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Repetitive transcranial magnetic stimulation modulates brain connectivity in children with self-limited epilepsy with centrotemporal spikes

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Abstract

Objective: Self-limited epilepsy with centrotemporal spikes (SeLECTS) is a common pediatric syndrome in which interictal epileptiform discharges (IEDs) emerge from the motor cortex and children often develop language deficits. IEDs may induce these language deficits by pathologically enhancing brain connectivity. Using a sham-controlled design, we test the impact of inhibitory low-frequency repetitive transcranial magnetic stimulation (rTMS) on connectivity and IEDs in SeLECTS.

Methods: Nineteen children participated in a cross-over study comparing active vs. sham motor cortex rTMS. Single pulses of TMS combined with EEG (spTMS-EEG) were applied to the motor cortex before and after rTMS to probe connectivity. Connectivity was quantified by calculating the weighted phase lag index (wPLI) between six regions of interest: bilateral motor cortices (implicated in SeLECTS) and bilateral inferior frontal and superior temporal regions (important for language). IED frequency before and after rTMS was also quantified.

Results: Active, but not sham, rTMS decreased wPLI connectivity between multiple regions, with the greatest reductions seen in superior temporal connections in the stimulated hemisphere. IED frequency decreased after active but not sham rTMS.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2025.02.018.

Significance: Low-frequency rTMS reduces pathologic hyperconnectivity and IEDs in children with SeLECTS, making it a promising avenue for therapeutic interventions for SeLECTS and potentially other pediatric epilepsy syndromes.

Keywords

Self-limited epilepsy with centrotemporal spikes (SeLECTS); Transcranial magnetic stimulation (TMS); Transcranial magnetic stimulation with electroencephalogram (TMS-EEG); Brain connectivity; Interictal epileptiform discharges (IEDs); Benign epilepsy with centrotemporal spikes (BECTS); Rolandic epilepsy

1. Introduction

Interictal epileptiform discharges (IEDs) are brief bursts of abnormal hypersynchronous cortical activity occurring in patients with epilepsy. Children with epilepsy who experience frequent IEDs often develop cognitive difficulties, particularly language problems [1]. Epilepsy and IEDs are thought to arise due to an imbalance between excitatory and inhibitory systems in the brain [2], which contribute to aberrant hyperconnectivity between the epileptic cortex (from which IEDs originate) and distant brain regions that include key nodes in the language network [3,4]. This hyperconnectivity can be especially detrimental during childhood when inhibitory circuits critical for motor and cognitive functions are maturing [5]. Furthermore, hyperconnectivity may persist even during IED-free periods [6] and is associated with worse language performance [7]. Thus, therapies aimed at reducing hyperconnectivity have the potential to alleviate cognitive deficits in children with epilepsy.

Transcranial magnetic stimulation (TMS) combined with electroencephalogram (EEG) is a powerful tool for investigating and modulating the neurophysiological properties of the brain [8,9]. Single pulses of TMS activate specific brain regions while EEG (spTMS-EEG) captures the resultant network responses as TMS evoked potentials (TEPs). TEPs can be measured locally and globally to assess cortical excitability and connectivity, respectively [10,11]. In addition to these time domain based metrics, inter-regional connectivity can also be investigated using phase synchronization measurements that analyze the relationship of EEG signals in different regions [12,13]. When repetitive pulses of TMS (rTMS) are applied in specific patterns, they modulate brain activity for a period exceeding the stimulation train, with low-frequency stimulation (≤1Hz) generally reducing cortical excitability [14]. rTMS affects not only excitability of the stimulated cortex, but also that of functionally connected brain regions [15]. Four sham-controlled trials in adults with epilepsy [16] and two open-label studies in children [17,18] suggest that rTMS suppresses IEDs, but sham-controlled studies in pediatric epilepsy are lacking.

This study investigates the impact of 1Hz rTMS on cortical excitability, connectivity, and IED frequency in 19 children with self-limited epilepsy with centrotemporal spikes (SeLECTS). SeLECTS provides a unique model for isolating the effect of IEDs on cognition. Though children with SeLECTS have only rare seizures and are generally otherwise healthy, they have frequent IEDs originating from one or both central motor regions and develop mild to moderate language difficulties [19]. Using a crossover design, we compared the impact of active vs. sham 1Hz rTMS applied to the motor cortex. We

measured excitability and connectivity from signals evoked by spTMS-EEG applied before and after the rTMS intervention. The connectivity analyses focused on six regions of interest (ROIs): the stimulated and contralateral motor cortices (implicated in the epilepsy), as well as the bilateral inferior frontal and superior temporal regions (important for language) [20]. We investigated the impact of rTMS on three measurements: 1) TEPs measured at the stimulated motor cortex and at the other five ROIs, providing a time-domain assessment of cortical excitability and connectivity, respectively; 2) the weighted phase lag index (wPLI) between regions [12], a phase-domain connectivity measure that is robust against the confounding effects of volume conduction; and 3) IED frequency. For wPLI, connectivity in the beta frequency band was the primary outcome, because it plays a critical role in the motor system function [21] and there is a direct increase in beta connectivity surrounding IEDs in SeLECTS [6]; alpha and theta frequency band connectivity were explored in secondary analyses as they have also been reported to be affected by SeLECTS [22,23]. We hypothesized that 1Hz rTMS would reduce aberrant hyperconnectivity and IEDs in SeLECTS, offering a step toward developing novel epilepsy treatments.

2. Methods

2.1. Participants

Children between the ages of 5–18 years with a diagnosis of SeLECTS based on seizure semiology and centrotemporal IEDs were eligble [19]. We excluded children with a history of prematurity (<35 weeks), serious neurologic problems (i.e., other epilepsies, head trauma with prolonged loss of consciousness, cerebrovascular accident or neuro-inflammatory disease), or focal deficits on neurologic exam. Children were recruited from Lucile Packard Children's Hospital. This study was approved by the Stanford University Institutional Review Board and registered with clinicaltrials.gov (NCT04325282). Written consent was obtained from parents and assent from children. Antiseizure medication (ASM) use and serum level were recorded.

2.2. TMS experiment

Overview (Fig. 1A): The study consisted of two sessions separated by at least 6 days to allow for wash-out of rTMS effects. Procedures were identical, except one session used active rTMS while the other used sham rTMS. Session order was randomized. Sessions were conducted in the late morning or early afternoon, with participants comfortably seated in a semi-reclined position.

EEG Recordings: EEG recordings were acquired using a BrainVision actiCHamp Pulse amplifier with 64-channel actiCAP with slim active electrodes, sampled at 25 kHz. Impedances were kept below 10 kΩ to balance feasible set-up time for children with adequate data quality [24,25].

