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Scalp high frequency oscillations (HFOs) in absence epilepsy: An independent component analysis (ICA) based approach

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ABSTRACT

Background: High frequency oscillations (HFOs) have provided a new insight in understanding ictogenesis and seizure localization. In absence seizures, HFOs were predominantly localized in the medial prefrontal cortex (MPFC) in MEG studies.
Methods: We studied HFOs (80–250 Hz) in scalp EEGs in patients with absence epilepsy, and evaluated their frequency bandwidth and spatial-temporal distribution. EEG of 9 patients with absence epilepsy (CAE:JAE–8:1; M:F = 7:2; age: 8.1 ± 2.1years; age at onset: 6.6 ± 1.3 years) were evaluated with scalp EEG (sampling rate: 2048 Hz). Finite impulse response filters on the unipolar or longitudinal bipolar montages were band-passed between 80 and 250 Hz using Cartool® and EEGLAB®. Sensitivity and paper speed were modified accordingly to study the HFOs. Thousand four hundred and thirty eight artifact free 'spike-wave' epileptiform discharges were analyzed. Sleep ictal SW discharges, defined as runs of 3 Hz GSWDs lasting ≥4 s in stages 1 and 2 sleep, were analyzed by independent component analysis and component time-frequency and channel time-frequency maps using cyclical tapering wavelet transform. A total of 926 HFOs were identified of 1438 GSWDS.
Results: The HFOs were associated with inter-ictal generalized spike-wave discharges (IiGSWDs-241/454), ictal GSWDs (IcGSWD-634/884), sporadic SWDs (sSWDs-51/100). The percentage of HFOs was higher in IcGSWD when compared to both IiGSWDs and sporadic SWDs together ($\chi^2 = 52.864$, d.o.f = 1, $p < 0.0001$). The mean frequency of HFOs was 96.4 ± 10.4 Hz. A channel wise analysis showed the maximum HFO band width in the right fronto-central region (F4 = 28 Hz, C4 = 24 Hz).
Conclusion: Narrow bandwidth interictal and ictal HFOs can be identified in scalp EEG of patients with absence epilepsy. Further characterization of the various properties of pHFOs will be helpful in opening up a domain of clinical evaluation and interpretation of the various epileptic disorders. To improve the insights into the onset and spread of absence seizures, and to study the network properties, one could analyze the HFOs in high density EEG arrays with multimodal integration using MEG or fMRI.

1. Introduction

Electroencephalograph (EEG) for clinical interpretation has for a long time been restricted to the Berger's frequency band (1–25 Hz). However, improvement in the acquisition systems with improved analog to digital conversion (ADC) has allowed researchers to look beyond the standard frequency bands. This has resulted in the evolution of the "fullband EEG (FbEEG)" which encompasses both the narrow band and wide band EEG (beyond the conventional 50–70 Hz) (Vanhatalo et al., 2005). FbEEG includes infra slow frequency oscillations (0.01–0.1 Hz), sub delta frequency analysis (0.1–0.9 Hz), Conventional Frequency Analysis (CFA: 1–70 Hz), high frequency oscillations (80–500/600 Hz), ultra high frequency oscillations (>600–1000 Hz) (Andrade-Valenca et al., 2011; Niedermeyer, 2005; Rodin et al., 2008; Rodin and Funke, 2006; Vanhatalo et al., 2005; Zafeiriou and Vargiami, 2012). The HFOs have been defined as brief low amplitude transients in the extracellular local field potentials (LFP) that are thought to

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originate from sub millimeter scale volumes. Though initially HFOs were extensively evaluated in depth studies, recent studies have shown that they can also be recorded from the scalp EEGs, recorded at high sampling rates and with appropriate filters (Kobayashi et al., 2011, 2010; Von Ellenrieder et al., 2014). Interictal HFOs in scalp EEG are mostly studied during slow wave sleep (Jirsch et al., 2006). Scalp HFOs are classified into ripples (80–250 Hz) and fast ripples (250–500/600 Hz) (Bragin et al., 2004; Worrell and Gotman, 2011).

Of particular interest over the past decade has been the determination of spatio-temporal properties of HFOs in both the invasive and scalp EEG records in patients undergoing epilepsy surgery. It has been established that the HFOs recorded from the scalp are of neocortical origin (Von Ellenrieder et al., 2014; Worrell and Gotman, 2011). Better outcomes have been noted when resection was tailored based on the pre-operative HFO localization (Worrell and Gotman, 2011). Ripples and fast ripples are also known to occur at seizure onset and faster activities of up to 500 Hz have been recorded at seizure onset (Modur et al., 2011). Filter technology incorporated in both the hardware and software play a very important role in the acquisition of data for HFO mapping. The system must also allow for higher sampling rates (>1024 Hz) in order to study a minimum frequency of 256 Hz. Hardware filters and sampling rate must be able to allow the recording of the higher frequencies and allow for the best reconstruction of the data without loss of information.

Various methods of extracting HFOs have been proposed such as manual visual identification of HFOs, semi-automated analysis and fully automated algorithms (Worrell and Gotman, 2011). Neurobiology physiological Biomarker (NBT) toolkit has recently launched an automated algorithm for studying HFOs in invasive electrodes using time frequency analysis (Burnos et al., 2014). One of the most commonly used method is the time frequency analysis of the signal using various transformations e.g., Gabor transform, wavelet transform (Kobayashi et al., 2011, 2010; Zijlmans et al., 2012).

