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Source analysis of epileptiform discharges in absence epilepsy using Magnetoencephalography (MEG)

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ABSTRACT

Purpose: Magnetoencephalography (MEG) was used to record and localize the sources of the epileptiform discharges, in absence epilepsy, at three different time intervals to infer the sources of involvement during generation and propagation.

Methods: Twenty patients with absence epilepsy (M:F = 1:1; age: 10.2 ± 3.4 years), which included 12 patients with childhood absence epilepsy (CAE) and 8 patients with juvenile absence epilepsy (JAE), were recruited in this prospective MEG based study. MEG epileptiform discharges were divided into three sub-groups based on the duration viz., 1 s (very short), > 1–9.9 s (short) and ≥10 s (long) and the discharges of each group were averaged independently in each patient. MEG source analysis was performed on these averaged discharges, of each of the subgroups, at the onset, during middle and offset.

Results: The source locations obtained, in lobar and gyri levels, were compared across these three groups of varying duration of discharges and in the CAE and JAE subjects. It was observed that the most frequent location of sources from the sublobar, limbic and frontal lobes in all the discharge groups at different time intervals. Also, it was noted that there were only subtle and variable degree of the differences of source localization of epileptic discharges among CAE and JAE subgroups.

Conclusion: The study provided novel findings regarding origin and propagation of sources of epileptiform discharges in patients with childhood and juvenile absence epilepsies. Such analysis further improves the understanding of network involvement of subcortical and cortical regions in these patients.

1. Introduction

Seizures have been classified broadly into generalized and focal based on the hemispheric involvement. Both hemispheres involving at the onset are known as generalized seizure whereas involving one hemisphere at the onset and later spreading to other regions of the brain known as focal seizures. Idiopathic generalized epilepsies (IGEs) constitute about one third of all epilepsies (Panayiotopoulos, 2005; Sinha et al., 2013). One of the commonly occurring IGE is absence epilepsy, which is well-defined and often considered as the prototype of IGE (Fisher et al., 2014).

Jasper and Kershman (1941) posed, way back in 1941, the question of 'generalized versus focal' onset of IGE and they proposed that the absence seizures had a subcortical origin. The first experimental model for spike-wave pattern was thalamic stimulation model in cats (Jasper and Drooglever-Fortuyn, 1947; Morison and Demsey, 1942). The term centrencephalic integrating system was introduced by Penfield (1952) for the diffuse neural system projecting to both hemispheres and it was thought to be located in the central regions such as brainstem and diencephalon. The spike-wave discharges are generated in the cortex as suggested by Gibbs and Gibbs (1952) was supported experimentally in cats by other authors (Bennett, 1953; Gloor, 1969). Hence, it was suggested that seizures originate in the frontal cortex, which rapidly propagates over the entire cortex through cortico-cortical pathways. IGE is the expression of a cortical abnormality and thalamus participates by the physiologic thalamo-cortical interaction (Lüders et al., 1984; Niedermeyer, 1972). Among all absence epilepsy theories the cortico-reticular theory still seems to be widely acceptable, although the relative contributions of cortex and thalamus and the exact mechanisms continue to be a matter of debate. Following the animal

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experiments, the later invasive human brain studies (depth recording) and now non-invasive studies (f-MRI, fMRI-EEG, MEG, etc.) of these syndromes have suggested varying areas of origin or focus of epileptic activity from various cortical and/or subcortical structures.

Absence epilepsy (AE) studies using EEG-fMRI have demonstrated variable involvement of bilateral thalami, parietal, precuneus, caudate nucleus and posterior cingulate regions (Aghakhani et al., 2004; Archer et al., 2003; Moeller et al., 2008; Salek-Haddadi et al., 2003). MEG studies in IGE are very few and are recent. It was realized that MEG might have better ability to localize deeper sources than EEG with high temporal and spatial resolution. The involvement of frontal, peri-insular and subcortical/thalamic areas had shown by various authors (Amor et al., 2009; Stefan et al., 2009; Westmijse et al., 2009) while Sakurai et al. (2010) found involvement of medial prefrontal activation, cingulate and precuneus using MEG. It is interesting to explore further howso called IGE syndromes have localized origin of the epileptiform activity.

With excellent temporal and spatial resolution of MEG, studying brain functions and abnormalities might help one to unravel the origin of epileptiform discharges in patients with AE. Also, MEG is non-invasive and sensitive for detecting origin of epileptiform discharges from subcortical structures (Gadad et al., 2017). It certainly might improve the current understanding regarding origin and propagation of epileptic activity. Hence, in this study, we carried out MEG source analysis of epileptic discharges (ED) in patients with absence epilepsy and analysed whether EDs are generalized or focal in origin.

2. Methods

This is a prospective, cross-sectional, hospital based study carried in the MEG research centre at a premier institute in south India. This study included 20 patients, diagnosed to have absence epilepsy 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. Fifteen patients were drug naive (n = 15) while 5 were on anti-epileptic drugs (AEDs = 5). All patients had daily absence seizures at presentation. The mean frequency of seizures was 13.6 ± 8.8/day (range: 4–40/day) and duration of seizures most commonly varied between 5 and 20 s. Hyperventilation could precipitate attacks in all of them. Twelve patients (age: 5–7.5 years, M:F = 4:8) had childhood absence epilepsy (CAE) and 8 patients (age: 8–16 years, M:F = 6:2) had juvenile absence epilepsy (JAE). This study was approved by the Institute Ethical Committee and written informed consent was obtained from patients and guardians of the children. All the subjects underwent a structured evaluation, including a detailed clinical, family, treatment history, neurological examination, routine 21 channel scalp digital EEG, and neuroimaging. All had EEG interictal and ictal discharges. Drug naïve patients were administered AEDs immediately after MEG recording, carried out on the same day of evaluation. In 5 patients, the dosage of AEDswas reduced to half the regular dose on the day of MEG recording, if the seizures were under control.

2.1. MRI of brain

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. Three fiducial markers (vitamin E capsules) were placed in nasion, left and right pre-auricular points during MRI acquisition for accurate integration of MEG with MRI. Brain electrical source analysis (BESA Research 6.0, BESA GmbH, Graefelfing, Germany) was used for analysis and the MR images, of each patient, were segmented, in BESA-MRI, in accordance with Talairach (one of the normalized brain map) for co-registration with MEG data. In BESA-MRI, individual anatomical information from subject's MRI was used for the generation of the forward model. It offers Finite Element Method (FEM) for modelling skin, skull, brain, cerebro-spinal fluid (CSF) and arbitrarily complex geometries. The calculated leadfields for the given sensor layout were then used directly in BESA Research for source localization.

2.2. MEG recording

All patients underwent MEG recordings, inside a magnetically shielded room (MSR), either in comfortable supine or sitting position using a whole head 306-channel MEG system (ElektaNeuromag® TRIUX™, Helsinki). Simultaneous EEG recording with 23 channels was performed based on standard 10–20 international system. Additional electrodes for electro-oculogram (EOG) and electrocardiogram (EKG) were connected for monitoring and eliminating the artifacts contamination caused by ocular and cardiac activity. For determining the relative position of the head with respect to the MEG sensors during acquisition and later for head movement correction, fivehead position indicator (HPI) coils were placed on the scalp. Digitization of 3 fiducial pointsviz. nasion, left and right pre-auricular points, HPI coils, EEG electrodes and additional points on the scalp/surface of the head were performed using 3D Polhemeus digitizer. These were used for transformation of MEG coordinate 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 < 5 mm was acceptable, during acquisition. Data was sampled at 2 kHz with band pass filter settings of DC to 660 Hz. Approximately 1 h MEG-EEG recording, with 15 min time blocks repeated 4 times with measurement of head position before and after each block. The recorded raw data was visually inspected 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 in MEG were identified and emphasiswas given to amplitude, duration, sharpness, and emergence from the background activity. The discharges were of varying duration. Previous studies have source localized the discharges which were longer than 3 s (Westmijse et al., 2009) and 4 s (Tenney et al., 2013). In this study, the epileptiform discharges were subdivided into three groups based upon the duration, namely (*a)* 1 s, (*b)* > 1 to 9.9 s and (*c)* ≥10 s, in order to detect differences in the source localization between the very short, short and long duration discharges. The purpose of dividing the EDs into subgroups is to understand the network involvement (whether same network or varying network) in the generation and propagation of EDs of varying duration. The EDs in each subgroup were independently collected and averaged with respect to the trigger points of first peak of spike/spike-wave in each subgroup for each of 20 patients. Averaging of EDs was performed for the reason (a) to have a higher signal to noise ratio (SNR), (b) there were morphologically similar EDs and (c) lack of difference in the source localization results for individual versus averaged EDs, which were performed in few patients as a pilot observation. The SNR was computed from the global field power (GFP), by taking the root of ratio of the mean power in the spike peak interval to the mean power in the pre-spike interval (0.5–1 s before peak) and it was more than a factor of two.

MEG data were filtered using band pass filters of 1–70 Hz. The ECG artifacts were removed by defining the spatial ECG artefact topography or by applying ICA. Source localization was performed on the individual patient MRI and the source coordinates transformed in accordance with Talairach space were noted for subsequent analysis of comparing distribution of sources across patients. In the first subgroup of patients with discharges 1 s, the first spike peak and the last distinct