TMS: TMS was administered using a MagVenture MagPro X100 stimulator equipped with a Cool-B65 figure-8 coil, and guided by the Localite TMS Navigator neuro-navigation system, registered to a representative magnetic resonance image (MRI) from unbiased average age-appropriate templates [26]. Electromyography (EMG) was measured from the abductor

pollicis brevis (APB) muscle. The coil was initially positioned 45° relative to midline and adjusted to identify the motor hotspot [27] eliciting the largest EMG deflection when the hand was relaxed. Localite was used to ensure the same position was stimulated on both days. On both days, the resting motor threshold (rMT) was determined as the minimum intensity required to evoke a peak-to-peak EMG signal of at least 50 μV in at least 5 out of 10 pulses [28]. Children and people taking ASMs often have elevated rMTs [25,29–31]. Therefore, if no EMG deflection was observed at maximal stimulator output (MSO), hot-spotting was performed with the hand slightly contracted and the rMT was defined as 100 % MSO. To minimize auditory contamination, in-ear headphones played noise matched in frequency to the TMS clicks at a volume at which children reported difficulty hearing clicks but without discomfort [32]. To minimize somatosensory contamination, a foam layer on the coil surface reduced TMS-induced vibration. Alertness was confirmed and maintained throughout sessions via monitoring patient behavior and EEG.

rTMS: We targeted rTMS to the hand motor hotspot of the hemisphere that had the greatest frequency of IEDs on most recent clinical EEG. We chose this location as IEDs in SeLECTS emerge from the motor cortex and stimulation of the hand region is tolerable [29]. We administered 1000 pulses of 1Hz active or sham rTMS at 90 % rMT, because it induces inhibition for at least 15–20 min, allowing adequate time to assess change in connectivity and IED frequency [8].

spTMS: Before and after rTMS, participants underwent 200-pulse blocks of spTMS-EEG administered to the same motor target, providing enough trials to ensure adequate signal-to-noise ratio [8,25]. Stimulation intensity was 120 % rMT (or 100 % MSO if rMT exceeded 84 % MSO), with pulses jittered at random intervals of 2–3 s. The spTMS-EEG was used to quantify the impact of rTMS.

2.3. Data analyses

spTMS-EEG Data Preprocessing: The spTMS–EEG data collected before and after rTMS were preprocessed together using an EEGLAB-based [33], custom-designed pipeline [25,34]. Data were epoched from −1000 to 1500 ms around the spTMS pulse. To eliminate the spTMS pulse artifact, an interpolation procedure was applied −2 to 12 ms relative to pulse onset. Data were down-sampled to 1 kHz, baseline-corrected (−500 to −10 ms), and high-pass filtered at 1Hz. Bad channels were rejected using a Wiener noise estimation [35], and further reduced via the SOUND algorithm [36]. Line noise was attenuated by a Butterworth band-stop filter (58–62 Hz). Independent component analysis, via the ICLabel algorithm [37], identified and eliminated artifacts. The signal was then low-pass filtered below 200 Hz and re-referenced to a common average. Trials with prominent remaining artifacts were rejected through visual inspection and were confirmed by a pediatric epileptologist (FB).

Regions of Interest (ROIs): We categorized the hemispheres as either ipsilateral or contralateral to the rTMS target (Fig. 1B). We focused on six ROIs: the ipsilateral and contralateral frontal, motor, and temporal regions. We chose these regions as IEDs emerge

from the motor cortex in SeLECTS and frontal and temporal regions are important for language processing [20].

TMS Evoked Potentials (TEPs; Fig. 2A): TEPs represent local cortical reactivity and also reflect how response to TMS propagates to functionally connectivity regions [8,11]. **Local TEPs,** measured at the stimulation site (ipsilateral motor ROI), capture both local and long-range excitatory and inhibitory inputs [10], serving as a measurement of cortical excitability. **Remote TEPs** recorded in distant brain regions (other five ROIs) serve as a measurement of connectivity between the stimulated and recorded regions [11]. For both measurements, spTMS epochs were averaged to create a "epoch-averaged regional TEP", from which we derived following measurements:

Local TEP: Motor cortex TEPs in children are simpler in morphology compared to adults, and are characterized by a positive peak at 60 ms (P60) and a negative peak at 100 ms (N100) (Fig. 2B) [29,38,39]. The P60 amplitude was defined as the maximum positive deflection between 30 and 80 ms, while the N100 was the maximum negative deflection within 70–150 ms following spTMS; latency windows were based on pediatric TEP studies and visual inspection of our data [31,40,41,42]. The latency of each component was defined as the time elapsed from pulse onset to the respective peak. We only analyzed amplitude and latency of the TEP from the stimulated motor cortex, because potentials induced in other brain regions by motor cortex stimulation are not well characterized yet in children, though an ipsilateral centroparietal negativity and a frontopolar positivity have been described [40].

Remote TEPs: We measured the area under the curve (AUC) of both local and remote TEPs at all ROIs. AUC provides a quantitative measure of signal magnitude and temporal characteristics, and previous reports suggest it changes after rTMS [43]. The AUC was computed by integrating absolute TEP values over two time windows: 10–80 ms and 10–1000 ms, capturing early and full TEP characteristics [38,39]. A single regional AUC value was calculated for each ROI using the epoch-averaged regional TEP, which was derived by averaging the TEPs across all electrodes in the ROI.

Weighted phase lag index (wPLI): We used wPLI as a second method to assess connectivity between ROIs (Fig. 2C). wPLI is a phase-based metric that is robust against the confounding effects of volume conduction in sensor-based EEG [12]. Beta-band (13–30 Hz) wPLI was used as our primary outcome as it increases immediately following IEDs in SeLECTS [6], and the beta frequency is highly associated with motor system function [21]. As connectivity in other frequency bands is also abnormal in SeLECTS, we investigated theta (4–7 Hz) and alpha (8–12 Hz) wPLI in secondary analyses.

Band-specific wPLI was calculated from 10 to 1000 ms of TEP using cross-spectral density within MATLAB-based Fieldtrip's toolbox [44]. The cross-spectral density was estimated using the multi-taper approach with discrete prolate spheroidal sequences (DPSS) as tapers, applying a 17 Hz spectral smoothing window for the band. The debiased squared wPLI estimator was employed to ensure accurate measurement of connectivity while accounting for bias in the estimation process. As such, wPLI measures the consistency of phase relationships, assigning greater weight based on the magnitude of the imaginary component,

thereby mitigating volume conduction effects. We calculated wPLI between all unique electrode pairs for each epoch (e.g., ipsi-frontal electrode #1 (iF1) and ipsi-motor electrode #1 (iM1) exemplified in Fig. 2C) and then averaged across epochs. Next, the wPLI values for electrode pairs spanning regions of interest (e.g. wPLI between ipsi-frontal and ipsi-motor electrodes) were averaged to yield a single regional connectivity value.

