


RESEARCH ARTICLE

How cerebral cortex protects itself from interictal spikes: The alpha/beta inhibition mechanism

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Abstract

Interactions between interictal epileptiform discharges (IEDs) and distant cortical regions subserve potential effects on cognition of patients with focal epilepsy. We hypothesize that “healthy” brain areas at a distance from the epileptic focus may respond to the interference of IEDs by generating inhibitory alpha and beta oscillations. We predict that more prominent alpha-beta oscillations can be found in patients with less impaired neurocognitive profile. We performed a source imaging magnetoencephalography study, including 41 focal epilepsy patients: 21 with frontal lobe epilepsy (FLE) and 20 with mesial temporal lobe epilepsy. We investigated the effect of anterior (i.e., frontal and temporal) IEDs on the oscillatory pattern over posterior head regions. We compared cortical oscillations (5–80 Hz) temporally linked to 3,749 IEDs (1,945 frontal and 1,803 temporal) versus an equal number of IED-free segments. We correlated results from IED triggered oscillations to global neurocognitive performance. Only frontal IEDs triggered alpha-beta oscillations over posterior head regions. IEDs with higher amplitude triggered alpha-beta oscillations of higher magnitude. The intensity of posterior head region alpha-beta oscillations significantly correlated with a better neuropsychological profile. Our study demonstrated that cerebral cortex protects itself from IEDs with generation of inhibitory alpha-beta oscillations at distant cortical regions. The association of more prominent oscillations with a better cognitive status suggests that this mechanism might play a role in determining the cognitive resilience in patients with FLE.

KEYWORDS

alpha, beta, epilepsy, inhibition, interictal epileptiform discharges, magnetoencephalography, oscillations

Abbreviations: FLE, frontal lobe epilepsy; IEDs, interictal epileptiform discharges; MEG, magnetoencephalography; ROI, region of interest; TF, time-frequency; TLE, mesial temporal lobe epilepsy.

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1 | INTRODUCTION

In patients with focal epilepsy, interictal epileptiform discharges (IEDs) routinely recorded via electroencephalography (EEG) or magnetoencephalography (MEG) are generated in the so-called irritative zone or

spike onset zone (Khoo et al., 2018; Rosenow & Luders, 2001). IEDs correspond to the sudden depolarization of a large yet restricted (focal) population of cortical neurons and their effects propagate far beyond the region of origin (Buzsáki, Anastassiou, & Koch, 2012; De Curtis & Avanzini, 2001; Tao, Baldwin, Hawes-Ebersole, Ebersole, 2007; Tao, Baldwin, Ray, Hawes-Ebersole, Ebersole, 2007; von Ellenrieder et al., 2016; von Ellenrieder, Beltrachini, Perucca, & Gotman, 2014).

The effects of IEDs at distant cortical regions are both transient and enduring. IEDs induce transient and time-locked modulation of metabolic activity of extended networks (Coito et al., 2015; Khoo et al., 2018; Kobayashi, Bagshaw, Grova, Dubeau, & Gotman, 2006; Pellegrino et al., 2016; Shamshiri et al., 2017; Xiao et al., 2016) and cognitive deficits implicating distant cortical regions (Aarts, Binnie, Smit, & Wilkins, 1984; Binnie, 2003; Binnie & Marston, 1992; Holmes, 2014). The chronic effects of IEDs may contribute to broad changes of cortical excitability and metabolism (Badawy, Curatolo, Newton, Berkovic, & Macdonell, 2007; Badawy, Vogrin, Lai, & Cook, 2015; Vlooswijk et al., 2010), cortical atrophy (Bernhardt et al., 2008, 2009; Labate et al., 2011), and cognitive impairment (Hermann, Lin, Jones, & Seidenberg, 2009; Oyegbile et al., 2004).

The means by which locally generated IEDs interact with remote cortical regions and possibly affect their function and overall cognition remain unclear. In this study, we tested the hypothesis that distant cortical regions “respond” to focal IEDs elsewhere by activating inhibition through cortical oscillations.

