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RESEARCH ARTICLE

Interaction of interictal epileptiform activity with sleep spindles is associated with cognitive deficits and adverse surgical outcome in pediatric focal epilepsy

Han Yu[1] | Woojoong Kim[2] | David K. Park[3] | Ji Hoon Phi[4] | Byung Chan Lim[2] | Jong-Hee Chae[2] | Seung-Ki Kim[4] | Ki Joong Kim[2] | Frank A. Provenzano[5] | Dion Khodagholy[1] | Jennifer N. Gelinas[5,6]

[1]Department of Electrical Engineering, Columbia University, New York, New York, USA

[2]Division of Pediatric Neurology, Department of Pediatrics, Pediatric Clinical Neuroscience Center, Seoul National University Children's Hospital, Seoul, South Korea

[3]Department of Biomedical Engineering, Columbia University, New York, New York, USA

[4]Division of Pediatric Neurosurgery, Department of Neurosurgery, Pediatric Clinical Neuroscience Center, Seoul National University Children's Hospital, Seoul, South Korea

[5]Department of Neurology, Columbia University, New York, New York, USA

[6]Institute for Genomic Medicine, Columbia University Medical Center, New York, New York, USA

Correspondence
Jennifer N. Gelinas, Institute for Genomic Medicine, Columbia University Medical Center, New York, NY 10032, USA.
Email: jng2146@cumc.columbia.edu

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Abstract

Objective: Temporal coordination between oscillations enables intercortical communication and is implicated in cognition. Focal epileptic activity can affect distributed neural networks and interfere with these interactions. Refractory pediatric epilepsies are often accompanied by substantial cognitive comorbidity, but mechanisms and predictors remain mostly unknown. Here, we investigate oscillatory coupling across large-scale networks in the developing brain.

Methods: We analyzed large-scale intracranial electroencephalographic recordings in children with medically refractory epilepsy undergoing presurgical workup ($n = 25$, aged 3–21 years). Interictal epileptiform discharges (IEDs), pathologic high-frequency oscillations (HFOs), and sleep spindles were detected. Spatiotemporal metrics of oscillatory coupling were determined and correlated with age, cognitive function, and postsurgical outcome.

Results: Children with epilepsy demonstrated significant temporal coupling of both IEDs and HFOs to sleep spindles in discrete brain regions. HFOs were associated with stronger coupling patterns than IEDs. These interactions involved tissue beyond the clinically identified epileptogenic zone and were ubiquitous across cortical regions. Increased spatial extent of coupling was most prominent in older children. Poor neurocognitive function was significantly correlated with high IED–spindle coupling strength and spatial extent; children with strong pathologic interactions additionally had decreased likelihood of postoperative seizure freedom.

Significance: Our findings identify pathologic large-scale oscillatory coupling patterns in the immature brain. These results suggest that such intercortical interactions could predict risk for adverse neurocognitive and surgical outcomes, with the potential to serve as novel therapeutic targets to restore physiologic development.

Han Yu and Woojoong Kim contributed equally to this work.

KEYWORDS

high-frequency oscillations, interictal discharges, oscillatory coupling, sleep

1 | INTRODUCTION

Functional and structural properties of neural networks are dynamic across the lifespan, but childhood is a critical epoch for brain maturation.[1] Effective connectivity between brain structures implicated in cognitive performance increases over years after birth, and functional networks become segregated and adaptively coactivated to facilitate flexible task completion well into adolescence.[2] The pediatric brain also demonstrates enhanced activity-dependent plasticity, which can predispose to pathologic adaptations.[3,4] Refractory pediatric epilepsy is often associated with frequent expression of epileptiform patterns, but how this activity affects developing neural networks is underexplored.

Interictal epileptiform activity has been linked to specific neuropsychological deficits and regression of developmental skills in children.[5] Understanding mechanisms and predictors of pediatric epilepsy-related cognitive dysfunction is of particular relevance given the greater impact of childhood onset compared to adult onset epilepsy on cognitive outcomes.[6] This epileptiform activity takes the form of interictal epileptiform discharges (IEDs; including sharp waves and spikes) and interictal high-frequency oscillations (HFOs), both of which facilitate identification of the epileptic network.[7,8] HFOs can be detected from scalp electroencephalogram (EEG) in children, permitting identification of these oscillations in a variety of pediatric epilepsies, which commonly have a neocortical localization.[9,10] The presence of HFOs has been linked to a more severe clinical epilepsy course,[11] may track with treatment response,[9] and is associated with increased neural spiking recruitment compared to IEDs.[12]

Non-rapid eye movement (NREM) sleep facilitates the coordination of physiologic activity between brain regions for long-term memory processes.[13–15] Specifically, the precise temporal coupling between physiologic ripple oscillations in the hippocampus and cortex is implicated in learning,[16,17] and modulation of the temporal association between hippocampal ripples and cortical spindles can enhance or impair memory depending on whether the coupling is increased or decreased, respectively.[18,19] This co-occurrence of oscillations is postulated to synchronize epochs of synaptic receptivity, effectively enhancing communication between brain regions.[20] Furthermore, artificially generated spindles only enhance memory when induced in appropriate phase-locking with spontaneously occurring slow oscillations.[21] In children, spindles are linked to cognitive performance in those with and without epilepsy.[22,23] The occurrence of interictal epileptiform activity is influenced by the cortical slow oscillation, but interictal epileptiform activity additionally disrupts ongoing network patterns.[24–26] IEDs have been demonstrated to reset the phase of the slow oscillation and strongly couple with spindles in adult patients with focal epilepsy and in a rodent model of temporal lobe epilepsy.[27,28] They have also been associated with a focal deficit of spindle generation in childhood epilepsy with centrotemporal spikes (CECTS).[29] Thus, the introduction of interactions between interictal epileptiform activity and NREM sleep oscillations could interfere with the spatiotemporally precise coupling relationships required for information processing across neural networks.[28]

We hypothesized that temporal coupling interactions between different types of interictal epileptiform activity and spindles could occur in the immature brain and have implications for neurodevelopment. To investigate, we analyzed intracranial EEG (iEEG) recordings from children with refractory focal epilepsy who required multiregional electrophysiological monitoring as part of the workup for resective epilepsy surgery. We found that spindles were coupled to both IEDs and HFOs across the pediatric age range. Coupling was most often mediated through medium- to long-range intercortical connections, although local coupling also occurred. Furthermore, the potency of interactions between interictal epileptiform activity and spindles was negatively correlated with cognitive function and surgical outcome. These interactions could contribute

Key Points

- Children with refractory epilepsy often have cognitive impairment, but neural mechanisms that contribute to this symptom remain unclear
- This study determined that interictal epileptic activity strongly couples with physiologic sleep oscillations in the immature brain
- As the strength and extent of this pathologic interaction increases, there is a higher likelihood of cognitive dysfunction in children
- Changes in network connectivity patterns during critical epochs of neurodevelopment could contribute to epilepsy progression and risk of worsening cognitive dysfunction

to the burden of cognitive comorbidity associated with refractory pediatric epilepsy and may enhance ability to predict children at risk for poor neurodevelopmental and surgical outcomes.