Frequency of Interictal Epileptiform Discharges (IEDs): IEDs were manually counted during each spTMS-EEG block, initially by a trained research assistant and confirmed by a board-certified epileptologist (FB) who were blinded to timing (pre vs. post rTMS) and session (sham vs. active rTMS).

2.4. Statistical analyses

We used the Wilcoxon signed-rank test [45], a non-parametric test appropriate for data that is not normally distributed, to assess changes in excitability, connectivity, and IED frequency *within* each session by comparing pre- and post-rTMS recordings for: (a) local TEP (P60, N100) amplitude and latency; (b) AUC of TEPs measured in all six ROIs; (c) wPLI between the six ROIs (15 unique region-to-region pairs); and (d) IED frequency. As a secondary analysis, we directly compared the changes induced by active vs. sham rTMS to one another (post minus pre-excitability, connectivity and IED values) with the Wilcoxon signed-rank test. Given the multiple ROIs investigated, we adjusted significance thresholds using principal component analysis, which accounts for the effective number of independent tests [46]. This method is suitable when data in each comparison are not completely independent, as is the case with EEG where signal represents summated activity from multiple regions. In contrast, correction methods that assume complete independence (e.g., Bonferroni) may set overly conservative thresholds that obscure meaningful findings [46,47].

Previous studies show that connectivity is acutely elevated when IEDs are present [6]. To quantify the influence of IEDs on connectivity, we tested whether: (a) IED frequency during baseline recordings (pre-rTMS) was associated with baseline connectivity; and (b) change in IED frequency after rTMS was associated with change in connectivity. We modeled these relationships using generalized estimated equations with an exchangeable correlation matrix that accounts for repeated measurements from each session [48]. To determine if rTMS changes connectivity beyond the impact it has on IED frequency, we conducted a sensitivity analysis excluding IED-containing epochs and focused on connectivity changes in IED-free epochs.

2.5. Supplementary analyses

First, we assessed if demographic, clinical or experimental factors affected modulation (Supplementary Material 1). Second, as evoked power is another TMS-EEG measure of excitability [49] that can be influenced by MEP amplitude [50], we investigated rTMS-induced changes in event related spectral perturbation (ERSP) (Supplementary Material 2). Third, we define the temporal pattern of connectivity changes, focusing on shorter time windows preceding and following spTMS pulses (Supplementary Material 3).

3. Results

3.1. Participants

Twenty-two right-handed children with SeLECTS were enrolled, but three children were excluded; two did not tolerate both sessions and one failed to stay awake (Supplementary Fig. 1). Thus, 19 children with SeLECTS, aged 7–13 years (10.0 ± 1.4), were included in the analyses. Eleven children (58 %) were taking ASMs (five took levetiracetam, four took oxcarbazepine, two took both). Average rMT was 89 ± 13 % MSO. Average IED frequency was 22 ± 42 per 5-min block; however, six children had the majority of IEDs (>10 IEDs/5-min), three had rare IEDs (<10 IEDs/5-min), and remaining children were IED-free during the entire session. No medications were changed between experimental sessions. For participant-specific data, see Supplementary Table 1. Detailed TEP information, including topographical and butterfly plots for all participants and blocks, included in Supplementary Material 4.

3.2. Impact of rTMS on cortical excitability

Local TEP: Amplitude and latency of the P60 and N100 peaks did not change after active or sham rTMS (Fig. 3B & Supplementary Table 2). The significance threshold was 0.05.

4. Impact of rTMS on functional connectivity

Remote TEP:

AUC of the remote TEPs did not change after active or sham rTMS (Fig. 3C & Supplementary Table 3) at any ROI. Based on the calculated effective number of independent tests, the significant threshold was set at 0.009 for comparing both pre-vs. post-rTMS and active vs. sham rTMS.

wPLI:

In the phase domain, active rTMS reduced beta-band wPLI connectivity between seven region-pairs (Fig. 4, double asterisks; Supplementary Table 4) whereas no changes were observed after sham rTMS. There was a trend of globally reduced connectivity after active rTMS, though some region-pairs did not meet the adjusted significance threshold (Fig. 4, single asterisk). Additionally, in four of the seven region-pairs where rTMS reduced connectivity compared to baseline, there was also a significant difference between the connectivity change induced by active vs. sham rTMS (Fig. 4, double daggers). The significant threshold was set at 0.008 for comparing pre-vs. post-rTMS, and at 0.007 for comparing active vs. sham rTMS.

Alpha-band connectivity between the contra-motor and ipsi-temporal regions and theta band connectivity between the ipsi-frontal and contra-frontal regions were reduced after active but not sham rTMS. In the alpha band, the connectivity reduction induced by active vs. sham rTMS also differed from one another (Supplementary Fig. 2 & Supplementary Tables 5–6).

5. Impact of rTMS on IED frequency

IED frequency significantly decreased from baseline after active (−11.2 ± 28.8 IEDs/5 min, p = 0.04) but not sham (0.8 ± 15.7, p = 0.46) rTMS. However, the impact of active vs. sham rTMS on IED frequency did not significantly differ (−12.1 ± 35.3; p = 0.12) (Fig. 5).

5.1. Impact of IEDs on connectivity

Participants with more IEDs had higher baseline wPLI connectivity (p <0.0001) (Fig. 6A). Change in IED frequency after rTMS also strongly correlated with change in connectivity (p < 0.0001) (Fig. 6B).

5.2. Impact of rTMS on wPLI connectivity in IED-free data

Given the reduction in IEDs after active rTMS and that IEDs are associated with elevated connectivity, we assessed whether the observed reduction in wPLI connectivity was solely attributable to decreased IED frequency or was also present in IED-free epochs. Connectivity was reduced in IED-free epochs after active but not sham rTMS (Fig. 7 & Supplementary Table 7). The significant threshold was set at 0.009 for comparing pre-vs. post-rTMS, and at 0.009 for comparing active vs. sham rTMS.

5.3. Supplementary analyses

First, TEPs did not significantly differ based on clinical factors (IED frequency, ASM use, and rMT), though power was limited (Supplementary Material 1). Second, the ERSP measured in the theta, alpha or beta frequencies did not change with active or sham rTMS at any ROI. While presence of MEPs did influence the ERSP, rTMS-induced changes in MEP amplitudes (and resulting change in the ERSP) are unlikely to explain the connectivity reductions we report (Supplementary Material 2). Third, rTMS-induced wPLI beta-band connectivity changes are not apparent in baseline EEG (preceding spTMS), suggesting that probing with spTMS is critical. Connectivity reductions are largest immediately following (10–500 ms) the spTMS but also persist in later (500–1000 ms) segments, suggesting rTMS affects connectivity both in circuits directly probed by spTMS and in wider networks (Supplementary Material 3).

