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Alterations of network synchrony after epileptic seizures: An analysis of post-ictal intracranial recordings in pediatric epilepsy patients

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ABSTRACT

Objective: Post-ictal EEG alterations have been identified in studies of intracranial recordings, but the clinical significance of post-ictal EEG activity is undetermined. The purpose of this study was to examine the relationship between peri-ictal EEG activity, surgical outcome, and extent of seizure propagation in a sample of pediatric epilepsy patients.

Methods: Intracranial EEG recordings were obtained from 19 patients (mean age = 11.4 years, range = 3–20 years) with 57 seizures used for analysis (mean = 3.0 seizures per patient). For each seizure, 3-min segments were extracted from adjacent pre-ictal and post-ictal epochs. To compare physiology of the epileptic network between epochs, we calculated the relative delta power (Δ) using discrete Fourier transformation and constructed functional networks based on broadband connectivity (conn). We investigated differences between the pre-ictal (Δ_{pre}, $conn_{pre}$) and post-ictal (Δ_{post}, $conn_{post}$) segments in focal-network (i.e., confined to seizure onset zone) versus distributed-network (i.e., diffuse ictal propagation) seizures.

Results: Distributed-network (DN) seizures exhibited increased post-ictal delta power and global EEG connectivity compared to focal-network (FN) seizures. Following DN seizures, patients with seizure-free outcomes exhibited a 14.7% mean increase in delta power and an 8.3% mean increase in global connectivity compared to pre-ictal baseline, which was dramatically less than values observed among seizure-persistent patients (29.6% and 47.1%, respectively).

Significance: Post-ictal differences between DN and FN seizures correlate with post-operative seizure persistence. We hypothesize that post-ictal deactivation of subcortical nuclei recruited during seizure propagation may account for this result while lending insights into mechanisms of post-operative seizure recurrence.

1. Introduction

Intractable pediatric epilepsy is a debilitating neurological condition associated with increased morbidity and adverse neurodevelopmental outcomes (Moshe et al., 2015). Surgical resection of the epileptogenic zone (EZ) is a valuable option for managing intractable seizures of suspected focal origin (Luders et al., 2006; Dwivedi et al., 2017), but an insufficient understanding of EZ structure and function has limited the efficacy of this intervention for decades (Spencer and Huh, 2008; Cossu et al., 2008). Researchers generally assert that the EZ constitutes a hypersynchronous network capable of initiating seizures and propagating them to distant regions (Lemieux et al., 2011). However, little is known about the mechanisms supporting these complex behaviors and how activity within the EZ evolves over time. Analysis of human intracranial EEG (IEEG) recordings demonstrates the existence of discernable network 'states' (i.e., pre-ictal, ictal, post-ictal, and inter-ictal) (Khambhati et al., 2015; Iasemidis et al., 2004), but studies examining the clinical significance and electrographic hallmarks of these

Abbreviations: L, left; R, right; F, frontal; T, temporal; O, occipital; Hemi, hemisphere; SOZ, seizure onset zone; FCD, focal cortical dysplasia; CVA, cerebrovascular accident; CHOP, Children's Hospital of Philadelphia, Philadelphia PA; MAYO, Mayo Clinic, Rochester MN; IEEG, intracranial electroencephalography

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states are lacking.

Prior studies of EZ states have focused on analyzing EEG activity in the ictal and pre-ictal intervals (Mormann et al., 2007). Consequently, the relevance of post-ictal activity has been sparsely examined (Remi and Noachtar, 2010; Rosenow, 2016). During the post-ictal window, patients may exhibit impaired memory, decreased awareness, altered cerebral metabolism, and changes in neurotransmitter profiles (Fisher and Schachter, 2000). Studies of human recordings have linked post-ictal generalized EEG suppression (PGES) to increased risk of cardiorespiratory collapse (Ryvlin et al., 2013) and sudden unexpected death in epilepsy (SUDEP) (Moseley et al., 2013; Lhatoo et al., 2010). The most common post-ictal EEG change observed across patients is a shift towards increased spectral power in the delta frequency range (≤ 4 Hz), (Kaibara and Blume, 1988) which has been shown to lateralize the side of seizure origin in adults with temporal lobe epilepsy (TLE) (Jan et al., 2001) and frontal lobe epilepsy (FLE) (Whitehead et al., 2016). In TLE patients, post-ictal delta activity over lateral fronto-parietal association cortices has also been linked to behavioral changes (Blumenfeld et al., 2004a) and impaired consciousness, (Englot et al., 2010) suggesting that generalized post-ictal slowing may facilitate the widespread cerebral dysfunction seen after some temporal lobe seizures.