2 | MATERIALS AND METHODS

2.1 | Subjects

We analyzed iEEG recordings from children with focal epilepsy who underwent clinical subdural electrode placement as part of the workup for epilepsy surgery between 2012 and 2020. Gathering and analysis of these data were approved by the institutional review board at Seoul National University Children's Hospital and Columbia University Medical Center. All data collection occurred at Seoul National University Children's Hospital. Each patient had a configuration of electrodes implanted based on clinical need, including subdural grids and strips, as well as depth electrodes.

Children with focal epilepsy were eligible if their presurgical workup included (1) high-quality continuous iEEG recordings of at least 400-Hz sampling rate of at least 48-h duration and including sleep, (2) placement of at least one 8×4 subdural grid (1-cm electrode spacing, center to center), and (3) availability of presurgical brain magnetic resonance imaging (MRI) and post-electrode implantation brain computed tomography (CT). Study size was determined by number of eligible patients available during the study epoch. Patients with a history of previous intracranial surgery, age older than 21 years, and suboptimal quality studies were excluded. Examples of suboptimal study quality included low sampling rate in iEEG recording and low resolution of brain CT. In addition, patients with highly disorganized backgrounds and/or frequent epochs of activity on the interictal–ictal continuum that precluded reliable identification of physiologic sleep transients were excluded. For seizure analysis, patients were included if they had clearly identified onset and propagation electrodes delineated in clinical electrophysiological reports. Patients were excluded from intelligence quotient (IQ) analysis if there was lack of verified accurate IQ score.

2.2 | Clinical information

Patient medical records were retrospectively analyzed. Collected information included patient's age at seizure onset, age at epilepsy surgery, brain MRI reports, and clinical iEEG reports. All patients were treated with antiseizure medications (1–6 medications) at the time of iEEG study. Clinical iEEG data were acquired as part of the routine workup for epilepsy surgery. Data were clinically interpreted using a combination of referential montage (referenced to epidural electrodes) and bipolar montage (based on pairs of neighboring electrodes). Each report detailed the date, time, semiology, onset, and propagation of seizures, as well as electrode numbers for localization of interictal activity. Epochs of iEEG data corresponding to seizures were clinically identified, and the clinical reports detailed the progression of electrode recruitment into the ictal pattern. Based on these reports, electrodes involved in ictal activity were classified into five zones: seizure onset (initial change from baseline), initial propagation (recruitment within 1 s), middle propagation zone (recruitment within 5 s), late propagation zone (recruitment within 30 s), and unrecruited zone. For a subset of patients, seizure onset and propagation could not be fully delineated, and these patients were excluded from analyses focusing on ictal features. Neuropsychological testing was performed as a standardized presurgical baseline evaluation. The Korean Educational Development Institute–Wechsler Intelligence Scale for Children test, which is a validated Korean version of the Wechsler Intelligence Scale for Children, was used for neurocognitive function evaluation and generated the IQ values. Wechsler intelligence tests have been demonstrated to be sensitive for assessment of cognitive function in children with high seizure burden, and appropriate versions were used based on individual patient age.

One patient did not undergo epilepsy surgery. Seizure outcomes were evaluated 2 years postoperatively using a combination of reported seizure frequency and a prolonged EEG study; 94% of patients classified as seizure-free (Engel class IA) based on patient/family report had minimal to no epileptiform activity detected on EEG, and 88% had been weaned from antiseizure medications by this time.

2.3 | iEEG data preprocessing and detections

Intracranial electrodes were localized using coregistration of MRI brain with postsurgical CT scan and projection into MNI305 space. Desikan–Killiany brain parcellation was used to attribute individual electrodes to brain regions. Epochs of NREM sleep were identified by reviewing synchronized video files in concert with increased delta/gamma frequency ratio in the iEEG spectrogram. Referential data were imported into MATLAB and resampled to 1250 Hz for compatibility with previously validated analytical toolboxes. Data within 12 h of clinically identified seizures were excluded from interictal analysis.

Detection algorithms employed to identify IEDs, HFOs, and spindles have all been previously utilized and

validated across rodent and human datasets.[27,28] For each patient, we calculated the occurrence rate and amplitude of IEDs and HFOs on each channel. These maps were manually inspected for accuracy. Channels were ranked according to IED and/or HFO amplitude, and separately ranked according to IED and/or HFO occurrence rate. Those with the highest combined ranking were selected as potential IED/HFO foci. Multiple foci were only identified in an individual patient if cross-correlation of detected IEDs/HFOs identified anatomically distinct patterns of involved channels, typically occupying different brain lobes. These foci were classified as either IED or HFO foci depending on the dominant activity pattern present. For additional details, please see Methods in Appendix S1.

2.4 | Oscillatory coupling measures

Correlation between IEDs/HFOs and spindles was calculated by generating cross-correlograms (CCGs), with statistical significance of individual coupling interactions determined using a modified convolution method to generate 95% confidence intervals (CIs). Coupling strength was quantified by a ratio of modulation derived from the CCG. Spatial extent of coupling strength was calculated by examining the change of coupling strength relative to interelectrode distance between coupled pairs. For details, please see Methods in Appendix S1.

2.5 | Statistical analysis

Significance of the regression model was calculated using an *F*-test, which tests whether the model fits significantly better than a degenerate model consisting of only a constant term. Differences between two probability distributions were compared using two-sample Kolmogorov–Smirnov (K-S) tests. Two-group data were analyzed, and estimation graphs were generated using a Data Analysis with Bootstrapped Estimation approach. Skewness and kurtosis were calculated from population distributions using the MATLAB toolbox. Correlations with clinical variables were calculated using Spearman correlation to minimize any effects of outliers. Significance level was $p < .05$.

