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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

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eplepsyres.2018.04.003.

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.

Keywords

Pediatric epilepsy; Intracranial electroencephalography; Post-ictal; Epilepsy surgery; Network connectivity

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 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 ≥ 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 ≥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, respectively. For inclusion in present analyses, seizures were required to occur at least one hour from the nearest adjacent seizure to ensure that segments were flanked by a sizable inter-ictal period.

2.3. Epoch extraction

For each seizure, three minute segments were extracted from the immediate pre-ictal and post-ictal windows (Fig. 1b). Continuous segments were divided into 180 consecutive non-overlapping 1-s epochs. The epoch duration was chosen to satisfy the quasi-stationarity requirements of the functional connectivity measures used in the study while preserving adequate spectral resolution of the delta (1–4 Hz) frequency band. Although the primary objective was to characterize the immediate peri-ictal window, analyses were repeated on a distal time window (i.e., 27–30 min from seizure offset) to assess whether post-ictal changes were sustained (see Fig. 5).

2.4. Relative delta power

To quantify relative delta power, epochs were linearly de-trended, tapered with a Hamming window (duration = 1 s), and fast Fourier transformed using MATLAB 2016a (Mathworks, Natick, MA). Extracted frequencies ranged from 0 Hz to 100 Hz (Nyquist frequency) with 1 Hz frequency resolution. Power estimates ($\mu V^2/Hz$) were obtained by squaring the absolute value of the Fourier coefficients and normalizing by the sampling rate. For each channel, the relative power spectrum was computed, and relative delta power was obtained by integrating across the 1–4 Hz frequency range. Relative delta power for each epoch was then computed by averaging values across channels. For each seizure, we computed the mean pre-ictal (Δ_{pre}) and post-ictal (Δ_{post}) delta power by averaging values across epochs (Fig. 1c). Then, to summarize the percent change in delta power across the seizure interval (i.e., the ratio of the peri-ictal change to the pre-ictal baseline), the delta ratio (Δ_{ratio}) was defined: $[(\Delta_{post} - \Delta_{pre})/\Delta_{pre}]$, with $\Delta_{ratio} > 0$ signifying increased delta power in post-ictal compared to pre-ictal epochs.

2.5. Broadband cross-correlation

Functional connectivity is useful for characterizing the similarity of electrical waveforms between pairs of electrodes, which is interpreted as the degree of interregional synchrony between remote neural populations. There exist many approaches for calculating functional connectivity from neural time-series data, with different techniques offering strengths and weaknesses depending on the examined biological system (Wendling et al., 2009; Ansari-Asl et al., 2006). Given our interest in broadband connectivity patterns, we favored a simple measure of amplitude cross-correlation (Spearman rank correlation) over other band-limited metrics (e.g., spectral coherence).

Functional connectivity was calculated within each epoch using the absolute value of the zero-lag Spearman rank correlation (min = 0, max = 1) between all possible electrode pairs and tabulated in an NxN adjacency matrix ($\boldsymbol{A}_{conn}$), where N is the number of electrodes (Tomlinson et al., 2017). Because Spearman coefficients are drawn from a non-normal

distribution, raw coefficients were Fisher-Z transformed prior to analysis (Cohen, 2014). Pairwise transformed coefficients (i.e., off-diagonal entries of $\boldsymbol{A}_{conn}$) were averaged to obtain the global connectivity strength for each epoch (Fig. 1c, bottom row). The mean pre-ictal ($conn_{pre}$) and post-ictal ($conn_{post}$) global connectivity strength were computed for each seizure by averaging across epochs. The connectivity ratio ($conn_{ratio}$) was then defined: $[(conn_{post} - conn_{pre})/conn_{pre}]$, with $conn_{ratio} > 0$ signifying increased network connectivity in the post-ictal compared to the pre-ictal interval.

2.6. Correlation between peri-ictal delta and broadband connectivity

Shifts in the slow-wave composition of the EEG may correlate with changes in global connectivity, given that the Spearman correlation is a broadband connectivity measure (Cohen, 2014). To assess whether changes in relative delta power (Δ) correlated with changes in global broadband connectivity strength (conn), we calculated the Pearson correlation coefficient, r, between Δ_{ratio} and $conn_{ratio}$.

2.7. Statistical testing

To address the primary hypothesis that focal-network (FN) and distributed-network (DN) seizures differ with regards to peri-ictal EEG measures of interest, we first conducted group comparisons (FN, n = 27 versus DN, n = 30) using two-tailed Student's t-tests. Then, to investigate whether surgical outcome was associated with peri-ictal changes, seizures were divided into four groups based on the outcome of the corresponding patient: ($FN_{sz\text{-}free}$, $FN_{sz\text{-}persist}$, $DN_{sz\text{-}free}$, $DN_{sz\text{-}persist}$). Because the number of seizures per group was small, and because patients contributed a variable number of seizures to each group, we report descriptive statistics and individual patient data without conducting explicit group comparisons in this secondary analysis. Unless otherwise noted, group statistics are reported as mean (μ) ± standard deviation (SD).