Although increased post-ictal delta power is a common observation, post-ictal shifts in EEG activity are not uniform across patients and may vary with seizure semiology. For instance, recent evidence from human scalp EEG recordings suggests that delta power increases more drastically following seizures that spread diffusely (i.e., secondarily generalized) compared to simple and/or complex partial seizures (Yang et al., 2012). Krishnan et al. (Krishnan et al., 2014) conducted a small study of adult IEEG recordings, finding that spike frequency consistently decreased following clinical seizures but changed inconsistently, if at all, following subclinical seizures. Deactivation of subcortical relay structures (e.g., thalamic nuclei) following diffuse seizure propagation may account for these observations, as subcortical deactivation is thought to suppress cortical activity and increase cortical slow-wave oscillations (Englot et al., 2010). Previous studies using single photon emission computed tomography (SPECT) have shown dramatic alterations in cerebral blood flow within midbrain structures during the process of secondary generalization of tonic-clonic seizures, (Blumenfeld et al., 2009) and compelling evidence from the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy ("SANTE") trial (Fisher et al., 2010) revealed that anterior thalamic stimulation can decrease the frequency of diffusely propagated seizures in some patients with medically-refractory epilepsy. Subcortical extension of the epileptogenic network has also been hypothesized as a risk factor for post-operative seizure recurrence (Guye et al., 2006; Tomlinson and Venkataraman, 2018; He et al., 2017; Keller et al., 2015; Bonilha et al., 2015) suggesting that patients with robust post-ictal EEG changes may be less likely to benefit from targeted cortical resections. Scrutinizing this hypothesis requires study of the relationship between peri-ictal EEG activity and epilepsy surgery outcome.

The purpose of this study was to examine the relationship between peri-ictal EEG activity, surgical outcome, and extent of seizure spread (i.e., focal versus distributed spread). Towards this goal, we extracted brief (3-min) pre-ictal and post-ictal EEG segments from a sample of 19 pediatric IEEG recordings. To characterize peri-ictal EEG activity, two widely-examined parameters were analyzed: (i) spectral power in the delta frequency band; and (ii) average broadband connectivity strength across electrodes. We predicted that distributed seizure propagation would lead to significantly greater post-ictal EEG changes compared to seizures that spread less extensively. Further, we hypothesized that patients with unfavorable (i.e., seizure-persistent) surgical outcomes would exhibit more widespread post-ictal EEG changes compared to patients with seizure-free outcomes.

2. Material and methods

2.1. Clinical data

The Children's Hospital of Philadelphia (CHOP) Institutional Review Board approved this study. Sixteen IEEG recordings were retrospectively accessed from a database of Phase II evaluations performed at CHOP between the years of 2002 and 2009. Informed consent was obtained from all patients prior to inclusion. The selection criteria for this study were adequate post-operative follow-up (minimum duration = 2 years), presence of at least one seizure meeting the inclusion criteria (discussed below), and availability of detailed clinical markings of the complete EEG records. Recordings were acquired using a Telefactor Beehive Cable Telemetry Encoder (CTE) digital synchronized video-EEG system with 16-bit amplification and 200 Hz sampling rate. Subdural platinum electrodes (Astro Med Corp, West Warwick, RI) with 2.3 mm exposure diameter and 10 mm inter-electrode distance were used. Online voltages were referenced to an outward-facing epidural electrode strip and passed through an analog anti-aliasing bandpass filter (frequency cut-offs at 0.1- and 70-Hz) and notch filter (60 Hz). Retrospective chart review provided clinical information for each patient including epilepsy duration, implantation site, magnetic resonance imaging (MRI) description, and histopathology. Post-surgical outcomes were assessed upon last patient contact using the modified Engel scale (Wieser et al., 2001) (Class I = seizure-free, Class $\geq$ II = seizure-persistence).

Three additional pediatric IEEG recordings were obtained from the publically-accessible International Epilepsy Electrophysiology Portal (IEEG Portal; ieeg.org) to bolster the sample size. Recordings from the IEEG Portal were performed at Mayo Clinic (MAYO; Rochester, MN) and were independently curated (A.N.K) without knowledge of the study's experimental procedures or hypotheses. MAYO recordings were sampled at 500 Hz, and electrodes were identical to those used by CHOP with regards to manufacturer and spacing. Surgical outcome was reported by MAYO neurologists using the International League Against Epilepsy (ILAE) outcome scale (Wieser et al., 2001) (I = seizure-free, $>$ I = seizure-persistence). The post-operative follow-up duration was not readily available for MAYO patients. To group patients by surgical outcome, patients with Engel (ILAE) score = I were marked 'Seizure-Free' while all other patients were marked as 'Seizure-Persist.'

2.2. Seizure annotation

Seizure markings for the IEEG Portal recordings were performed by a team of neurologists from the Hospital of the University of Pennsylvania (HUP) and MAYO (for additional details, see Khambhati et al., 2015). For CHOP recordings, two experienced pediatric epileptologists (authors B.E.P and E.D.M) independently inspected full-duration recordings and identified all seizures, noting the following parameters: (i) time of earliest electrographic change at ictal onset; (ii) time of unequivocal electrographic offset; (Litt et al., 2001) and (iii) seizure onset electrodes. For each seizure, observations from the clinical EEG report were obtained (R.M.K.). All seizures in the analysis were initially focal in onset. One author (E.D.M) blind to patient identity inspected each seizure and classified them as 'focal-network' or 'distributed-network' based on the extent of regions involved in seizure propagation, using the following definitions: focal-network seizures remained confined to the seizure onset electrodes whereas distributed-network seizures exhibited widespread generalization to surrounding tissues (i.e., spreading to $\geq$75% of total electrodes and encompassing at least two distinct recording grids). Representative seizures are shown in Fig. 1a and Fig. S1. Previous intracranial EEG studies attempting to categorize seizures based on the extent of ictal propagation have arrived at similar terminology. For example, Khambhati et al. (Khambhati et al., 2016) categorized seizures as 'distributed' or 'focal' based on the presence or absence of generalization beyond the seizure onset zone,