3 | RESULTS

3.1 | Demographics of pediatric patients

We investigated the spatial and temporal interaction between IEDs, HFOs, and spindles in the developing brain using iEEG data. A total of 81 children underwent iEEG in Seoul National University Children's Hospital as part of the presurgical workup for medically refractory epilepsy. Twenty-two patients were excluded because they did not meet inclusion criteria. Additional patients were excluded during imaging and EEG analysis, resulting in a total of 25 patients available for analysis (Figure S1A). Median age at seizure onset was 8 years (range = 1–18 years), with a median age at iEEG study of 14 years (range = 3–21 years), leading to a variable duration of epilepsy prior to surgical workup (Figure S1B). All but one patient underwent subsequent surgical resection, but five additional patients had resection margin limited due to proximity to eloquent areas. Among patients who had surgical resection ($n = 24$), 58% ($n = 14$) remained seizure-free after 2 years. Additional patient characteristics are summarized in Table S1.

3.2 | IEDs and HFOs are correlated with sleep spindles in pediatric focal epilepsy

For each patient, we detected interictal activity occurring during NREM sleep. The majority of patients exhibited waveforms consistent with IEDs ($n = 24$), but 11 of these also manifested HFOs and one patient had HFOs in the absence of detectable IEDs (Figure S1C). We identified individual foci of IED and putative pathologic HFO activity within each patient using a combination of clinical determination with amplitude and propagation measures. This approach resulted in 1–3 foci per patient, with each focus occupying a different anatomical lobe. In animal models and adult patients with epilepsy, a proportion of IEDs have been found to correlate with subsequent expression of a spindle oscillation.[27,28] We found that both IEDs and HFOs were significantly correlated with spindle activity across a subset of electrodes in children with epilepsy (Figure 1A–F). All patients exhibited robust coupling of IEDs or HFOs to spindles. These interactions were spatially localized, with a proportion of electrodes that did not display significant coupling (Figure 1C,F). Although both IEDs and HFOs displayed coupling with spindles, HFOs were associated with higher overall interaction strength and an increased proportion of events capable of strongly interacting with spindles as quantified by the right-shifted cumulative distribution of HFO versus IED coupling strength (Figure 1G; IED skewness = 3.5019, kurtosis = 3.09; HFO skewness = .39, kurtosis = 2.61; two-sample K-S test: $p < .001$). These results indicate that different types of interictal activity converge in their ability to couple with spindles in the immature brain, but that HFOs have enhanced potency. We did not find significant statistical correlations between the strength of IED/HFO–spindle coupling and patient age at iEEG study, epilepsy onset age, or duration of epilepsy across the entire range of our population (Figure 1H; IED/HFO coupling

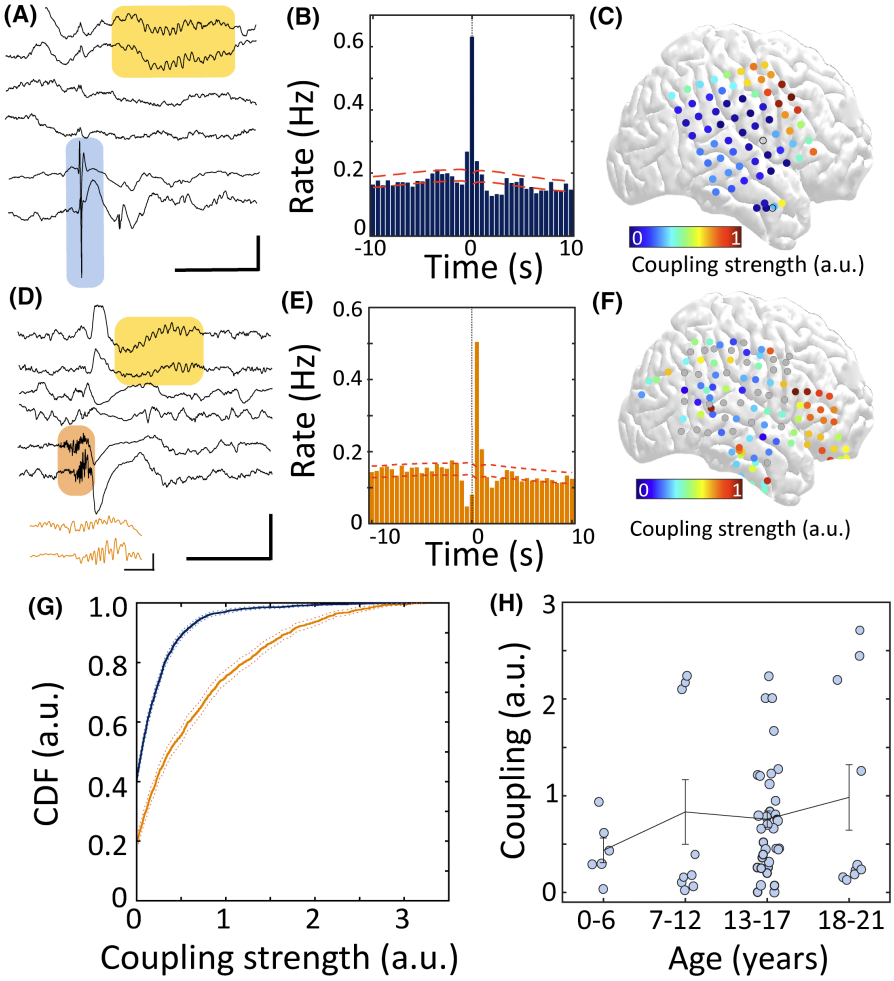

FIGURE 1 Interictal epileptiform discharges (IEDs) and high-frequency oscillations (HFOs) induce sleep spindles in pediatric focal epilepsy. (A) Sample raw traces of detected IEDs (shaded blue box) and coupled cortical spindles (shaded yellow box). Scale bar = 1 s, 1 mV. (B) Sample cross-correlogram demonstrating significant IED–spindle coupling. IED occurrence time is used as reference (time = 0 s, vertical dashed line; dashed red lines represent 95% confidence interval [CI]). (C) Sample spatial distribution of IED–spindle coupling strength projected onto the lateral cortical surface. Color represents strength of significant IED–spindle coupling. Electrodes in white represent absence of significant coupling. (D) Sample raw traces of detected HFOs (shaded orange box) and coupled cortical spindles (shaded yellow box). Scale bar = 1 s, 1 mV. (E) Sample cross-correlogram demonstrating significant HFO–spindle coupling. HFO occurrence time is used as reference (time = 0 s, vertical dashed line; dashed red lines represent 95% CI). (F) Sample spatial distribution of HFO–spindle coupling strength projected onto the lateral cortical surface. Color represents strength of significant HFO–spindle coupling. Electrodes in gray were of insufficient quality for analysis. (G) Cumulative distribution of IED–spindle (blue) and HFO–spindle (orange) coupling strength across all channels (IED: 23 patients, 42 foci, 2516 channels; HFO: 12 patients, 21 foci, 1414 channels). (H) IED/HFO–spindle coupling strength separated by patient age at time of intracranial electroencephalographic study; all IED/HFO foci from each patient are presented. CDF, cumulative distribution function.

strength and epilepsy duration: Spearman $\rho = -.012$, $p = .93$; IED/HFO coupling strength and age at epilepsy onset: Spearman $\rho = .14$, $p = .29$), indicating that other patient- and epilepsy-related variables are likely to contribute.