3. Results

3.1. Clinical data

Patient characteristics from the study sample are presented in Table 1. Fifty-seven seizures from 19 patients (mean age = 11.4 ± 4.5 years) were examined. In total, 9 patients experienced post-surgical seizure freedom ('Sz-Free') whereas 10 patients suffered seizure recurrence ('Sz-Persist'). Recording implants ranged from 56 to 124 electrodes (97.5 ± 18.3 electrodes) and did not differ between Sz-Free and Sz-Persist patients (Wilcoxon rank sum test, $p = 0.59$). No group differences in the percentage of total electrodes within the SOZ were observed (Wilcoxon rank sum test, $p = 0.24$). Among patients with available histopathological data (n = 16/19, 84.2%), the predominant finding was Taylor-type focal cortical dysplasia (13/16, 81.3%). The majority of seizures (42/57, 73.7%) originated from extra-temporal electrodes.

3.2. Distributed-network (DN) versus focal-network (FN) seizures

We first compared peri-ictal measures of interest between DN and FN seizure groups (Fig. 2). Overall, the mean seizure duration in the study was 76.1 ± 87.7 s, which did not differ between DN (75.8 ± 57.2 s) and FN groups (76.5 ± 113.7 s; $p = 0.98$). When pre-ictal

connectivity was assessed (Fig. 2a), we observed greater $conn_{pre}$ for DN seizures (0.301 ± 0.047) compared to FN seizures (0.266 ± 0.043; $p = 0.005$). In the post-ictal window, $conn_{post}$ was significantly elevated for DN seizures (0.380 ± 0.115) compared to FN seizures (0.273 ± 0.055; $p = 4.63 \times 10^{-5}$). The connectivity ratio ($conn_{ratio}$) was also significantly greater among DN seizures (0.264 ± 0.327) compared to FN seizures (0.028 ± 0.119; $p = 8.12 \times 10^{-4}$).

Similar trends emerged when peri-ictal delta power was examined (Fig. 2b). In the pre-ictal window, a modest difference in Δ_{pre} was observed between DN (0.614 ± 0.069) and FN seizures (0.559 ± 0.063; $p = 0.003$). Post-ictal delta power (Δ_{post}) was significantly greater for DN (0.740 ± 0.072) versus FN seizures (0.591 ± 0.079; $p = 5.95 \times 10^{-10}$). Finally, the delta ratio (Δ_{ratio}) was significantly greater for DN seizures (0.216 ± 0.159) compared to FN seizures (0.061 ± 0.127; $p = 1.72 \times 10^{-4}$). Together, these results demonstrate more robust peri-ictal shifts in EEG delta power and connectivity among seizures that propagate in a distributed fashion compared to seizures that remain confined to the seizure onset zone.

3.3. Relationship between extent of seizure propagation, surgical outcome, and peri-ictal measures

In the first round of analysis, we observed extensive variability in peri-ictal EEG measures when seizures were grouped according to the extent of ictal propagation. In the second round of analysis, we aimed to assess whether interaction with another variable (i.e., surgical outcome) may be driving heterogeneity within the electrographically-de-fined seizure groups. Towards this goal, four seizure subtypes were designated (Fig. 3): $DN_{sz\text{-}free}$ (n = 16), $DN_{sz\text{-}persist}$ (n = 14), $FN_{sz\text{-}free}$ (n = 18), and $FN_{sz\text{-}persist}$ (n = 9).

In the pre-ictal window, $conn_{pre}$ was similar across the four seizure groups (Fig. 3a, left). In the post-ictal window, however, $conn_{post}$ was considerably higher in $DN_{sz\text{-}persist}$ seizures (0.462 ± 0.117) compared to the other three seizure types. The average $conn_{ratio}$ among $DN_{sz\text{-}persist}$ seizures was 0.471 ± 0.348 compared to much lower values in the other seizure groups (Fig. 3a, right): $DN_{sz\text{-}free}$ (0.083 ± 0.163), $FN_{sz\text{-}persist}$ (0.012 ± 0.159), $FN_{sz\text{-}free}$ (0.036 ± 0.098). When peri-ictal delta power was examined (Fig. 3b), the critical finding was an increased Δ_{ratio} for $DN_{sz\text{-}persist}$ seizures (0.296 ± 0.173) compared to the other three seizure types: $DN_{sz\text{-}free}$ (0.147 ± 0.111), $FN_{sz\text{-}persist}$ (0.045 ± 0.154), $FN_{sz\text{-}free}$ (0.069 ± 0.116).

A complete accounting of individual seizure data (Δ_{ratio}, $conn_{ratio}$) is presented in Fig. 4. Among $FN_{sz\text{-}free}$, $FN_{sz\text{-}persist}$, and $DN_{sz\text{-}free}$ seizures, most exhibited small peri-ictal changes in delta power and global connectivity. In contrast, most $DN_{sz\text{-}persist}$ seizures exhibited dramatic peri-ictal shifts in these parameters. Overall, the results demonstrate that the percent peri-ictal change in delta power and connectivity strength are increased for distributed network seizures compared to focal network seizures, and these effects are most robust among the group of seizure-persistent patients examined in the study.

3.4. Correlation between peri-ictal delta power and broadband connectivity changes

To assess whether shifts in slow-wave activity were associated with changes in global connectivity, the correlation (Pearson) between Δ_{ratio} and $conn_{ratio}$ was calculated (Fig. 3c).

