Seizure 58 (2018) 55–61

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Hypsarrhythmia in epileptic spasms: Synchrony in chaos

Vera Nenadovic[a,1], Robyn Whitney[b,1], Jason Boulet[b,d], Miguel A. Cortez[b,c,d,*]

[a] Lawrence Bloomberg School of Nursing, University of Toronto, Toronto, Ontario, Canada
[b] Division of Neurology, The Hospital for Sick Children, Toronto, Ontario, Canada
[c] Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada
[d] PGCRL Neurosciences and Mental Health Program, SickKids Research Institute, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 18 January 2018
Received in revised form 21 March 2018
Accepted 29 March 2018
Available online xxx

Keywords:
Hypsarrhythmia
Infantile spasms
EEG
Phase synchronization
Brain dynamics

ABSTRACT

Purpose: Hypsarrhythmia is an electroencephalographic pattern associated with epileptic spasms and West syndrome. West syndrome is a devastating epileptic encephalopathy, originating in infancy. Hypsarrhythmia has been deemed to be the interictal brain activity, while the electrodecremental event associated with the spasms is denoted as the ictal event. Though characterized as chaotic, asynchronous and disorganized based on visual inspection of the EEG, little is known of the dynamics of hypsarrhythmia and how it impacts the developmental arrest of these infants.
Methods: As an exploratory and feasibility study, we explored the dynamics of both hypsarrhythmia and electrodecremental events with EEG phase synchronization methods, and in a convenience sample of three outpatients with epileptic spasms. As ictal events are associated with prolonged phase synchronization, we hypothesized that if hypsarrhythmia was indeed the interictal brain activity that it would have lower phase synchronization than the electrodecremental event (ictal phase).
Results: We calculated both the phase synchronization index and the temporal variability of the index in three patients with infantile spasms. Two patients had hypsarrhythmia and electrodecremental events and one had hemi-hypsarrhythmia. We found that the hypsarrhythmia pattern was a more synchronized state than the electrodecremental event.
Conclusions: We have observed that the hypsarrhythmia pattern may represent a more synchronized state than the electrodecremental event in infants with epileptic spasms. However, larger studies are needed to replicate and validate these findings. Additionally, further inquiry is required to determine the impact that increased synchronization may have on developmental outcomes in infants with epileptic spasms.

1. Introduction

Hypsarrhythmia refers to the abnormal electroencephalographic (EEG) pattern observed in infants with epileptic spasms, which is an epileptic encephalopathy that presents in infancy [1,2,3]. Infants typically present in the first year of life, with the peak onset at 6 months of age [1,2,3]. Classically, the term West Syndrome has been used to describe the triad of epileptic spasms, hypsarrhythmia and developmental regression [3]. Hypsarrhythmia refers to the interictal EEG pattern and based on visual inspection, is characterized by high voltage, asynchronous slow waves with multi-focal spikes, which vary in duration and location [3,4]. The electrodecremental event denotes the ictal pattern associated with spasms and based on visual inspection is characterized by diffuse voltage attenuation of EEG waveforms [3,4]. The finding of hypsarrhythmia on EEG is of great concern to paediatric neurologists, as it can be associated with poor neurological outcomes. Thus both the resolution of spasms and normalization of the EEG are pivotal treatment goals [5,6].

Hypsarrhythmia has been characterized as a chaotic, asynchronous and disorganized pattern, based on visual inspection of the EEG tracing [1,4,7]. This characterization was challenged over a decade ago from a dynamic systems perspective [8]. It has been postulated that hypsarrhythmia should be regarded as a form of non-convulsive status epilepticus, based on dynamic systems and the associated impacts on cognition and development [9]. Characterizing the dynamics of hypsarrhythmia may help hasten investigations in infants with regression or subtle delays in

* Corresponding author at: Division of Neurology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada.
E-mail address: miguel.cortez@sickkids.ca (M.A. Cortez).
[1] Both authors contributed equally.

https://doi.org/10.1016/j.seizure.2018.03.026
1059-1311/

development and thus result in earlier treatment [9]. To determine if the pattern of hypsarrhythmia represents an ictal phenomenon, research is required to determine if there is increased local neuronal synchronization during this state [10,11].

Digital EEG analysis has shown that the waveform is a complex signal with more information than can be ascertained by visual inspection. Use of EEG analytics using nonlinear signal processing techniques continues to reveal hidden changes [12]. Phase synchronization is an analytic process which evaluates the relationship of the phases of two signals, independent of their amplitudes. In seizure recordings, the evaluation of EEG by this method has shown that there are differences in the phase synchrony between electrodes in seizure-free recordings compared with those with seizures [13,14]. We reason that evaluating the phase synchrony between EEG electrodes in recordings of hypsarrhythmia and electrodecremental events, would characterize these electrographic events.