6. Discussion

Pediatric epilepsy is a severe neurologic disorder that diminishes quality of life not only due to seizures but also because of associated neuropsychiatric comorbidities. IEDs are pathologic bursts of hypersynchronous electrical activity that disrupt attention and processing speed [3] and may lead to long-term changes in functional connectivity [3,4,6]. IEDs in childhood furthermore influence brain networks during critical developmental windows. As compared to the broad, non-specific effects of ASMs, neurostimulation with rTMS is a promising focal intervention that reduces IED frequency and modulates connectivity in adults [16]. Here, we assessed the impact of rTMS on three neurophysiologic measurements relevant to epilepsy pathology: cortical excitability (measured via TEPs), connectivity (via TEPs and wPLI), and IED frequency. While TEPs did not change, rTMS reduced wPLI connectivity widely throughout the brain. Active rTMS reduced IED

frequency compared to baseline, though the difference between active and sham stimulation did not reach significance in our small sample.

We examined cortical excitability because low-frequency rTMS is thought to induce local cortical inhibition [15]. While excitability can be measured via motor evoked potentials (MEPs), we focused on local TEPs instead, because TEPs capture cortico-cortical interactions rather than corticospinal ones and can be reliably measured in children whose motor threshold exceeds MSO [8]. Generators of TEPs are not fully understood, but pharmacological studies suggest that the P60 is associated with cortical inhibitory mechanisms [51], and the N100 is a long-range inhibitory response related to GABA-B [10]. Prior studies investigating the effects of low-frequency rTMS on TEPs report mixed findings. Healthy adults showed increased P60 and N100 amplitude after 1Hz rTMS [43], whereas children with untreated attention deficit hyperactivity disorder (ADHD) had reduced N100 amplitudes [52]. In our pilot study of nine children with SeLECTS, there was no change in N100 after rTMS [29]. Based on these prior studies, we initially hypothesized that 1 Hz rTMS would lead to a decrease in both P60 and N100 amplitudes, but we found no change in either P60 or N100 peaks. Several factors may explain this discrepancy from our original hypothesis. One consideration is that since children have higher rMT than adults [31], the standard practice of basing TMS intensity on rMT may be less appropriate because there is a greater disassociation between the intensity needed to elicit an MEP vs. a TEP. Hence, we may hit a ceiling effect with TEP amplitudes such that it is difficult to shift TEPs with rTMS. Arguing against this, we did not see greater TEP modulation when focusing on children with lower rMT (Supplementary Material 1). A second consideration is that rTMS impact may be disease-specific. Children with ADHD might have reduced baseline inhibition and thus be more responsive to inhibitory neuromodulation [52], whereas children with a motor cortex epilepsy may develop compensatory inhibitory input to the motor cortex and thus be less responsive to inhibitory rTMS [53]. A third consideration is that rTMS may not alter cortical excitability as previously accepted in the literature. Several recent studies failed to find consistent modulation in MEPs or TEPs with several forms of rTMS [54,55]. While 1 Hz rTMS was initially thought to act through direct cortical inhibition, its therapeutic effects may instead arise primarily through modulation of network-level dynamics [56]. This aligns with our findings of reduced phase-based connectivity without changes in local TEPs. In epilepsy, where dysfunction in inhibitory signaling leads to pathological synchronization between regions [2], rTMS may help restore typical patterns of inter-regional communication even without measurably altering local excitability. This network-level mechanism could explain why we observed broader effects on connectivity rather than changes in traditional markers of cortical inhibition.

We next investigated the impact of rTMS on connectivity, hypothesizing that inhibition of the motor cortex with 1Hz rTMS would decrease its connectivity with other brain regions. We investigated two measurements: a temporal-domain measure (TEPs) and a phase-domain measure (wPLI). The TEP or “inductive” approach [11], assumes that connectivity between the stimulated region and remote regions can be quantified by measuring the amplitude of the TEPs in those remote regions, with higher values suggesting stronger connectivity. This method provides temporally specific measurements but is limited to interrogating connectivity of the stimulated cortex. In contrast, wPLI provides inferences

about connectivity between regions remote from the site of stimulation [12]. While TEPs did not change, wPLI connectivity decreased, particularly between frontal and temporal regions. Why do inferences from these two measures differ? One possibility is that rTMS influences distributed networks rather than only the stimulated cortex, thus rendering the inductive approach insensitive. Prior work similarly demonstrated that rTMS of the primary motor cortex changed TEP amplitudes in bilateral premotor cortices more so than in the stimulated primary motor cortex [57]. Another possibility is that the phase-based measures are more sensitive to connectivity changes in epilepsy. In line with this, a study measuring coherence (another phase-based measure) of spTMS-EEG signal found increased connectivity in adults with genetic generalized epilepsies compared to controls [13]. Since typically-developing controls were not included in our study for ethical reasons, this prior work contextualizes our findings by suggesting that reduction in connectivity after rTMS indicates normalization of brain responses. These studies highlight the importance of including phase-based measures to quantify the effects of neuromodulation on connectivity.

We next explored whether rTMS reduced IEDs given the therapeutic implications. There was a significant reduction in IEDs compared to baseline after active but not sham rTMS, aligning with the *Cochrane Review's* conclusion that there is reasonable evidence that rTMS reduces IEDs [16]. While active rTMS was not significantly better than sham in reducing IEDs, our power was limited as only nine participants had IEDs during the experiment. This is not unexpected as IEDs are sleep-potentiated in SeLECTS but we measured EEG during wakefulness to ensure a consistent behavioral state [6,58]. Recently, two small open-label studies found that multiple doses of 1Hz rTMS reduce IEDs during sleep in children with SeLECTS [17,18]. Exploring the impact of rTMS on IEDs in sleep using sham-controlled methods will be a critical next step.

Finally, we assessed if reduction in connectivity was solely attributable to IED reduction, as IEDs themselves are associated with transient increases in connectivity [3,6]. While we confirmed that there is a strong relationship between IEDs and connectivity, we noted that connectivity was reduced even during IED-free epochs, suggesting that the effect of rTMS on connectivity extends beyond its IED-suppressing effects. The directional relationship between IEDs and connectivity remains unclear. rTMS might reduce IEDs, leading to altered connectivity. Alternatively, rTMS may reduce connectivity, thereby lowering the likelihood of IED generation. Several studies have investigated this relationship [59,60]. One found that real IEDs measured from epilepsy patients increased connectivity whereas simulated IEDs introduced into healthy control recordings did not [60], suggesting that hyperconnectivity in epilepsy stems from inherent pathophysiological networks rather than just acute effects of IEDs waveform. Causal modeling of SeLECTS EEG-fMRI data showed that IEDs alter network architecture, increasing connectivity between the motor area and the thalamus [59]. Together, these findings suggest that IEDs may acutely drive hyperconnectivity which then becomes a persistent feature even during periods without IEDs. Although we did not directly investigate this causality, the simultaneous reduction in both IEDs and connectivity highlight the therapeutic potential of rTMS in addressing epilepsy-related hyperconnectivity.