3.3 | Interictal coupling patterns span short- to long-range anatomic connectivity

To identify the anatomical distribution of IED/HFO–spindle coupling, we first localized each IED/HFO focus and determined which were significantly coupled to spindles. IEDs and HFOs were observed across cortical regions, but in contrast to most adult cohorts, there was limited clinical electrode placement in limbic structures.[30,31] Interictal foci located in all cortical regions were capable of significant spindle coupling, with a lateral temporal and parietal predominance for IEDs and HFOs, respectively (Figure 2A,B, left). Similarly, we found that electrodes exhibiting spindle coupling were broadly distributed throughout cortex (Figure 2A,B, right). Spindles coupled to IEDs and

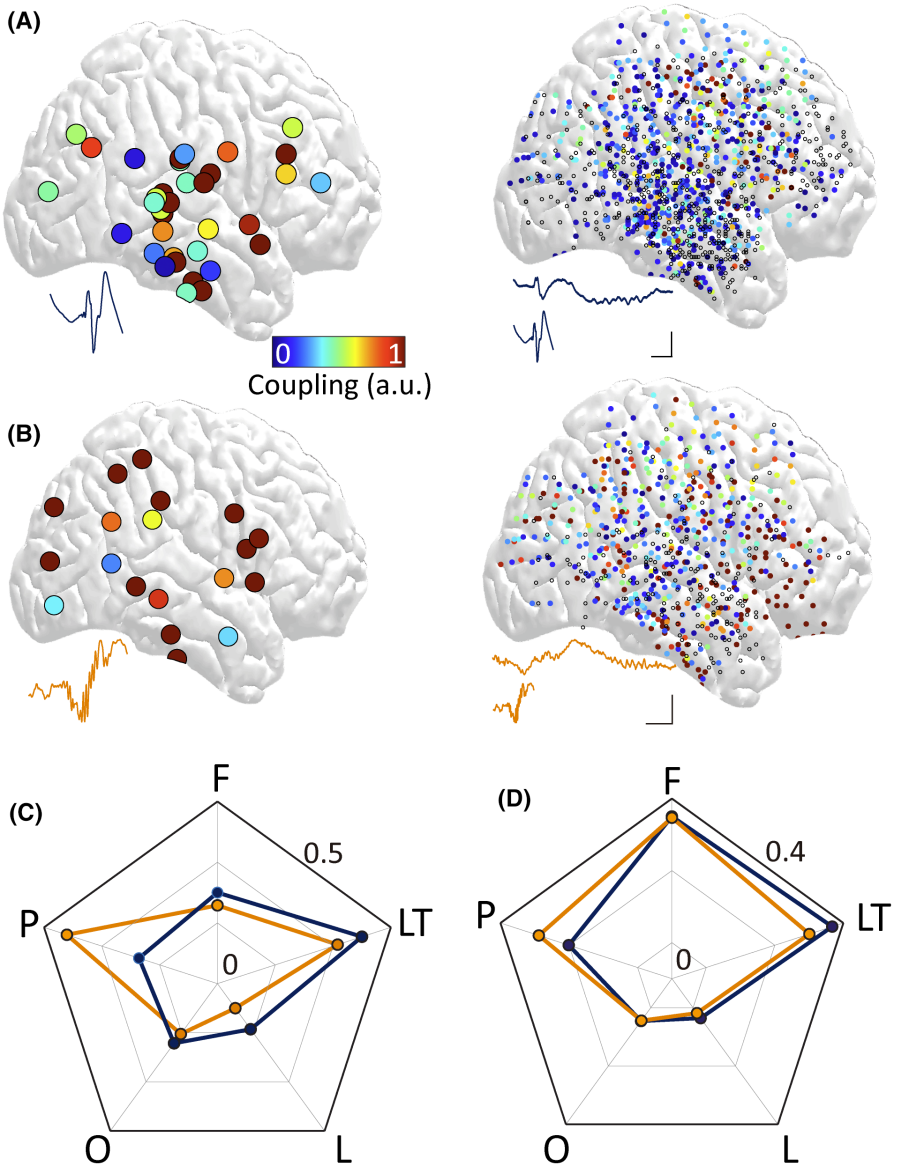

FIGURE 2 Interictal epileptiform discharges (IEDs) and high-frequency oscillations (HFOs) engage in spindle coupling via predominantly neocortical connections. (A) Anatomical location of electrodes expressing IEDs that couple to spindles across all patients (left) and anatomical location of electrodes expressing spindles that are coupled to IEDs across all patients (right) projected onto lateral cortical surface (left hemisphere view; right hemisphere locations converted to left for display purposes). Scale bars = 500 ms, 1 mV; normalized coupling values used. (B) Anatomical location of electrodes expressing HFOs that couple to spindles across all patients (left) and anatomical location of electrodes expressing spindles that are coupled to HFOs across all patients (right) projected onto lateral cortical surface (left hemisphere view; right hemisphere locations converted to left for display purposes). Scale bars = 500 ms, 1 mV; color bar as in panel A. (C) Distribution of the proportion of electrodes expressing IEDs (blue) and HFOs (orange) coupled to spindles across all patients divided by anatomical lobe. (D) Distribution of the proportion of electrodes expressing spindles coupled to IEDs (blue) and HFOs (orange) across all patients divided by anatomical lobe. F, frontal; L, limbic; LT, lateral temporal; O, occipital; P, parietal.

HFOs were common in frontal, lateral temporal, and parietal regions but rare in limbic structures, which could at least in part reflect lack of clinical electrodes placed in this region. Although the anatomical localization of IEDs and HFOs was different across patients, anatomical distributions of spindle coupling patterns were similar (Figure 2C,D). In patients with multiple IED or HFO foci, the localization of coupled spindles for each focus was typically overlapping but distinct. Therefore, pathologic coupling interactions between IEDs/HFOs and spindles are not restricted to specific brain regions, and can develop ubiquitously across neocortex.