Cortical oscillations have a prominent and multifaceted role in cortical function (Buzsáki & Draguhn, 2004), including a fine-tuning of cortical inhibition. The functional value of oscillations is largely determined by their frequency (da Silva, 2013), with alpha and beta oscillations having remarkable inhibitory effects. Alpha oscillations, originally associated to lack of exogenous or endogenous processing (Gloor, 1969), can reduce cortical excitability (Romei et al., 2007; Sauseng, Klimesch, Gerloff, & Hummel, 2009), decrease metabolic demands (Scheeringa et al., 2011) and, most importantly, maintain the functional integrity of brain networks by gating unwanted information (Händel, Haarmeier, & Jensen, 2011; Jensen & Mazaheri, 2010; Kelly, Lalor, Reilly, & Foxe, 2006; Klimesch, Sauseng, & Hanslmayr, 2007; Waldhauser, Johansson, & Hanslmayr, 2012; Worden, Foxe, Wang, & Simpson, 2000). Beta oscillations preserve and promote the ongoing computation of a cortical region by inhibiting the initiation of novel activities (Engel & Fries, 2010). Spontaneous beta oscillations impair motor performance (Gilbertson et al., 2005; Pellegrino et al., 2012; Swann et al., 2009), whereas externally driven beta oscillations slow down voluntary movements (Pogosyan, Gaynor, Eusebio, & Brown, 2009) and inhibit cortical excitability (Bologna et al., 2019; Joundi, Jenkinson, Brittain, Aziz, & Brown, 2012; Tinkhauser et al., 2017). Transient changes of cortical oscillations in alpha/beta as well as other frequency bands in relation to a given event have been studied as event-related synchronization and event-related desynchronization (ERS/ERD) and their variants, such as event-related spectral perturbation. A synchronization in a given frequency band corresponds to a transient increase of power with respect to a baseline, whereas a desynchronization corresponds to a transient decrease of

spectral power (Grandchamp & Delorme, 2011; Pfurtscheller, 2001; Pfurtscheller, Graitmann, Huggins, Levine, & Schuh, 2003; Pfurtscheller & Lopes da Silva, 1999; Tombini et al., 2009).

We predicted that the cerebral cortex may counteract potential disruptive effects of IEDs with generation of alpha and beta oscillations (ERS), and that this could influence cognition. To test our hypothesis, we studied patients with a diagnosis of frontal lobe epilepsy (FLE) as well as patients with mesial temporal lobe epilepsy (TLE). Patients underwent MEG recordings, from which we investigated the presence of IEDs-related oscillations over posterior head regions. Among patients evaluated for epilepsy surgery, TLE and FLE are the most represented and are paradigmatic of two different types of epilepsy: FLE being neocortical and TLE deep and archicortical. In addition, both TLE and FLE are characterized by anterior quadrant IEDs, providing perfect clinical presentation to assess the effect at a distance in the posterior quadrant regions of the brain, while mitigating the effect of volume conduction.

2 | MATERIALS AND METHODS

2.1 | Patients

This study was approved by the Research Ethics Board of the Montreal Neurological Institute and Hospital – McGill University Health Center and complies with the Declaration of Helsinki and its later amendments. All participants signed a written informed consent prior to enrollment. We reviewed all patients at the Montreal Neurological Institute and Hospital who underwent MEG recordings between 2006 and 2016 in the context of presurgical workup of drug resistant focal epilepsy. We only included patients with FLE or TLE for whom at least 10 IEDs (spikes or sharp waves) were captured during about 1 hr recording. We excluded patients with: (a) MEG magnetization artifact, (b) large cortical lesions which would hamper MRI cortical reconstruction and MEG head modeling, (c) frequent IEDs (more than 1 IED/5 s) which would compromise a reliable assessment of baseline activity, (d) patients in whom the predominant IEDs presented as bursts of rhythmic fast activity, polyspikes and spike and wave complexes, which last more than 300 ms and are generated within an interplay between cortical-subcortical structures, (e) patients presenting with seizures in the scanner. The diagnosis of FLE and TLE was made in agreement with the guidelines of the International League Against Epilepsy (ILAE, <https://www.ilae.org/guidelines>) and taking into consideration all available information available in the context of the presurgical workup performed at the Montreal Neurological Institute. This information included, but was not limited to, clinical presentation/semiology, Video-EEG monitoring, MRI findings, neuropsychological assessment.

2.2 | Cognitive assessment

The degree of cognitive impairment was extracted from the standard clinical neuropsychological evaluation pertaining to standard-of-care

pre-surgical workup at the Montreal Neurological Institute, prior to and independently from MEG data analysis. Global functioning takes into consideration all tests performed by the patients and the clinical impression by the clinical neuropsychologist who performed the evaluation. To each of these classes a numerical value, grading from 1 (Extremely Low) to 7 (Superior), was assigned to allow stratification of data from each patient. We opted for this approach for multiple reasons: (a) As expected, FLE patients were rather heterogeneous with respect to lateralization and location of the focus. As such, the clinical neuropsychological tests performed for pre-surgical assessment was tailored according to the clinical questions regarding cognitive function; (b) Our interest was focused on the possible protective effect of posterior oscillations on global performance and functioning, rather than on mapping the impairment of specific cognitive domain as function of focus site (see also Section 4).