7. Limitations

Certain limitations warrant discussion. First, we lacked individual MRIs. This limits the spatial specificity of our findings. While individual source localization would be valuable, the broad connectivity changes suggest rTMS effects are distributed rather than specific to the motor cortex. IEDs in SeLECTS also lead to widespread connectivity increases [3,4,6], suggesting that motor cortex activity (whether spontaneous from IEDs or induced by TMS) influences broad networks. Volume conduction is unlikely to explain these findings as our connectivity metric, wPLI, is stringent against it. Lack of individual MRIs also limited our ability to adjust coil angle relative to individual anatomy. We used standard targeting procedures and optimized based on MEP amplitude, but in the future, individual MRIs and real-time TEP software could optimize TEP signal quality and minimize somatosensory or motor contributions [8]. Second, participants did not perform a task to confirm consistent alertness during measurements, as we did not feel children could do so without compromising EEG quality. This is notable, because TEPs and connectivity are state-dependent and IEDs are more prominent in SeLECTS during drowsiness and sleep [6,58]. We mitigated these concerns by interacting with the children between stimulation blocks and monitoring the EEG during stimulation. Therefore, we believe state changes do not explain our findings. Third, our small sample size limited our ability to estimate the impact that clinical variables, such as ASMs and age, have on rTMS effects [30,31]. Our crossover design accounts for within-participant variability, but future studies with larger cohorts are needed. Fourth, while we did our best to mask somatosensory contributions to TEPs [61], these components may still contribute to the signal. Our use of a sham-control and cross-over design, however, limit the impact these features are expected to have on our conclusions. Fifth, our TMS-EEG preprocessing pipeline takes a conservative approach to artifact removal (e.g. using a longer interpolation window around the pulse and a broad band-stop filter) favoring robust noise reduction in the later TEPs over potential signal loss. This is reasonable, as children have less developed early TEPs [31], but future advancements in preprocessing may allow for closer investigation of early TEPs.

Sixth, while this study shows that rTMS reduces connectivity in SeLECTS, it does not establish the clinical utility of doing so. Single rTMS doses induce transient modulation, with repeated doses required to induce durable effects [62]. We did not explore the duration of connectivity suppression, nor did we evaluate the impact of rTMS on cognition, as we generally would not expect measurable changes in cognition within minutes. We believe hyperconnectivity is an intriguing target as it is associated with poor outcomes in several pediatric epilepsy syndromes [7,63]. Currently, we lack interventions that directly target the underlying neural circuit dysfunction causing cognitive problems in epilepsy. Unlike systemic ASMs, rTMS could provide focal modulation of specific circuits involved in language and cognitive processing and thus represents a novel, non-invasive approach. Clinical trials investigating whether daily rTMS sessions given over weeks induce lasting reductions in both hyperconnectivity and cognitive difficulties are needed. Optimization of stimulation targets for these trials must be based on the goal of therapy; for example, targeting the language network itself or highly connected regions like the supplementary motor area [64,65] may be more effective at improving language than targeting the epileptic

onset zone as we did here. Technological advances, like multi-locus stimulation approaches [66], will be critical in optimizing among this wide parameter space.

8. Conclusion

This study demonstrates that rTMS reduces brain connectivity and IEDs in children with epilepsy. Together, these findings position rTMS as an important non-invasive method for probing how epilepsy and IEDs affect cognition and suggest that rTMS could be a promising non-pharmacological option for treating pediatric epilepsy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Registration and Data Availability Statement:

The data analyzed in this study was gathered as part of a clinical trial (NCT04325282) of spTMS-EEG in SeLECTS. There are no reproduced materials. Code with example data used for illustrating the methodologies of TEP and connectivity analysis is publicly available at https://github.com/Pediatric-Neurostimulation-Laboratory/rTMSConnectivity. The full data is available from the corresponding author on reasonable request.

Abbreviations:

SeLECTS	Self-limited epilepsy with centrotemporal spikes
IEDs	Interictal epileptiform discharges
TMS	Transcranial magnetic stimulation
EEG	electroencephalogram
spTMS-EEG	single pulses of TMS combined with EEG
rTMS	repetitive transcranial magnetic stimulation
TEPs	TMS evoked potentials
ROIs	regions of interest
wPLI	weighted phase lag index
ASM	antiseizure medication
MRI	magnetic resonance image
EMG	electromyography

APB	abductor pollicis brevis
rMT	resting motor threshold
MSO	maximal stimulator output
AUC	area under the curve

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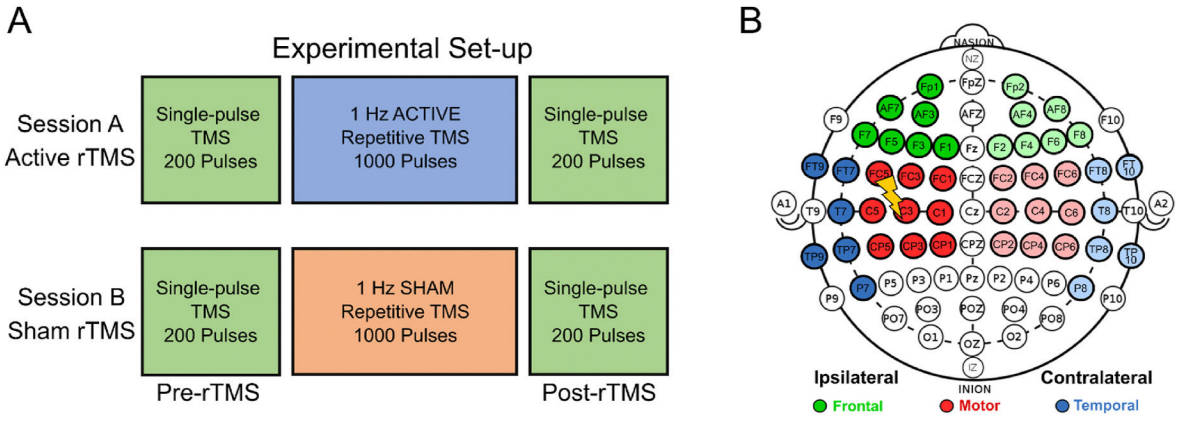

Fig. 1.

TMS and EEG Data Collection. A: Experimental protocol with participants undergoing spTMS-EEG to the motor cortex (green boxes) before and after either active (blue) or sham (orange) rTMS. Session order was randomized on a per-participant basis. B: High-density EEG was recorded. The hemisphere to which rTMS was applied is called “ipsilateral” and the opposite hemisphere “contralateral.” Regions of interest included: ipsilateral and contralateral frontal (green), motor (red), and temporal (blue).