If hypsarrhythmia is chaotic, then the EEG signals from each electrode should have no temporal relationships. If hypsarrhythmia represents an ictal state, then EEG phase synchrony among electrodes would be high phase synchronization, as is found in other seizure types [13]. Clinically, differentiating ictal and interictal states is important in infants with epileptic spasms [10]. Further, being able to quantify the ictal and interictal states could lead to the utilization of phase synchronization as a method of early detection for patients at risk.

Our research in traumatic brain injury showed that greater phase synchronization and less variability among EEG electrodes was associated with poor neurological outcome [15]. If hypsarrhythmia is a synchronized state, this could possibly contribute to cognitive regression. Phase synchronization can occur locally between neurons or can be long-range through a common input to multiple neurons and neuronal networks [16,17,18,19,20]. Phase synchronization exists across multiple bandwidths and exhibits variability in the form of temporal fluctuations [14,15,17,19]. Our dual objectives were exploration and feasibility to characterize the phase synchrony and temporal variability of hypsarrhythmia and electrodecremental events in infants with epileptic spasms referred to our outpatient clinic.

2. Methods

2.1. Clinical data

A review was undertaken of the medical histories, diagnostic imaging and EEG findings of a convenience sample of three infants with epileptic spasms, who were referred to our outpatient clinic for 30 min EEG recording with video at Hospital for Sick Children in Toronto, Ontario, Canada. Research Ethics Board approval was obtained at the Hospital for Sick Children prior to study initiation.

2.2. EEG acquisition

EEG recordings from the three patients were analysed by a Canadian Board Certified Neurophysiologist (MAC). Two of the patients (referred to as patient 1 and patient 2) had the hypsarrhythmia pattern and electrodecremental events and one patient (identified as patient 3) had hemi-hypsarrhythmia involving only the right hemisphere on sleep EEG.

Scalp EEGs for the patients were acquired in accordance with hospital protocol by Canadian Board Registered EEG technologists, using the International 10–20 system of electrode placement. The recordings consisted of 19 electrodes, referenced to an electrode 1 cm below the midline parietal (Pz) which was labelled Pz' (Pz prime) reference system. The EEGs were at least 30 min in length. All EEGs were acquired with the Stellate Harmonie® (sampling rate 500 Hz) system. The recordings had a bandpass filter of 1 to 70 Hz and all patients had electromyographic (EMG) electrodes to record muscle movement, and electrocardiogram (EKG) leads. The EEGs were read on a reformatted anterior-posterior bipolar montage.

2.3. EEG epoch and frequency selection

A muscle and movement artefact-freeartefact-free epoch of 10 s was selected per patient EEG, representing the bilateral hypsarrhythmia pattern, the electrodecremental events, and the right hemi-hypsarrhythmia. Our previous publications have shown that multiple epochs of 10 s representing the same pattern are not statistically significantly different from each other [14,20]. Thus for ease of calculation and feasibility of using this method in an outpatient setting, 10 s is sufficient for analysis of the EEG pattern of interest. Frequencies of interest were the delta bandwidth (3 Hz) that is generated by the cortex along with the alpha (10 Hz) and beta (15 Hz) bandwidths, both of which are generated by the thalamus [22,23]. As the electrodecremental events are much shorter in length than epochs of hypsarrhythmia, epochs were selected to include the EEG activity pre and post the event and the time point of the event identified based on visual inspection.

2.4. EEG phase synchronization, volume conduction and temporal variability

We have used the same methods for phase synchronization and have published extensively elsewhere on this [15,24,21]. To summarize, the Laplacian (second-order spatial derivative) is utilized, first to minimize the effects of volume conduction so that the phase synchronization can be accurately interpreted [24]. This step is followed by the Hilbert transform to extract the instantaneous phase [25]. The resultant synchronization, *R* index, is then calculated as the degree of phase locking between two EEG electrodes using the circular variance of the phase difference [13]. The phase differences are measured between the phase of each electrode and that of the remaining 18 EEG electrodes in a standard 10–20 system EEG montage, resulting in 171 *R* index values as a function of time: one for each non-repeating channel pair.

Phase synchrony is well suited for analysis of both the hypsarrhythmia and the electrodecremental event (EDE) as the calculation is independent of amplitude. The EDE occurs with a decrease in EEG amplitude to between 5 and 25 microvolts from the high amplitude of 500 to 700 microvolts of the hypsarrhythmia pattern [26]. The temporal variability is related to the change in the *R* index values over time. It was calculated as the mean value of the square of the derivative of the *R* index time series [15]. Temporal variability was calculated for each epoch for each EEG per patient.

Processing time per patient recording averaged 10 min which includes: identifying the epochs, extracting the data, running the software. The software stores the calculated indices that can be reviewed or extracted for further statistical analysis.

2.5. Statistical analysis

Descriptive statistics, specifically means and standard deviations were used to describe the R index (resultant synchronization) and temporal variability during hypsarrhythmia and the electrodecremental event of each infant. Note that the first two patients had electrodecremental events, but the third did not. The means of the synchronization index and temporal variability during hypsarrhythmia and the electrodecremental event were then compared using a *t*-test. Statistical significance was considered if $p < .05$ (StataCorp LLC, Texas, USA).