A significant linear correlation was observed between Δ_{ratio} and $conn_{ratio}$ among the $DN_{sz\text{-}free}$ ($r = 0.878$, $p < 0.001$), $FN_{sz\text{-}free}$ ($r = 0.932$, $p < 0.001$), and $FN_{sz\text{-}persist}$ ($r = 0.882$, $p < 0.001$) seizure types. However, the correlation between these measures among $DN_{sz\text{-}persist}$ seizures was non-significant ($r = 0.210$, $p = 0.47$). This result suggests that peri-ictal changes in global EEG connectivity among $DN_{sz\text{-}persist}$ seizures are not related to changes in EEG delta activity.

3.5. Post-ictal differences are sustained beyond the immediate post-ictal window

Finally, although our primary aim was to characterize the window immediately adjacent to seizure onset and offset, we repeated our analysis using a distal post-ictal time window (27–30 mins from seizure offset) (Fig. 5). For connectivity, $conn_{ratio}$ was highest among $DN_{sz\text{-}persist}$ seizures (0.149 ± 0.107) compared to $DN_{sz\text{-}free}$ (−0.034 ± 0.105), $FN_{sz\text{-}persist}$ (−0.052 ± 0.083), and $FN_{sz\text{-}free}$ (−0.048 ± 0.088) groups. For relative delta power, Δ_{ratio} was highest for $DN_{sz\text{-}persist}$ seizures (0.163 ± 0.112) and lower for the other seizure groups: $DN_{sz\text{-}free}$ (0.004 ± 0.110), $FN_{sz\text{-}persist}$ (0.003 ± 0.103), and $FN_{sz\text{-}free}$ (−0.043 ± 0.118).

4. Discussion

In this study, we examined the relationship between peri-ictal EEG activity, surgical outcome, and extent of seizure propagation (i.e., focal versus distributed spread) within a group of 19 pediatric epilepsy surgery patients. We found that seizures engaging distributed propagation networks (distributed-network, DN) exhibited greater post-ictal increases in delta power and broadband connectivity compared to focal-network (FN) seizures that remain confined to the seizure onset zone (Fig. 2). Further, we demonstrated that post-ictal differences between DN and FN seizures correlate with surgical outcome (Figs. 3–5).

The network mechanisms driving widespread post-ictal EEG changes are poorly understood, but a leading hypothesis is that subcortical nuclei are deactivated following seizure termination (Blumenfeld et al., 2004a; Englot et al., 2010; Lado and Moshé, 2008). Recent work has suggested that subcortical relay nuclei can serve as hubs or “gateways” to facilitate widespread seizure propagation (Milton, 2003; Blumenfeld et al., 2009). In this subcortical deactivation model, deep structures (e.g., thalamic nuclei) connected to cortical seizure foci are disrupted after recruitment during the ictal phase, leading to a window of subcortical deactivation and impaired functioning in the post-ictal interval (Englot et al., 2009). As subcortical networks are implicated in cortical arousal processes (Englot et al., 2010; Englot et al., 2009), the result may be widespread cortical deactivation that could contribute to the loss of consciousness, increased fronto-parietal slowing, decreased spike activity, and impaired cerebral blood flow seen after some seizures (Blumenfeld et al., 2004a; Englot et al., 2010; Englot et al., 2009; Blumenfeld et al., 2004b).

Critically, involvement of subcortical structures in the epileptogenic network has been posited 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). In this study, large post-ictal shifts towards increased delta power and global EEG connectivity were preferentially observed among patients with unfavorable (seizure-persistent) outcomes (Figs. 3–5). Seizures examined among the seizure-free group, on the other hand, induced

minimal changes in delta power and global connectivity, even for seizures that engaged distributed cortical networks. In the context of the subcortical network hypothesis, widespread post-ictal EEG changes following $DN_{sz\text{-}persist}$ seizures may relate to deactivation of subcortical relay nuclei and resultant shifts in global spectral activity and connectivity at the cortical surface. Here, the hypothesis is that $DN_{sz\text{-}persist}$ seizures are able to propagate beyond the seizure onset zone (SOZ) by engaging subcortical networks with dense reciprocal connections to the cortex. In the process of (or immediately following) seizure termination, these subcortical relay stations become disrupted, leading to a subsequent depression of cortical activity (e.g., spike activity, fast oscillations, etc.). In contrast, the subset of DN seizures that resulted in minimal post-ictal EEG changes tended to occur in patients who ultimately experienced seizure-free outcomes. One account of this finding posits that this group of patients exhibited less robust involvement of subcortical relay structures during ictal propagation, resulting in minimal post-ictal changes at the cortical surface. Previous studies have shown that increased connectivity between cortical and subcortical structures is a risk factor for post-surgical seizure persistence (He et al., 2017; Keller et al., 2015; Bonilha et al., 2015). Thus, we propose that subcortical nuclei are more central to epileptogenic network connectivity and ictal spread among patients with seizure-persistent outcomes compared to seizure-free patients. Future research recording simultaneously from cortical and subcortical regions is needed to validate this hypothesis. Intriguingly, this population may stand to benefit from the advances in deep brain stimulation (DBS) research, with evidence coming from the SANTE trial, (Fisher et al., 2010) which validated the benefit of anterior thalamic stimulation in reducing the frequency of secondarily generalized seizures among certain patients with medically-refractory epilepsy.