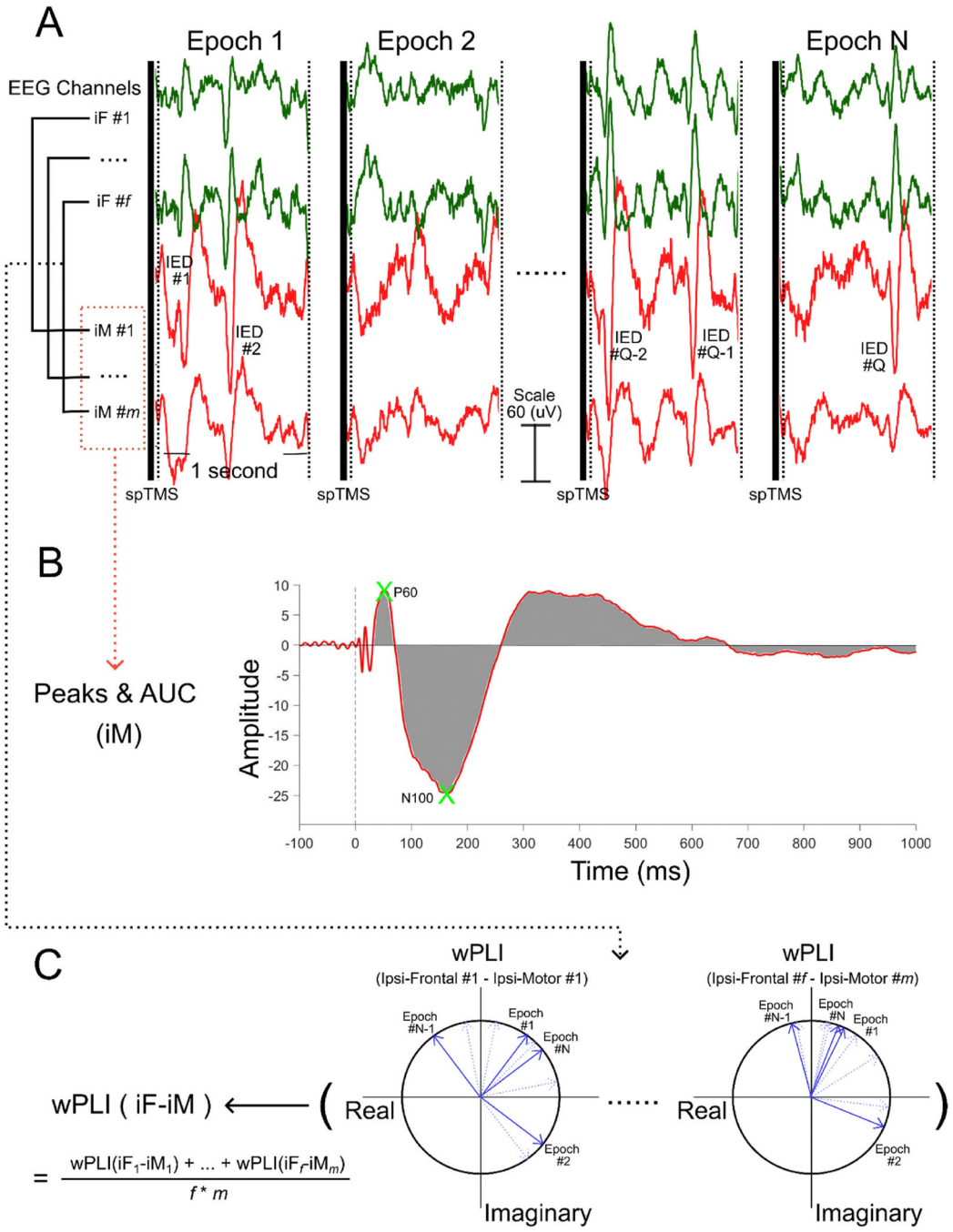

Fig. 2.

Excitability and connectivity measurement derivation. A: Representative EEG signals measured immediately after single pulses of TMS (spTMS), with exemplary IEDs. One second of EEG is epoched around each spTMS for analyses. B: TEP peak amplitudes and latencies as well as area under the curve (AUC) are calculated after averaging all epochs and all channels within a region of interest together. Here we illustrate a TEP from the ipsilateral motor (iM) region. C: Illustration of wPLI calculation between the ipsilateral frontal (iF) and ipsilateral motor (iM) regions. 1 = first electrode in frontal or motor region, *f* = last electrode

in frontal, *m* = last electrode in motor, *f*m* = total number of unique electrode pairs between frontal and motor regions.