We next determined the anatomical characteristics of IED/HFO-generating and spindle-coupled electrode pairs. Approximately 35% of interactions initiated by IEDs or HFOs were located outside of the lobe

containing the interictal focus. However, up to 15% of IED/HFO–spindle pairs were located within the same parcellated region (Figure 3A). The distance between interictal focus and coupled spindle electrode displayed a skewed distribution, with a peak at approximately 4 cm (IED–spindle = 42.88 ± 1.59 mm; HFO–spindle = 40.24 ± 1.04 mm), and a tail extending to longer distances (K-S two sample test: $p = .018$;IED: $n = 232$ strongly coupled pairs, skewness = .35, kurtosis = 2.30; HFO: $n = 398$ strongly coupled pairs, skewness = .46, kurtosis = 2.91). Distributions of coupling distances were significantly different between IEDs and HFOs, with HFOs exhibiting a higher proportion of longer distance interactions (Figure 3A). Coupled pairs were identified between all lobes for both IEDs and HFOs (Figure 3B,C, Table S2). Thus, a combination of local and long-range connections prominently involving neocortical structures mediate IED/HFO coupling interactions in pediatric patients, in contrast to adult patients, where a higher propensity for long-range patterns and involvement of limbic structures is observed.[27]

3.4 | Brain regions that demonstrate spindles coupled to IEDs and HFOs extend beyond the ictal network

To investigate the relationship between ictal activity and interictal coupling patterns, we analyzed electrodes exhibiting ictal EEG signatures. Ictal onsets and progressive recruitment into the ictal pattern were characterized for patients with predominance of IEDs and HFOs (Figure 4A,B, Figure S1C). On average, 72.36 ± 5.66% of the electrodes designated as the clinical seizure onset + initial propagation zone also expressed interictal patterns (IED/HFO), whereas 45.32 ± 7.98% of these electrodes expressed spindles that were coupled to IEDs/HFOs (Figure 4C; unpaired mean difference across patients = −.27 [95% CI = −.445 to −.0827], p-value of the two-sided permutation by t-test = .0086). No patients demonstrated significant (above chance) overlap between these groups of electrodes ($p > .05$; permutation test with null distribution generated by shuffling; Figure 4D). The average distance between the centroid of the seizure onset zone and spindles coupled to interictal activity was approximately 3.5 cm (Figure 4E; IED: 3.63 ± .09 cm, HFO: 3.49 ± .13 cm). The distance distribution for HFO-coupled spindle regions relative to seizure onset zone was left-shifted relative to that for IEDs, but both distributions exhibited heavy tails toward longer distances (IED: skewness = .39, kurtosis = 2.65, 37.78 ± 1.11 mm; HFO: skewness = .37, kurtosis = 2.33, 33.09 ± 2.21 mm; K-S two-sample test: $p = .011$). These results support an interictal coupling network that can overlap with, but also extends beyond, brain regions responsible for generating and propagating ictal activity.

3.5 | Spatial extent of IED/HFO–spindle coupling is correlated with developmental age

To estimate the degree to which large-scale networks were participating in these interictal coupling patterns,

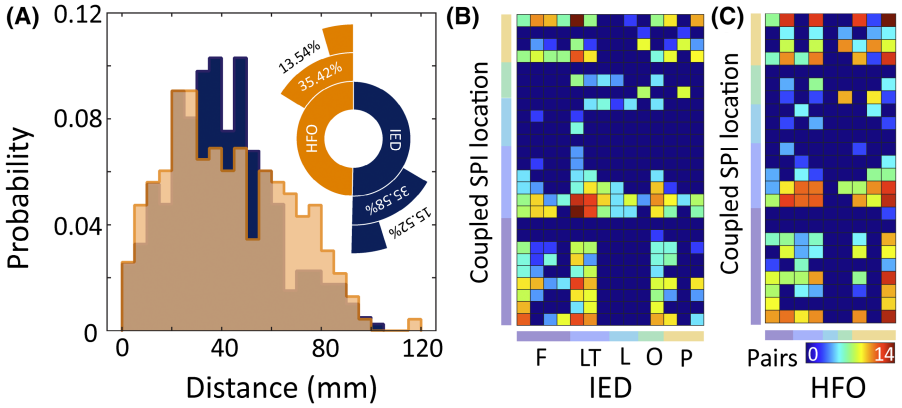

FIGURE 3 A combination of local and long-range connections mediate coupling of spindles with interictal activity. (A) Histogram of distances between pairs of electrodes that interact via interictal epileptiform discharge (IED)–spindle coupling (blue) and high-frequency oscillation (HFO)–spindle coupling. Inset shows proportion of IED–spindle (blue) and HFO–spindle (orange) pairs located within the same parcellated region (outer circle) and within the same anatomic lobe (inner circle). Percentages are inclusive (i.e. pairs within the same parcellated region are included in the pairs within the same lobe). IED: $n = 22$ patients, 1231 coupled pairs; HFO: $n = 12$ patients, 960 coupled pairs. (B) Number of IED–spindle pairs per brain region; warmer colors indicate more pairs; ordered list of individual brain regions is in Table S2. (C) Number of HFO–spindle pairs per brain region; warmer colors indicate more pairs; ordered list of individual brain regions is in Table S2. F, frontal; L, limbic; LT, lateral temporal; O, occipital; P, parietal; SPI, spindle.