The correlation analysis of peri-ictal delta power and connectivity revealed another noteworthy divergence between $DN_{sz\text{-}persist}$ seizures and the other seizure types (Fig. 3c). When $DN_{sz\text{-}free}$, $FN_{sz\text{-}free}$, and $FN_{sz\text{-}persist}$ seizure types were examined, a tight linear correlation between Δ_{ratio} and $conn_{ratio}$ was observed. However, the correlation between these measures was non-significant among $DN_{sz\text{-}persist}$ seizures. The absence of a relationship between these measures suggests that the large connectivity changes following $DN_{sz\text{-}persist}$ seizures are not attributable to spectral shifts towards increased slow-wave activity. For the other three seizure types, one may consider the possibility that observed changes in post-ictal connectivity are reflecting the shift towards slower EEG oscillations (and decreased wave cycles per epoch). This divergence suggests that increased global connectivity following $DN_{sz\text{-}persist}$ seizures is driven by a synchronization process that is fundamentally distinct from the other seizure types, one that is independent of delta power modulation. We speculate that widespread increases in connectivity strength following $DN_{sz\text{-}persist}$ seizures reflect the extension of the network into subcortical regions, which serve as hubs organizing synchronized activity across disparate regions of cortex. Alternatively, increased post-ictal connectivity among $DN_{sz\text{-}persist}$ seizures may be correlated with changes in a different frequency band. Future studies characterizing this distinct pattern of synchronization may yield insights into the mechanism of post-surgical seizure recurrence.

Finally, although our primary aim was to characterize the window immediately adjacent to seizure onset and offset, we repeated our analysis in a distal post-ictal window 27–30 minutes after seizure termination (Fig. 5). Interestingly, we found that post-ictal increases in connectivity and delta power were sustained among $DN_{sz\text{-}persist}$ seizures in this later window, albeit to a less dramatic extent. Consensus regarding the duration and time-course of the post-ictal period has not been reached, and very few studies have examined this question among pediatric patients. One study (Arkilo et al., 2013) examined post-ictal activity in a sample of 13 pediatric patients, finding that post-ictal waveforms returned to inter-ictal baseline rhythms after an average of ~60–120 mins, depending on the region of seizure onset. We therefore suspect that the post-ictal differences between $DN_{sz\text{-}persist}$ seizures and the other seizure types may extend beyond the 30-min analysis window examined in the present study. Future work incorporating longer peri-ictal EEG segments is needed to test this prediction.

The primary weakness of this study is the small number of patients and seizures included in the analysis. While all pediatric IEEG studies suffer from this limitation, increasing the sample size will allow us to construct seizure groups based on specific electrographic features (e.g., repetitive spiking, low voltage fast activity, burst suppression) to conduct more nuanced peri-ictal comparisons. Further, due to the limited number seizures analyzed, we were unable to conduct systematic comparison between temporal and extra-temporal seizures. Additionally, our inability to characterize seizures as focal versus secondarily generalized due to limited cortical sampling necessitated the use of the “focal-network” versus “distributed-network” classification scheme, which oversimplifies the process of seizure propagation. All IEEG studies share the possibility of under-sampling the epileptogenic network or seizure onset zone (Holtkamp et al., 2012). Future research with more robust sampling may strengthen the present results by minimizing misclassification error. Finally, although this work raises interesting translational questions about predicting surgical outcomes on the basis of pre-surgical EEG characteristics, this study was neither designed nor powered to assess the predictive utility of these analyses at the individual-seizure or individual-patient level. Such translational work is the subject of ongoing study in our lab.

In conclusion, this study examined the relationship between peri-ictal EEG activity, extent of seizure spread, and post-operative seizure control among 19 pediatric epilepsy surgery patients. We observed greater post-ictal increases in delta power and connectivity strength following distributed seizures compared to seizures that remained confined to the seizure onset zone. Further, we provide novel evidence that post-ictal EEG changes are related to epilepsy surgery outcome. We interpret this finding to suggest that epileptogenic network configuration is fundamentally different in patients with seizure-free versus seizure-persistent surgical outcomes, which may shed light on mechanisms of post-operative seizure recurrence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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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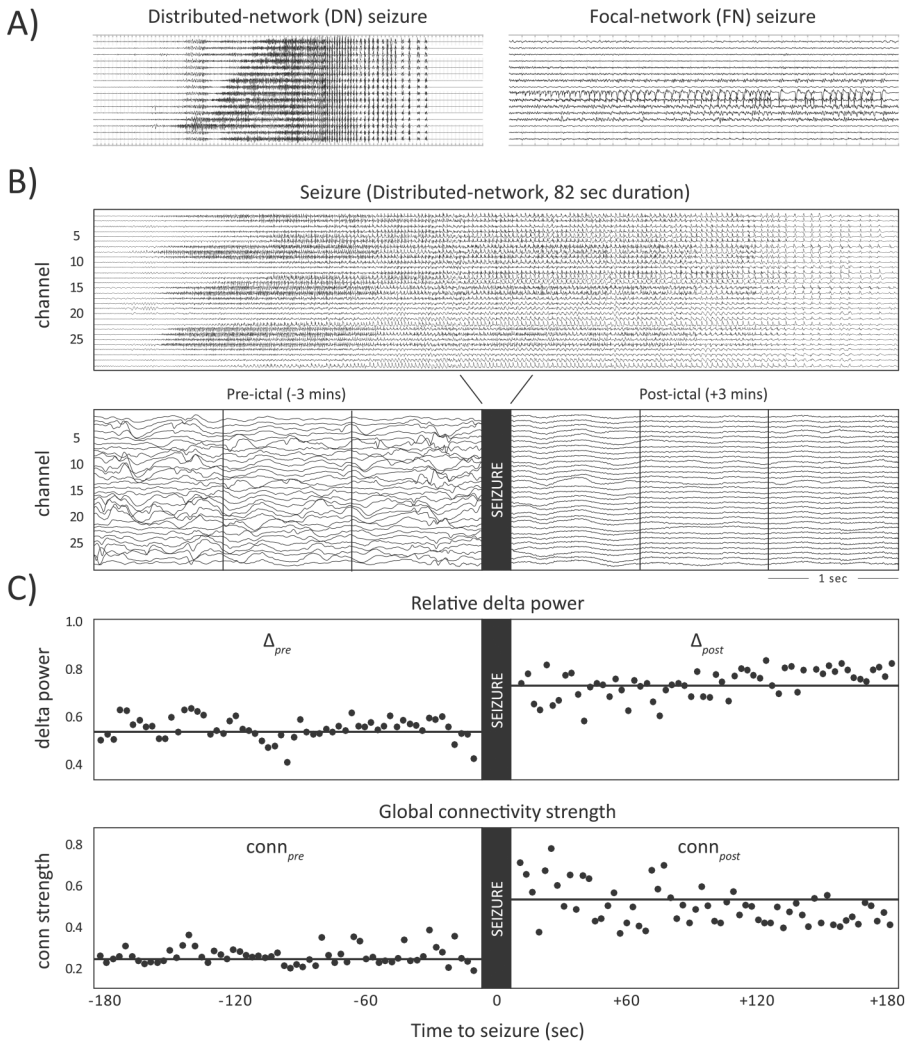

Fig. 1.

EEG extraction and analysis pipeline. A) Representative ictal traces from two seizures (distributed-network, *left*; focal-network, *right*) are displayed. Sixteen electrodes are shown per seizure, and vertical lines appear at one second intervals. B) *Upper*: Distributed-network (DN) seizure from CHOP01 is shown (electrodes plotted = 30, duration = 82 s). *Lower*: Pre-ictal and post-ictal EEG segments were extracted. Each three-minute segment was divided into 180 non-overlapping 1-s epochs prior to analysis. Three representative pre-ictal and post-ictal epochs are shown (electrodes plotted = 30). C) *Upper*: The mean relative delta power (Δ; 1–4 Hz) for each epoch is shown. Thick horizontal lines correspond to the mean across epochs (Δ_{pre}; Δ_{post}). A clear shift towards increased post-ictal delta power is exhibited. *Lower*: The mean global connectivity strength was computed and plotted across pre-ictal ($conn_{pre}$) and post-ictal ($conn_{post}$) segments.

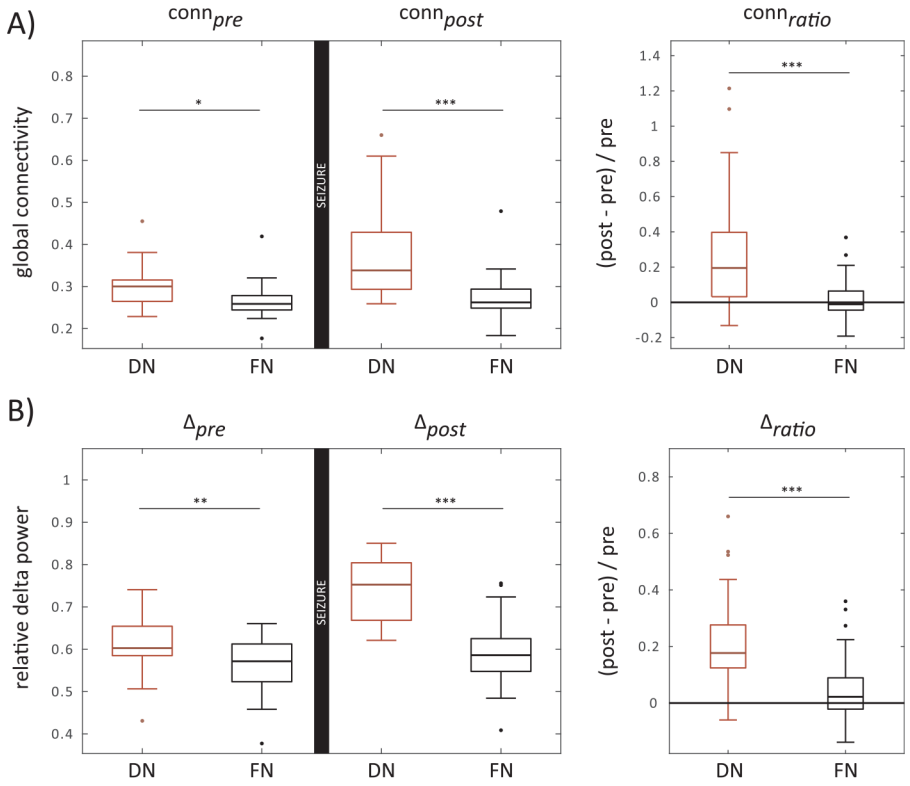

Fig. 2.

Post-ictal connectivity and relative delta power are increased in distributed-network (DN) versus focal-network (FN) seizures. *A) *Left*: Global broadband connectivity was computed in the pre-ictal (conn$_{pre}$) and post-ictal (conn$_{post}$) intervals. Right: The connectivity ratio (conn$_{ratio}$) was significantly greater in DN seizures (0.264 ± 0.327) compared to FN seizures (0.028 ± 0.119; $p = 8.12 \times 10^{-4}$). B) *Left*: Relative delta power (Δ_{pre}; Δ_{post}) was compared between DS and NS seizures. A significant difference in Δ_{pre} was observed ($p = 0.003$), though a larger group difference was found in the post-ictal window ($p = 5.95 \times 10^{-10}$). *Right*: The delta ratio (Δ_{ratio}) was significantly greater for DN seizures compared to FN seizures ($p = 1.72 \times 10^{-4}$). Pairwise group comparisons were conducted using two-tailed Student's *t*-tests: $p < 0.05$ (*), $p < 0.005$ (**), $p < 0.001$ (***).

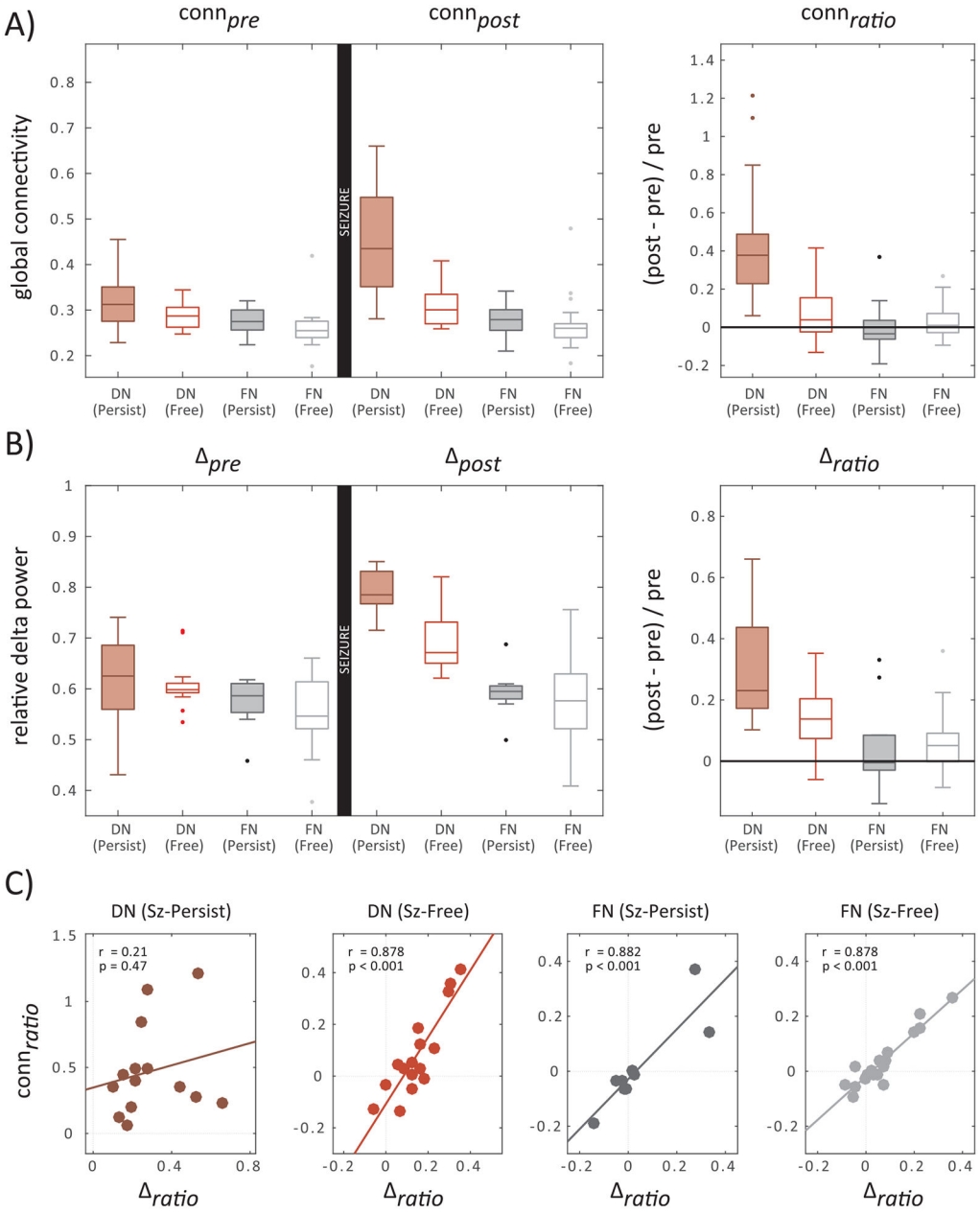

Fig. 3.

Post-ictal differences between distributed-network (DN) and focal-network (FN) seizures are driven by patients with unfavorable surgical outcome. A) *Left*: In the post-ictal window, global connectivity strength ($conn_{post}$) was elevated in $DN_{sz\text{-}persist}$ seizures compared to the other three seizure types. *Right*: The connectivity ratio ($conn_{ratio}$) revealed a 47.1 ± 34.8% increase (mean ± SD) in global connectivity strength following $DN_{sz\text{-}persist}$ seizures. B) *Left*: Relative post-ictal delta power (Δ_{post}) was highest among $DN_{sz\text{-}persist}$ compared to the other seizure types. *Right*: $DN_{sz\text{-}persist}$ seizures exhibited the largest Δ_{ratio} among seizure types. C) A strong, significant linear Pearson correlation (r) between delta power ratio (Δ_{ratio}) and connectivity ratio ($conn_{ratio}$) was observed for $DN_{sz\text{-}free}$ (r = 0.878, $p < 0.001$), $FN_{sz\text{-}free}$ (r =

0.878, $p < 0.001$), and $FN_{sz\text{-}persist}$ (r = 0.882, $p < 0.001$) seizures. The correlation between these measures was not significant for $DN_{sz\text{-}persist}$ seizures (r = 0.210, $p = 0.47$).