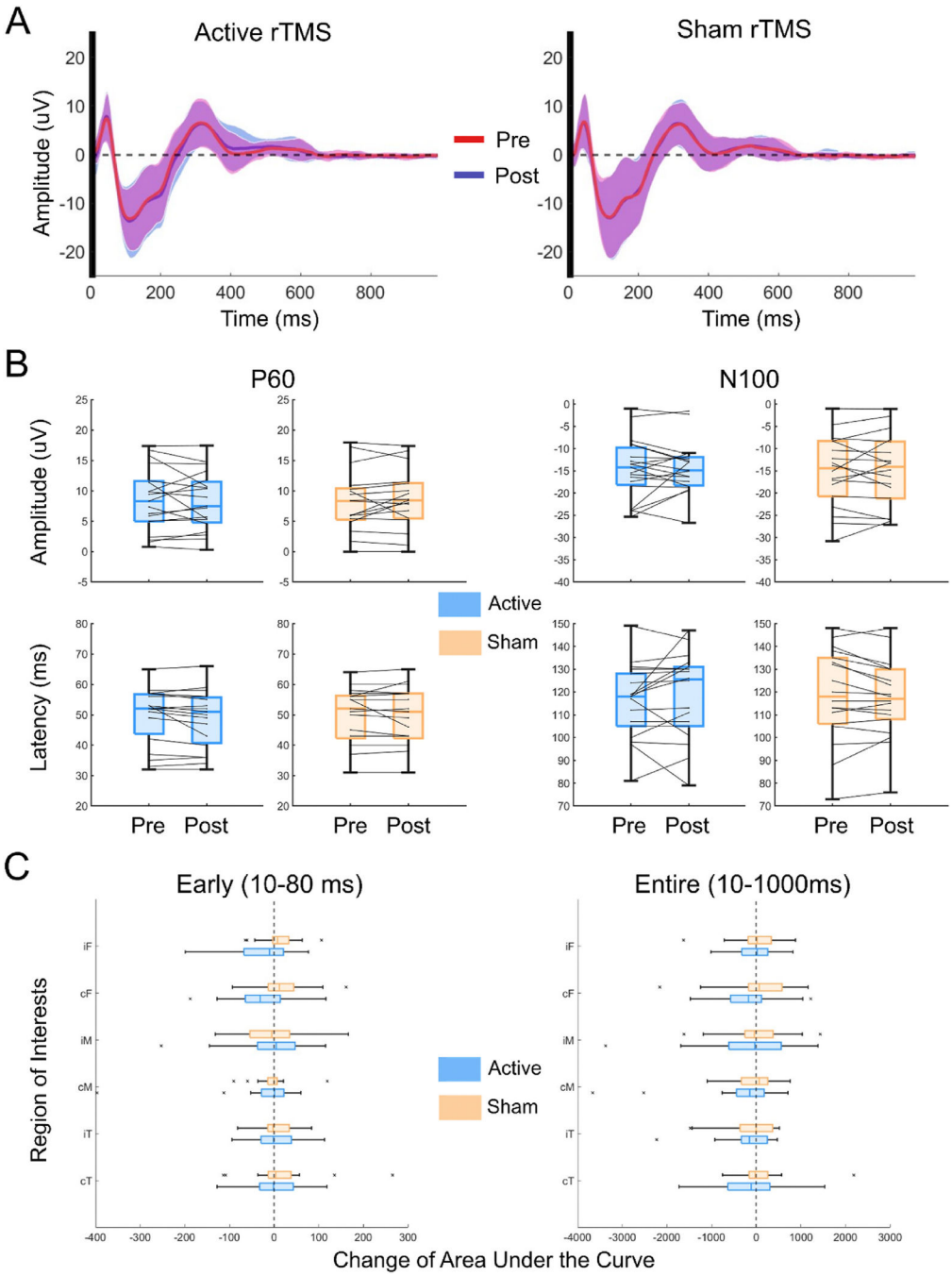

Fig. 3.

Impact of rTMS on cortical excitability. A: Visualization of the group-average (n = 19) local TMS evoked potentials (TEP) at the stimulated site measured pre- (red) and post- (blue) active (left panel) and sham (right panel) rTMS. B: TEPs (P60 [left] and N100 [right] amplitudes and latencies) pre- and post-rTMS. There were no significant changes in any of these measurements. C: Change in the area under the curve (AUC) of the TEP in the 10–80 ms (left panel) and 10–1000 ms (right panel) windows for the six regions of interest. There were no significant changes.

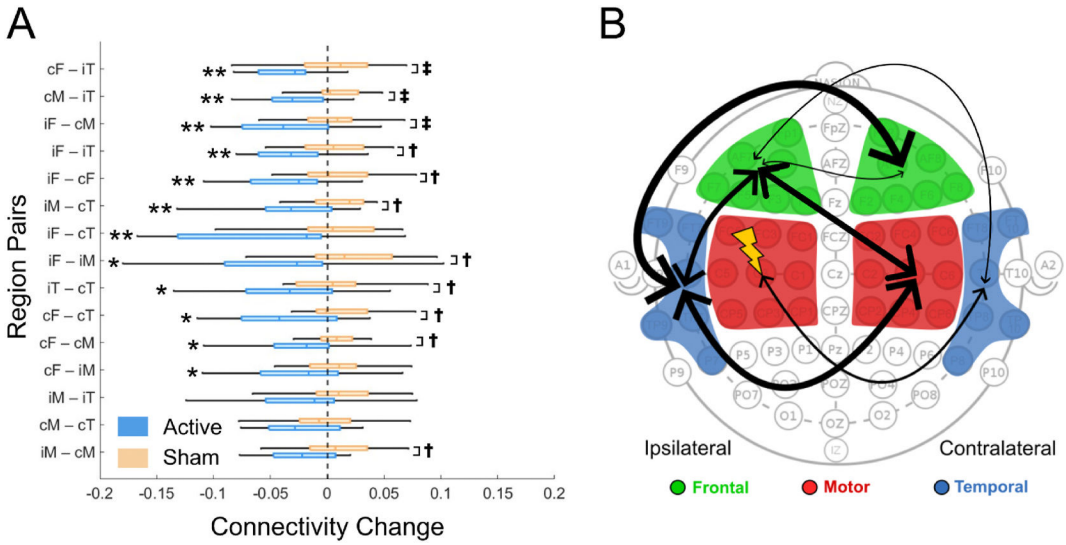

Fig. 4.

Impact of 1 Hz rTMS on wPLI connectivity. A: Active (blue) but not sham (orange) rTMS reduces connectivity in multiple brain regions in children with SeLECTS. i-: Ipsilateral-, c-: Contralateral-; -F: Frontal, -M: Motor, -T: Temporal. Regions are ordered based on the significance (p values). Dashed line represents no change from baseline. **$p < 0.0076$ (adjusted significance threshold for comparing pre-vs. post-rTMS); ‡$p < 0.0071$ (adjusted significance threshold for comparing active vs. sham rTMS); */† indicate $p < 0.05$ but not meeting the adjusted threshold. B: Black arrows connect regions between which there was a significant reduction in connectivity after active rTMS. Arrow weight based on significance of reduction.

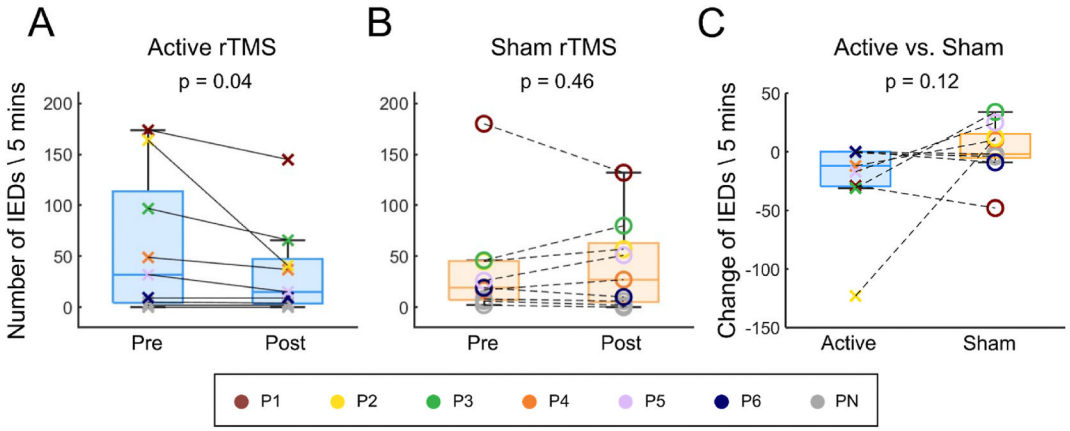

Fig. 5.

Impact of rTMS on IED frequency in children with SeLECTS. Frequency of IEDs pre vs. post (A) active and (B) sham rTMS. C: Change of IED after active vs. sham rTMS. For clarity, each participant with frequent IEDs is represented with an individual color (P1-P6) while the remaining 13 participants with few or no IEDs (PN) are represented in gray.