2.3 | MEG and MRI data acquisition

Details on data acquisition have been previously reported in (Chowdhury et al., 2018; Pellegrino et al., 2016, 2018, 2020). Briefly, MEG signals were recorded with a CTF system (MISL, Vancouver, Canada) equipped with 275 axial gradiometers. Dedicated sensors were applied to detect eye movements and electrocardiogram (ECG). The position of the head in the Dewar was continuously monitored through three localization coils placed on anatomical landmarks (left and right preauricular points and nasion), which were continuously tracked by the CTF Continuous Head Localization system. Prior to starting each MEG acquisition, at least 200 head points were digitized using a Polhemus localization system, for accurate MRI-MEG co-registration. The acquisition lasted about 1 hr and was divided in blocks lasting 6 min each. The sampling rate was set to 600 Hz or higher. All recordings were performed in a quiet magnetically and acoustically shielded room, with the patient lying in a supine position. Patients were given the following instruction: "Clear your mind and stay relaxed." For each individual, a high-resolution anatomical brain MRI was acquired for estimation of the head model. The MRI scan was performed with a Siemens Tim Trio 3T scanner and the following parameters: T1W MPRAGE sequence, 1 mm isotropic 3D images, 192 sagittal slices, 256×256 matrix, TE = 2.98 ms, TR = 2.3 s.

2.4 | MEG data processing

MEG data analysis was performed with the Brainstorm toolbox, the Fieldtrip toolbox and MATLAB (The Mathworks, version 2017b) (Oostenveld, Fries, Maris, & Schoffelen, 2011; Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011). MEG data was preprocessed applying: (a) third-order spatial gradient noise cancelation, (b) DC offset removal, (c) 60-Hz line frequency notch, (d) resampling to 600 Hz. MEG data was visually inspected applying a standard online bandpass filter (0.3–70 Hz) and IEDs were identified and marked at their peak. IEDs occurring at the time of artifacts (including ECG and eye

movements) were not considered (Xiao et al., 2016; Pellegrino et al., 2020). For each IED, a corresponding "control marker" was placed at a time-point free from visible epileptiform activity or artifacts, minimally 5 s away from any IED. Non-filtered MEG data was then segmented in epochs lasting 2 s and centered around the markers (both for IEDs and control markers). As IEDs typically last 70–300 ms, we opted for a 2-s window around the IEDs. This window allowed to study oscillations both at the time of IEDs and for at least 500 ms after them (5 full cycles at 10 Hz) and to appreciate the temporal dynamic of the oscillatory pattern. Most often, ERS/ERD analysis is performed on data acquired with an experimental design in which it is possible to control the number of stimuli, the inter-trial interval, the degree of vigilance of the participants and set early on what data section will be considered as baseline. In our case, none of the above was possible, as IEDs typically occur randomly, their number can vary from patient to patient, the inter-IEDs stimulus cannot be controlled (we excluded patients with too frequent IEDs to minimize the bias) and the vigilance state fluctuates over the course of the recording (see Supporting Information). We therefore opted for a method to minimize the confounding, with the selection of a number of "control" epochs randomly drawn over the duration of the recording. Baseline normalization of both IEDs epochs and control epochs made the signal comparable across patients and suitable for group analysis. Having multiple control markers corresponded to having multiple reference points which capture different brain states and avoiding the influence of only one (arbitrary) baseline.

2.5 | Source imaging

The estimation of forward and inverse models was performed for each recording block, in order to minimize the effect of possible head movements. The forward model was built based on the individual high-resolution anatomical MRI. Brain segmentation and cortical reconstruction were performed with the Freesurfer toolbox (Dale, Fischl, & Sereno, 1999). The resulted cortical surfaces and the corresponding subject-specific anatomical parcellation with Desikan–Killiany cortical atlas (Desikan et al., 2006) were then imported into Brainstorm. MEG-MRI co-registration was ensured using a surface fitting procedure, applying a rigid geometrical transformation (three rotations, three translations) between the head shape reconstructed from the MRI and the fiducial points previously digitized (nasion, right and left preauricular points + 200 additional head points). The source space for source imaging corresponded to the mesh of the "mid" cortical layer, equidistant from the white/gray matter interface and the pia mater. This mesh was then downsampled to 8,000 cortical vertices. The distributed source model consisted in placing dipolar sources on every vertex of the mesh, oriented perpendicularly to the cortical surface. The forward model to estimate the contribution of every cortical dipole to MEG sensor data was built using a 1-layer boundary element method (BEM) (Kybic, Clerc, Faugeras, Keriven, & Papadopoulos, 2006), considering the inner-skull surface, setting the conductivity to 0.33 S/m. For the BEM model, we considered the

implementation of the OpenMEEG toolbox (Gramfort, Papadopoulos, Olivi, & Clerc, 2010) freely available in Brainstorm software. The resolution of the inverse problem was then performed applying the whitened and depth-weighted linear L2-minimum norm estimate (Hämäläinen & Ilmoniemi, 1994). The dipole orientation was constrained to be normal to the cortical surface. Diagonal noise covariance was estimated from a 2 s segment, free from artifacts and any epileptiform activity (denoted here as “baseline”). A common imaging kernel was computed for each registration block and then applied to obtain single epoch cortical reconstructions. This procedure resulted in the estimation of time-series for each vertex of the cortical surface, for the duration of each epoch, that is, for each IED or each corresponding control marker. It also allowed avoiding the coregistration of multiple MEG runs, as data was further analyzed within the same individual cortical space.