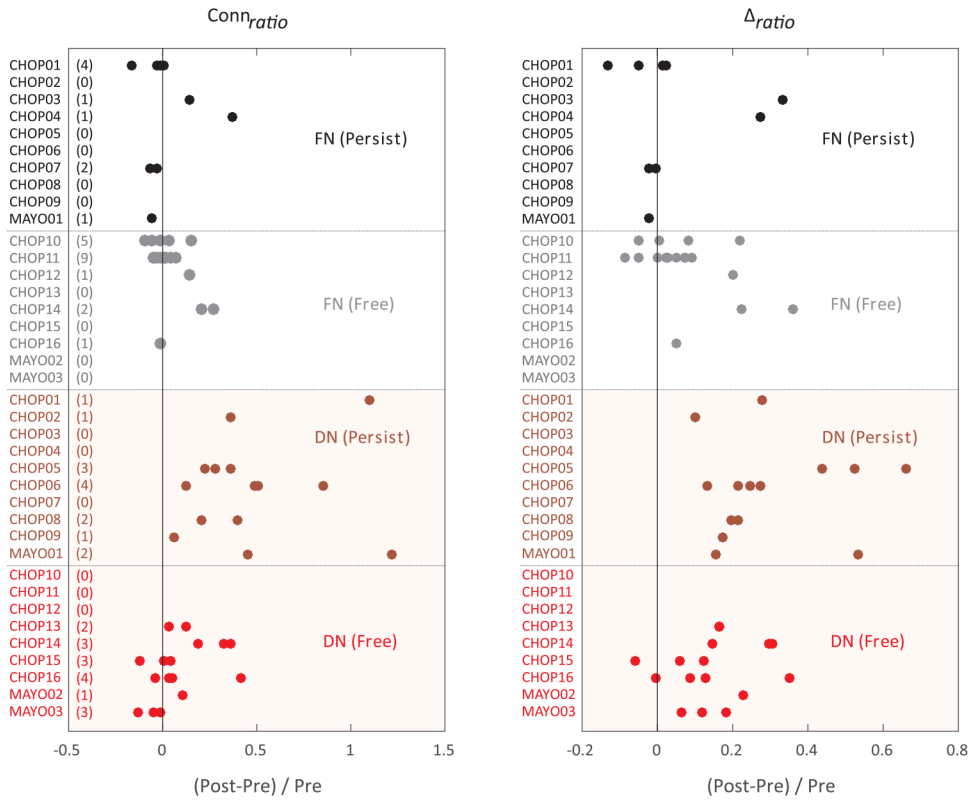

Fig. 4.

Peri-ictal results for individual seizures. Seizure-wise results from the proximal time window (± 3 min) are shown for the connectivity ratio ($conn_{ratio}$) and delta power ratio (Δ_{ratio}). Patients are grouped by Seizure-Free and Seizure-Persist surgical outcomes. The number of seizures contributed by each patient to the distributed-network (DN) and focal-network (FN) seizure groups are shown in parentheses.