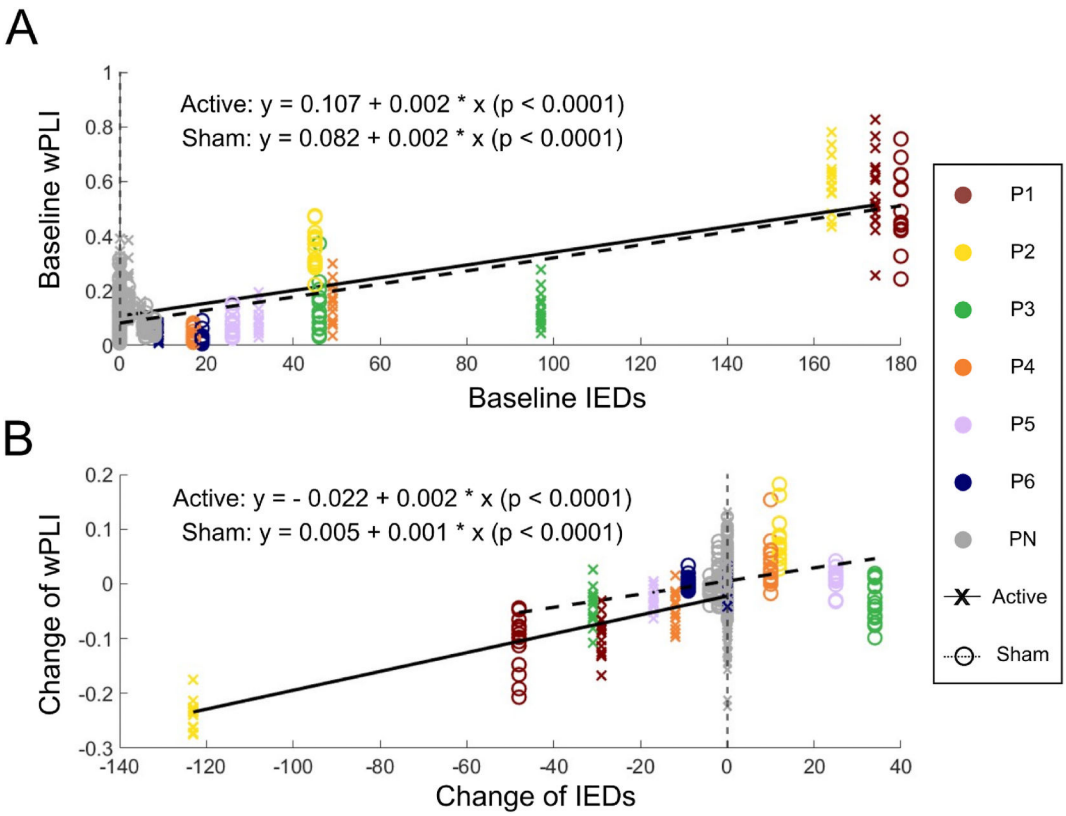

Fig. 6.

Association of interictal epileptiform discharges (IEDs) and brain connectivity. A: Baseline connectivity measured during both the active (x) and sham (o) sessions was higher in those with higher baseline IED frequency. B: Change in connectivity is associated with change in IED frequency during both the active and sham rTMS sessions. More participants showed a decrease in IEDs on the active day than the sham day. Each x-axis position contains one participant's connectivity values for all 15 region-pairs. Colored points represent the sub-group of participants (P1-P6) who had frequent IEDs (>10 during baseline recording). Gray points (PN) represent participants who had less than 10 IEDs during the baseline. The solid line is the model fit for the active session and the dashed line is the model fit for the sham session.

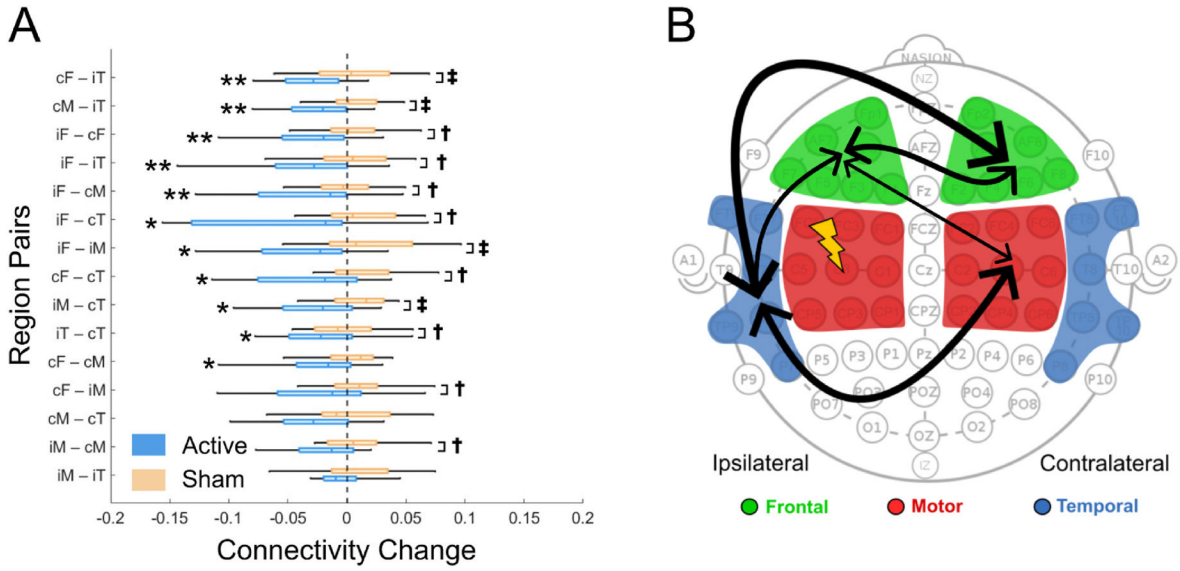

Fig. 7.

Impact of 1 Hz rTMS on wPLI connectivity during IED-free periods. A: Active (blue) but not sham (orange) rTMS reduces connectivity in multiple brain regions in children with SeLECTS during IED-free period. i-: Ipsilateral-, c-: Contralateral-; -F: Frontal, -M: Motor, -T: Temporal. Regions are ordered based on the significance (p values). Dashed line represents no change from baseline. **p < 0.0086 (adjusted significance threshold for comparing pre-vs. post-rTMS); ‡p < 0.0091 (adjusted significance threshold for comparing active vs. sham rTMS); */† indicate p < 0.05 but not meeting the adjusted threshold. B: Black arrows connect regions between which there was a significant reduction in connectivity after active rTMS. Arrow weight based on significance of reduction.