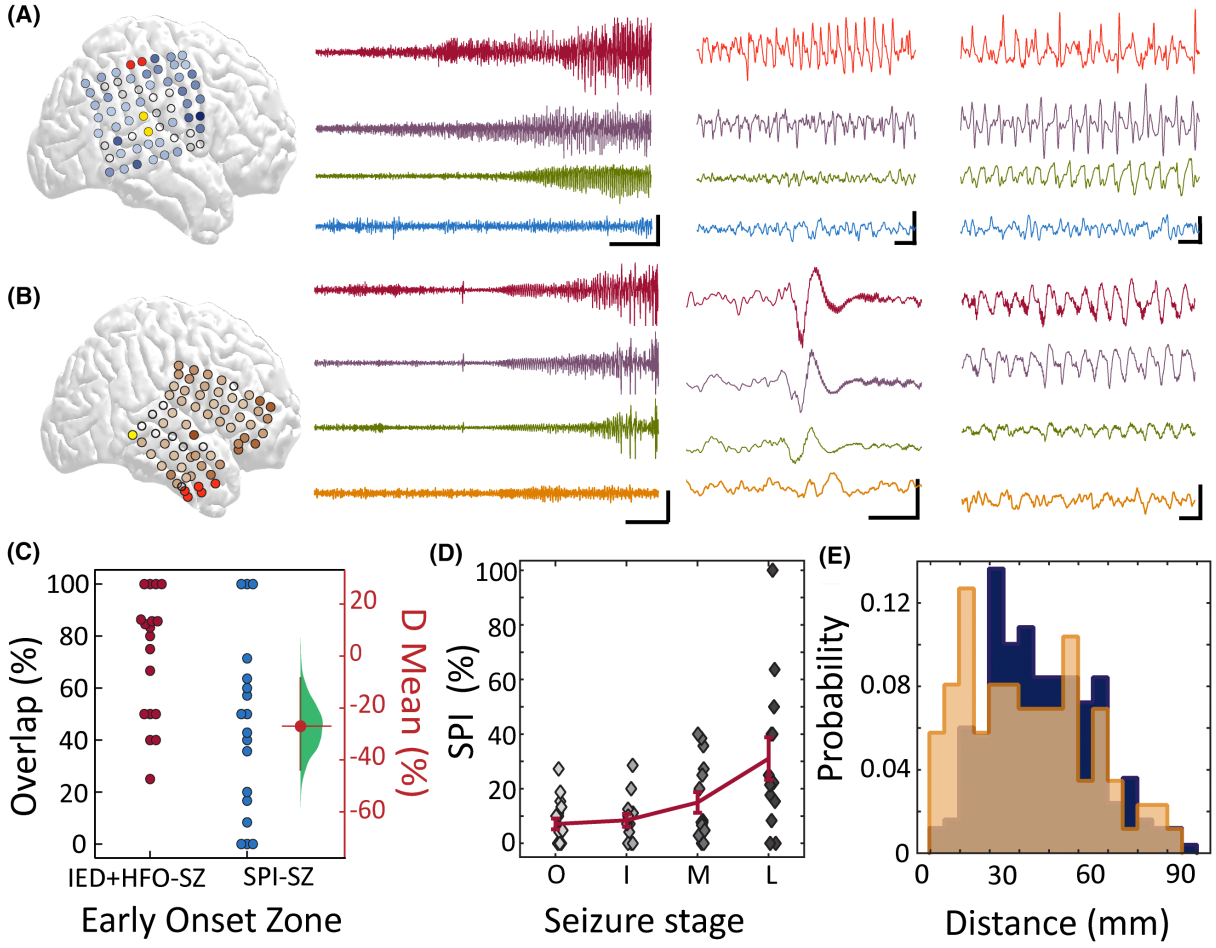

FIGURE 4 Brain regions that demonstrate spindles coupled to interictal epileptiform discharges (IEDs) and high-frequency oscillations (HFOs) extend beyond the ictal network. (A) Sample patient brain displaying localization of seizure onset zone (red), IED foci (yellow), and regions with spindles coupled to IEDs (blue). Sample raw compressed seizure onset is shown (left, scale bar = 5 s, 500 μV) with expanded view of onset pattern (middle, scale bar = 500 ms, 500 μV) and propagation pattern (right, scale bar = 500 ms, 500 μV) from electrodes in the seizure onset zone (red), middle propagation zone (purple), and late propagation zone (green). Traces from the IED–spindle coupling zone (blue) are not recruited into the initial ictal rhythm. (B) Sample patient brain displaying localization of seizure onset zone (red), HFO foci (yellow), and regions with spindles coupled to HFOs (brown). Sample raw compressed seizure onset is shown (left, scale bar = 5 s, 500 μV) with expanded view of onset pattern (middle, scale bar = 500 ms, 500 μV) and propagation pattern (right, scale bar = 500 ms, 500 μV) from electrodes in the seizure onset zone (red), middle propagation zone (purple), and late propagation zone (green). Traces from the HFO–spindle coupling zone (orange) are not recruited into the initial ictal rhythm. (C) Percentage of overlap between electrodes constituting the seizure onset + initial propagation zone and those expressing IEDs/HFOs (red) as well as those expressing IED/HFO-coupled spindles (blue). The filled curve on the right shows the distribution of the mean difference under the null hypothesis derived by permutated observed data; $n = 18$ patients. (D) Percentage of total electrodes expressing IED/HFO-coupled spindles that are recruited into successive stages of ictal activity. Diamonds are individual data points for each patient. Line plot indicates the average value for each propagation stage, and the error bars indicate the standard errors of means. I, initial propagation; L, late propagation; M, middle propagation; O, onset. (E) Histograms for distance between electrodes expressing IED-coupled (blue) and HFO-coupled (orange) spindles and centroid of seizure onset zone (IED: skewness = .39, kurtosis = 2.65, 37.78 ± 1.11 mm; HFO: skewness = .37, kurtosis = 2.33, 33.09 ± 2.21 mm. Kolmogorov–Smirnov two-sample test: $p = .011$). SZ, seizure.

we quantified the spatial extent of IED/HFO–spindle coupling. Because sampling of the brain was substantial (due to the consistent use of subdural grids), but variable across patients, we derived a measure based on the sum of interelectrode distances weighted by the normalized coupling strength of the two electrodes. This approach estimated the amount of brain surface affected by pathologic coupling and minimized the contribution of total area of electrode coverage.[32] Higher values of this spatial extent measure indicated a more extensive brain area displaying high coupling strength. We found that patients demonstrated a range of interictal coupling spatial extent, from highly localized to broad expression (Figure 5A). Given this variation in spatial extent of