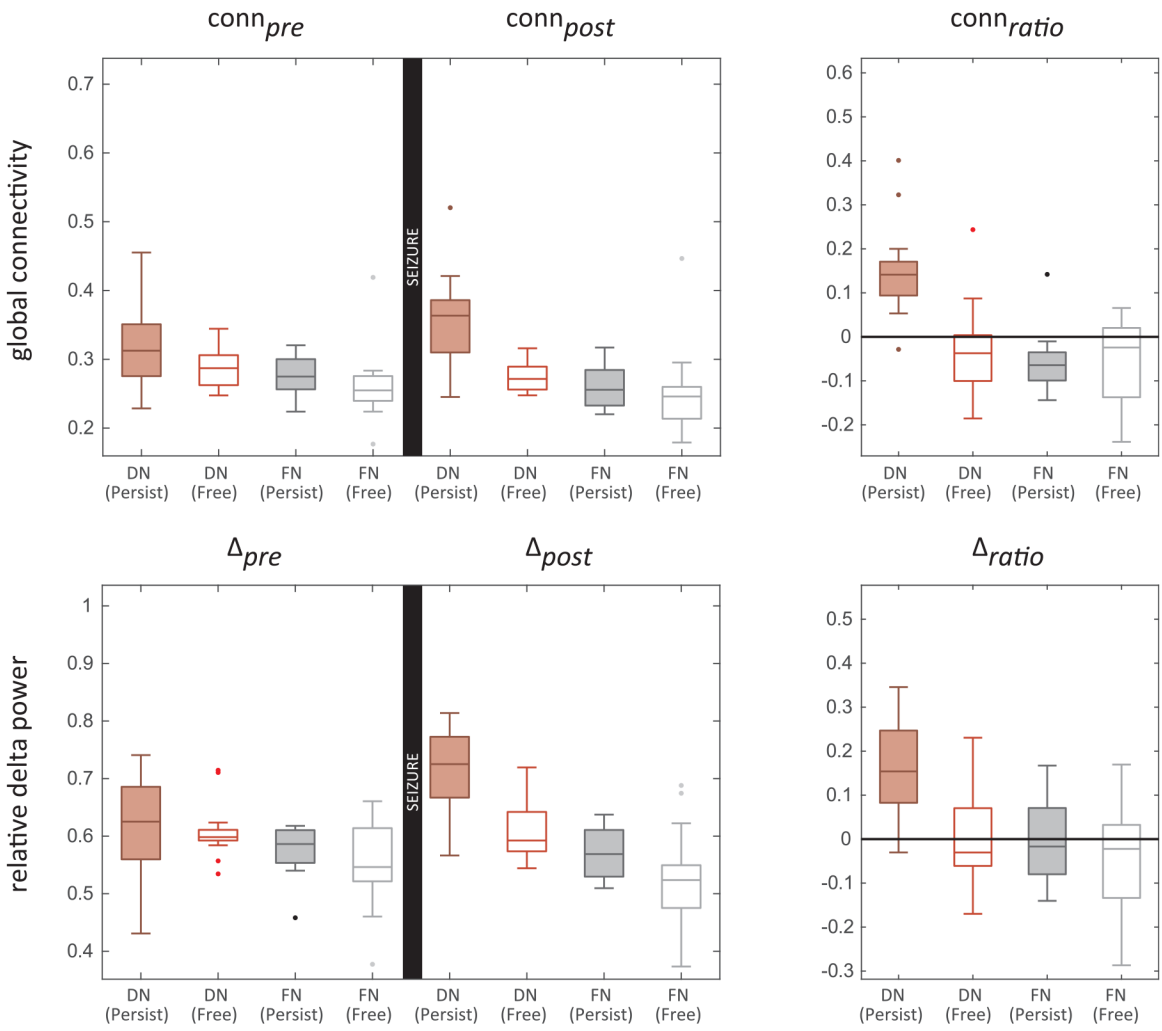

Fig. 5.

Electrographic findings are sustained beyond the immediate peri-ictal window. In addition to analyzing immediate peri-ictal intervals, segments occurring 27–30 min from seizure offset were examined. A) *Left*: In the distal time window, conn$_{post}$ was elevated in DN$_{sz\text{-}persist}$ seizures. *Right*: The connectivity ratio (conn$_{ratio}$) revealed a sustained post-ictal increase in global connectivity for DN$_{sz\text{-}persist}$ seizures. B) *Left*: Post-ictal relative delta power (Δ_{post}) was highest among DS$_{sz\text{-}persist}$ seizures. *Right*: The Δ_{ratio} was greatest among DN$_{sz\text{-}persist}$ seizures.

Table 1

Patient characteristics.

Patient (n = 19)	Age (years)	Gender	Surgical outcome	Pathology description	Implant location	Active electrodes	Electrodes in SOZ (%)	Seizures (FN, n)	Seizures (DN, n)
CHOPOl	18	M	ENGEL-3	Dysplasia 2A	LF	100	4.0	4	1
CHOP02	7	M	ENGEL-4	Dysplasia 2A	RF	99	41.4	0	1
CHOP03	16	F	ENGEL-4	Dysplasia 2A	RF	94	11.7	1	0
CHOP04	10	M	ENGEL-3	Dysplasia 2A	LF	108	29.6	1	0
CHOP05	11	M	ENGEL-3	Dysplasia 2A	LF	124	21.0	0	3
CHOPO6	15	F	ENGEL-3	Dysplasia 2A	RF	64	25.0	0	4
CHOP07	7	M	ENGEL-4	Dysplasia 1A	RT	110	59.1	2	0
CHOP08	8	M	ENGEL-4	Microdysgenesis	RF	98	100.0	0	2
CHOP09	6	F	ENGEL-4	Dysplasia 2A	RF	104	49.0	0	1
MAYO01	10	M	ILAE-4	N/A	RF	56	16.1	1	2
CHOP10	20	F	ENGEL-1	Dysplasia 2A	LT, LF	99	22.2	5	0
CHOP11	11	F	ENGEL-1	CVA Old and New	RF	116	15.5	9	0
CHOP12	12	M	ENGEL-1	Dysplasia 2A	L-Hemi	108	26.9	1	0
CHOP13	16	M	ENGEL-1	Dysplasia 2A	RF	116	9.5	0	2
CHOP14	3	F	ENGEL-1	Ganglioglioma	RT	74	46.0	2	3
CHOP15	8	M	ENGEL-1	Dysplasia 2B	LT	107	27.1	0	3
CHOP16	14	M	ENGEL-1	Dysplasia 2B	RF	84	28.6	1	4
MAYO02	16	M	ILAE-1	N/A	LO	79	7.6	0	1
MAYO03	9	M	ILAE-1	N/A	LF	112	3.6	0	3

Nineteen pediatric patients were studied (13 male, mean age = 11.4 years). Taylor-type focal cortical dysplasia (FCD) was the most common pathological finding. The modified Engel (CHOP) and ILAE outcome (MAYO) scales were used to assess surgical outcome. Patients with Engel (ILAE) score = 1 were designated Sz-Free (n = 9). In total, 57 seizures were examined (distributed-network, DN = 30; focal-network, FN = 27).