Idiopathic generalized epilepsy (IGE) constitutes nearly a third of all epilepsies (Jallon and Latour, 2005). Childhood absence epilepsy (CAE) is the prototype of IGE with typical absence seizures in children of school age (5–8 years) and Juvenile Absence Epilepsy (JAE) has its onset between 9–20 years of age (Hirsch and Panayiotopoulos, 2008, 2005; Panayiotopoulos, 2005). Scalp EEG in absence seizures reveals a typical high amplitude spike and slow wave complexes, rhythmic at 3 Hz with gradual slowdown from initial to terminal phase and lasting for 4 to 20 s (Gupta et al., 2011; Hirsch and Panayiotopoulos, 2008, 2005; Westmijse et al., 2009). Infra slow oscillations have been demonstrated in ictal generalized spike wave discharges in absence epilepsy (Rodin et al., 2008). Studies have shown that in patients presenting with generalized seizure discharges such as continuous spike waves during slow wave sleep (CSWS), HFOs of frequency 97.7–140.6 Hz (mean 119.5 Hz) were noted and these patients had associated cognitive regression (Kobayashi et al., 2010). Recent studies have shown cognitive deficits and behavioral changes in patients presenting with IGE syndrome, which was once believed to be a safer type of epilepsy (Hughes, 2009). Pathological HFOs are known to affect physiological HFOs which are required for higher cognitive functioning. Hence we tried to look for HFOs in absence epilepsy.

In this study, using independent component analysis and time frequency maps, we intended to elucidate: (1) Occurrence of HFOs in scalp EEG of CAE and JAE, (2) Characterize the spatial relation of HFOs to the epileptiform activity (interictal epileptiform discharges v/s ictal events), (3) The frequency of occurrence of HFOs in ictal records, (4) Channel wise analysis of the frequency bandwidth of HFOs and (5) the frequency range of the HFOs in sleep ictal records.

2. Methods

This analytical study was carried out in the department of neurology at a university teaching hospital and a tertiary care center for epilepsy patients from June 2013 to March 2014. Children diagnosed to have absence epilepsy (childhood/juvenile) as per ILAE criteria were included for the study. Written informed consent was obtained from the legal guardians (parents) of the subjects.

2.1. Subjects

Fifteen children presenting with history of seizures with semiology suggestive of absence epilepsy were evaluated. As a part of regular workup for epilepsy, these patients were evaluated with routine scalp EEG and imaging (CT and/or MRI of brain). Of the 15 patients with absence epilepsy, 12 presented with childhood absence epilepsy (CAE) while 3 had juvenile absence epilepsy (JAE). Out of the 15 patients, 6 of them did not have any interictal–ictal epileptiform activity. Hence, data from nine EEGs were analyzed.

2.2. Data acquisition

The routine scalp EEG was recorded using the standard 10–20 system referenced to the A1 and A2 earlobe electrodes. The EEG was recorded in Galileo NT PMS, EBNeuro® system. A separate montage was created with the following acquisition parameters: Low Frequency Cut off: 0.3 Hz, High Frequency cut off: open, sampling rate: 2048 Hz, impedance: <5000 Ω. After the initial calibration steps, the child was allowed to sleep for up to 40–45 min. After this, they were tested with hyperventilation, 3 repetitions of 2 min each to precipitate absence seizures followed by photic stimulation (PS – done as part of the routine recording but not included in the analysis).

2.3. Data preprocessing

The data recorded was stored for further analysis in both European Data Format (EDF) and American Standard Code for Information Interchange (ASCII) format. Cartool® was used for visual analysis and EEGLAB® in MATLAB 2013 for semi-automated analysis. The following segments were identified in the EEG – (1) Awake, (2) Drowsy, (3) Sleep (Stage 1 and 2) and (4) Hyperventilation. The following interictal – ictal discharge patterns were identified: (1) inter-ictal generalized spike-wave discharges (IiGSWDs) – these were noted across all channels but lasting less than 4 s and never associated with clinical manifestations; (2) Ictal GSWDs (IcGSWD) – these lasted for >4 s both in sleep/awake state and during awake state were associated with clinical manifestation. (3) Sporadic SWDs (sSWDs – spike wave discharges noted in isolated channels). These were additional inter-ictal discharges but were limited to few channels rather than all the channels (Fig. 1). An ictus of absence was defined as a clinical manifestation of sudden onset impairment of consciousness with EEG showing generalized discharges of high amplitude spike, double or triple spike and slow-wave complexes lasting greater than 4 s. In sleep stages 1 and 2, the ictus was defined when there were 3 Hz GSWDs lasting >4 s (Gupta et al., 2011; Hirsch and Panayiotopoulos, 2008; Westmijse et al., 2009).

2.4. HFO analysis

2.4.1. Manual analysis

All the data obtained in EDF formats, were exported to Cartool®. A non-causal Butterworth filter with a high pass frequency of 80 Hz, a low pass frequency of 250 Hz and notch filter at 50 Hz was used. Slow DC shifts were removed. The sensitivity and paper speed was modified (sensitivity: 1–2 μV/mm, temporal resolution: