GFP exceeds the noise level from the pre-spike interval), (*b*) peak and (*c*) offset (trailing edge of the spike at which the GFP exceeds the noise level from the pre-spike interval), in order to detect differences in the source localization from onset to offset (Fig. 1). The signal-to-noise ratio (SNR) as found from