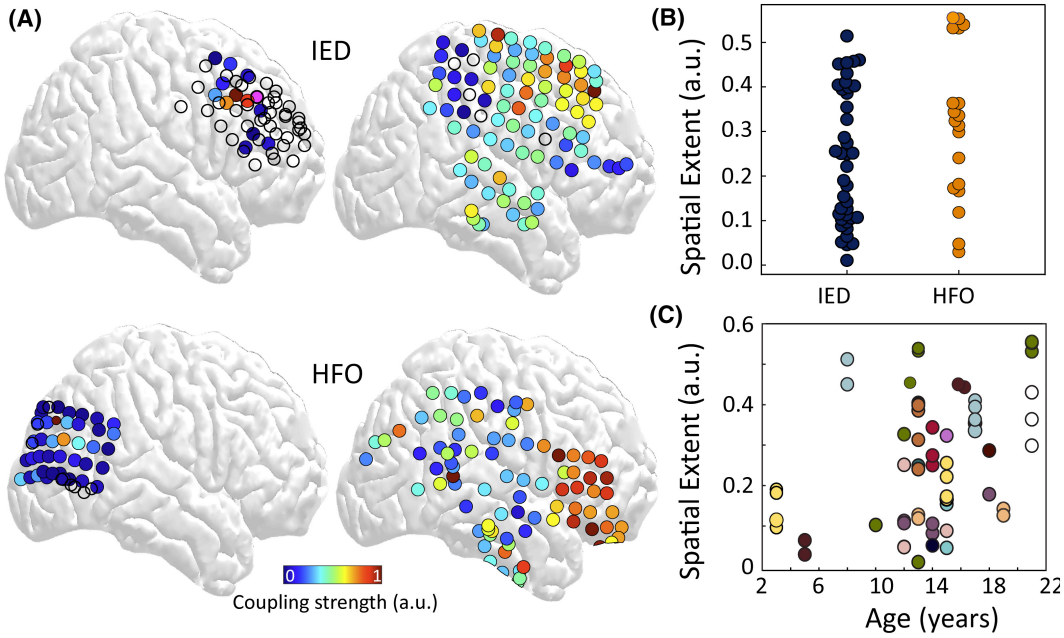

FIGURE 5 Spatial extent of interictal epileptiform discharge (IED)/high-frequency oscillation (HFO)–spindle coupling is correlated with developmental age. (A) Sample variability in spatial extent of spindle coupling for both IED and HFO foci; four sample patients are shown with different spatial extents. Warmer colors indicate larger normalized IED/HFO–spindle coupling strength. (B) Spatial extent of HFO–spindle coupling (orange) compared to IED–spindle coupling ($n = 25$ patients; blue: n =40 IED foci; orange: n =19 HFO foci). (C) Significant correlation of coupling spatial extent and age at intracranial electroencephalogram; each color represents data from one patient ($n = 25$ patients, 59 interictal foci; Spearman $\rho = .36$, two-tailed p =.0048).

pathologic coupling across our patient population, we sought to identify predictors. We found that HFOs had a trend toward generation of broader spatial extent of spindle coupling compared to IEDs (Figure 5B; unpaired t-test:$p = .057$ [95% CI = −.0024 to .16]). Furthermore, there was a positive correlation of pathologic coupling spatial extent with age (Figure 5C; $n = 25$ patients, 59 interictal foci; Spearman $\rho = .36$, two-tail p =.0048), suggesting that expression of this network property was developmentally regulated. Spatial extent did not significantly correlate with age at epilepsy onset (Spearman $\rho = .090$, $p = .50$) or disease duration (Spearman $\rho = .19$, $p = .14$).

3.6 | Increased strength and spatial extent of IED/HFO–spindle coupling are correlated with decreased cognitive and seizure outcomes

The degree of neuropsychological impairment observed in pediatric patients with refractory epilepsy is variable and challenging to predict.[33] We found prominent coupling between IEDs and HFOs in these patients that could affect brain areas extending beyond the identified epileptogenic network and hypothesized that such interactions could disrupt physiologic functions required for development of cognitive skills. We used full-scale IQ as a general indicator of cognitive ability that was available for all patients. IQ was negatively correlated with the strength of interictal coupling ($n = 22$ patients, Spearman $\rho = -.43$, $p = .047$) and measures of its spatial extent ($n = 22$ patients, Spearman $\rho = -.48$, $p = .023$; Figure 6A,B). Occurrence rate of IEDs/HFOs ($n = 22$ patients, Spearman $\rho = -.37$, $p = .094$) had a trend toward negative correlation with IQ as well. To determine the degree to which rate of interictal activity was collinear with our coupling measures, we calculated variance inflation factors. The variance inflation factors between interictal rate and coupling strength (1.19) as well as coupling spatial extent (1.04) indicated a low level of collinearity. Therefore, strong and broad IED/HFO–spindle coupling in children with epilepsy may predict risk for poor cognitive outcomes, in a manner that cannot be predicted by burden of interictal activity alone. In contrast, there was no significant correlation between IQ and several clinical variables, including epilepsy duration, age at the time of iEEG study, and age at onset of epilepsy (IQ and epilepsy duration: Spearman $\rho = -.075$, p=.74; IQ and age at iEEG study: Spearman $\rho = .025$, p=.91; IQ and age at epilepsy onset: Spearman $\rho = .021$, p=.93). For patients who underwent resective surgery, we investigated a relationship between postoperative seizure outcome and interictal coupling interactions. High IED/HFO–spindle coupling strength was associated with lower

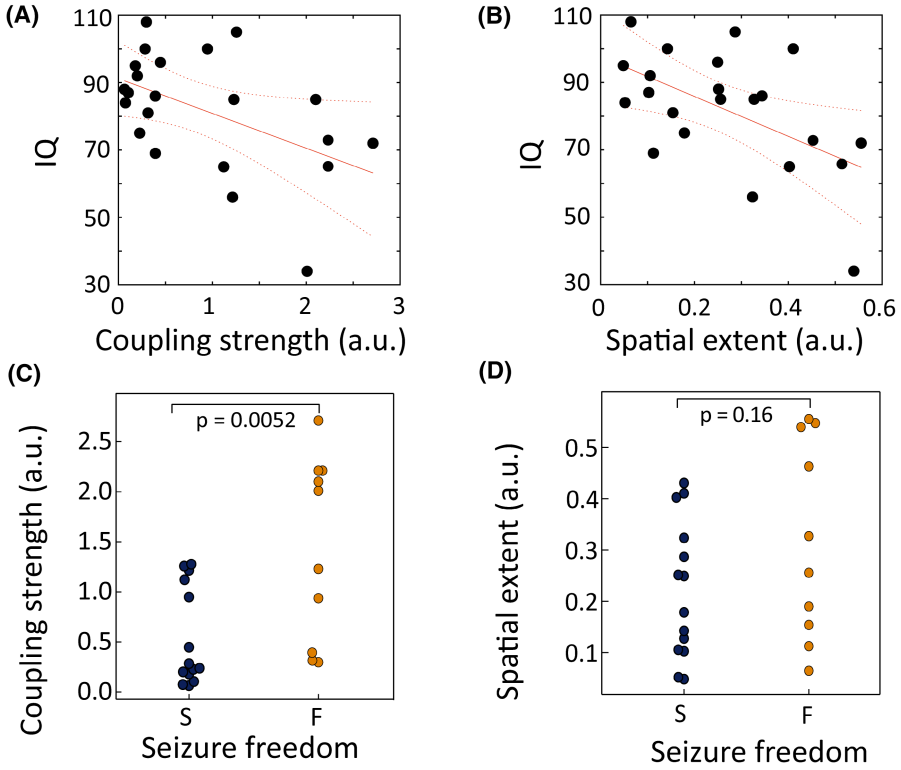

FIGURE 6 Increased strength and spatial extent of interictal epileptiform discharge (IED)/high-frequency oscillation (HFO)–spindle coupling is correlated with decreased cognitive and seizure outcomes. (A) Significant negative correlation between patient intelligence quotient (IQ) and IED/HFO–spindle coupling strength. (B) Significant negative correlation between patient IQ and spatial extent of IED/HFO–spindle coupling. (C) Relationship between IED/HFO coupling strength and likelihood of seizure freedom after resective surgery. (D) Relationship between spatial extent of IED/HFO–spindle coupling and likelihood of seizure freedom after resective surgery. F, fail: $n = 10$ patients; S, succeed: $n = 14$ patients.

likelihood of seizure freedom (<Engel class IA), with a nonsignificant trend for spatial extent (Figure 6C,D; coupling strength–seizure outcome: two-sided *t*-test $p = .0052$ [95% CI = .30–1.49]; coupling spatial extent–seizure outcome: two-sided *t*-test, $p = .16$ [95% CI = −.040 to .23]). These findings remain correlational, but suggest functional relevance of interictal coupling patterns to cognition and intractability to focal resection.

4 | DISCUSSION

We demonstrate that interictal epileptiform patterns, including IEDs and HFOs, consistently interact with sleep oscillations in pediatric patients with focal epilepsy in a developmentally regulated manner. These coupling relationships extend across intercortical networks and are most prominent outside of the seizure onset zone. The spatial extent and strength of oscillatory coupling mediated by interictal epileptic activity are negatively correlated with cognitive function and may contribute to prediction of likelihood of seizure freedom after resective surgery.

IEDs are strongly coupled with cortical spindles in mature rodents and adult patients with focal epilepsy,[27,28] but whether these types of interactions could be expressed by immature neural networks was not known. We found that IEDs and HFOs were coupled to spindles in the immature brain as early as 3 years of age, with a tendency for more spatially extensive patterns observed with increasing age at time of iEEG study. Because global connectivity also increases with brain maturation,[34,35] it is possible that pathologic interactions are similarly facilitated alongside those that are physiologic across the developmental trajectory. Similarly, regions that exhibit prominent spindle coupling are anatomically closer to the clinically defined seizure onset zone in pediatric compared to adult patients, although these regions are still typically distant from the IED/HFO focus itself. Such results could be in line with the focal deficit in spindle occurrence at the IED focus of CECTS.[29] Determining whether these differences are driven by development- or disease duration-specific factors requires further longitudinal investigation.

We found that HFOs on average induced stronger coupling compared to IEDs. This increased potency

for coupling interactions could be linked to evidence suggesting that HFOs better predict epileptogenicity and epilepsy severity.[10,36,37] In comparison to IEDs, the presence of HFOs results in higher neural spiking rate and preferential firing for a subset of neurons.[12] This increased neural activation may facilitate driving of corticothalamic connections responsible for spindle generation and result in a more robust and distributed network response. Our results further indicate that the capacity for HFOs or IEDs to couple with spindles is not anatomically restricted; coupling was initiated by each interictal activity focus regardless of its originating brain region. Pediatric cohorts commonly have a higher proportion of neocortical epilepsy, and this permitted an anatomically diverse survey of neocortical networks. Of note, our dataset had few patients with limbic epilepsy, precluding direct comparison of limbic and neocortical epileptic networks due to limited clinical sampling of limbic structures. Interictal foci located in parietal cortex were particularly well represented and were frequently involved in coupling interactions, potentially reflecting their strong functional connectivity with multiple brain regions.[38]

IEDs and HFOs are both implicated in impairment of neurocognitive function.[39,40] Consistent with these results, we show a trend toward negative correlation of interictal activity with IQ in our patient cohort. The mechanisms by which interictal activity interferes in different cognitive processes can be linked to abnormalities outside of the seizure onset zone,[41] and disturbances in expected global brain connectivity patterns are associated with neurocognitive dysfunction in patients with epilepsy.[42,43] Coupling of interictal activity with oscillatory patterns that are longer in duration and more widely distributed than the interictal activity itself could contribute to mediating such effects. We found that higher strength and spatial extent of spindle coupling patterns to interictal activity are correlated with poorer neurocognitive function in pediatric patients with focal epilepsy. Such a relationship is particularly relevant given the observed abnormalities in spindle properties in children with epilepsy and neurodevelopmental disorders.[23,44] Oscillatory coupling properties in our patient population were independent of interictal occurrence rate, suggesting that they represent independent predictors for cognitive abnormalities. Of note, we excluded patients with severe background abnormalities that precluded reliable detection of spindles. Patients with such disorganized sleep activity are more likely to have impaired cognition and could represent the extreme of disrupted global connectivity patterns. Understanding predictors for the emergence of such patterns and their relationship to pathologic coupling interactions is a critical focus for future work.

Although seizure outcomes after resective epilepsy surgery are highly multifactorial,[45] our results indicated that preoperative increased strength of IED/HFO–spindle coupling was associated with decreased likelihood of seizure freedom. Because seizure freedom rates in patients who undergo resection for extratemporal epilepsy is commonly <60%,[46] additional outcome predictors could facilitate clinical decision-making. Furthermore, increased duration of epilepsy is correlated with poorer outcomes, although with low certainty of evidence.[46,47] Changes to oscillatory coupling across large-scale networks during development could suggest a mechanism by which pediatric focal epilepsy becomes more resistant to focused resection over time.

Focal epilepsy can result in far-ranging brain dysfunction in mature neural networks.[48–51] Immature networks must undergo specific spatiotemporal alterations to permit subsequent expression of physiologic brain functions.[52,53] Addition of interictal epileptic activity to such networks increases the potential complexity and variability of resultant effects. We identify IED/HFO–spindle coupling as a robust phenomenon in pediatric focal epilepsy. This oscillatory interaction could influence network connectivity patterns during critical epochs of neurodevelopment and contribute to disease progression through risk of cognitive dysfunction and refractoriness to surgical intervention. Prospective studies will facilitate understanding of whether such patterns could serve as network biomarkers and targets for therapeutic interventions that address large-scale network dysfunction in epilepsy.

AUTHOR CONTRIBUTIONS

Woojoong Kim and Jennifer N. Gelinas conceived the project. Ji Hoon Phi, Byung Chan Lim, Jong-Hee Chae, Seung-Ki Kim, Ki Joong Kim, and Woojoong Kim performed data acquisition. Han Yu, Woojoong Kim, David K. Park, Frank A. Provenzano, and Jennifer N. Gelinas performed data analysis. Woojoong Kim, Han Yu, and Jennifer N. Gelinas wrote the manuscript with contributions from the other authors. Dion Khodagholy contributed to conceiving the project and performed data analysis.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

ORCID

David K. Park https://orcid.org/0000-0001-9725-0193
Jennifer N. Gelinas https://orcid.org/0000-0002-1164-638X

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