2.6 | Time-frequency analysis

An initial analysis was performed on six regions of interest (ROIs) located in posterior head regions: left and right inferior-parietal cortex, left and right precuneus, left and right peri-calcarine cortex. These ROIs were selected because they are representative of associative regions belonging to the default mode network (precuneus and inferior parietal cortex), primary cortices (calcarine), areas with deeper sulci/located deeply in the cortical mantle (precuneus, calcarine) versus those which are more superficial and more accessible to MEG (inferior parietal). ROIs were selected from the Desikan-Kiliany atlas, as labeled automatically by the Freesurfer toolbox. The Time-Frequency (TF) decomposition was computed with the following parameters: (a) Morlet wavelet, (b) central frequency = 1 Hz, (c) FWHM = 3 s, (d) frequency range = 5–80 Hz, (e) time-window = 2 s (–1 s + 1 s, with 0 corresponding the IED or control marker). TF decomposition was applied to the reconstructed time-course of each vertex of the ROI and then the magnitude of the TF representation was averaged within each ROI. This procedure was repeated for all epochs (all IEDs and “control markers”). Thereafter, IEDs and control TF were normalized over the “baseline” (ratio). For each patient, the resulting normalized TF representations were then averaged by trial group (two groups: IEDs and control markers), resulting in only two average TF representations (IEDs and control markers), per ROI, per patient, for group level statistical analysis. By averaging events (IEDs or control markers) within patients, we did not take into account intra-subject variability, but overcame the issue of having a different number of IEDs across subjects. Group level statistical analysis was performed applying the cluster-based permutation method as implemented in the Fieldtrip toolbox (Maris & Oostenveld, 2007; Oostenveld et al., 2011) (https://www.fieldtriptoolbox.org/tutorial/cluster_permutation_freq/). The null hypothesis corresponded to no difference between the magnitude of the oscillations between IED and “control” TF, assessed using *t* statistics. Clusters in the TF domain were then defined over the time versus frequency dimensions. The strength of each cluster was defined as

the sum of *t* values of the TF bins (along with time and frequency dimensions) of the cluster, allowing the consideration of both the size of the cluster and its statistical significance ($p < .05$). The same procedure was applied to the entire group of patients as well as to FLE and TLE groups separately. For visualization purposes and to provide an estimate of within-subject effects (Figure 1), we also computed intra-subject paired *t* values taking into the normalized TF of every IED and the corresponding control marker TF. This additional analysis step was restricted to time and frequency bins of interest.

In order to better assess the spatial distribution of the effects of IEDs on oscillations, we performed a vertex-wise TF analysis. This analysis focused on the frequency range showing a significant effect at the first ROI level analysis (i.e., 12–16 Hz) and for the entire time-window under investigation (–1 s to +1 s). TF decomposition was computed using the same parameters described above for each vertex of the posterior quadrant. Similarly, TF maps of the posterior quadrant were normalized by the baseline TF map. Resulting maps were then spatially smoothed with full width at half maximum of 3 mm (Worsley et al., 2009), averaged by frequency range, trial group (IEDs and control markers) and finally by subject, before being projected onto a template cortical surface extracted from the ICBM MRI (Mazziotta et al., 2001) using Brainstorm non-linear surface to surface registration tool. Therefore, the group level statistical analysis relied on two average maps per subject (IEDs and control markers). Statistical analysis was performed using the fieldtrip toolbox and with the same approach described above. This time, the clusters of *t*-maps comparing IEDs and control markers were built over the spatio-temporal dimensions, and the same statistical significance $p < .05$. A supplementary analysis without “control markers” and comparing the effect of several normalization procedures was also performed and can be found in the Supporting Information.

2.7 | Relationship between IEDs number and amplitude versus alpha/beta oscillations

We tested whether the oscillations induced in the posterior head regions by anterior IEDs depend on IEDs characteristics such as number and amplitude.

2.7.1 | IEDs number

The relationship between IEDs number and alpha/beta oscillations in the posterior head regions was tested with Pearson's correlation coefficients, computed between the number of IEDs for each patient and the strength of alpha/beta oscillations, for each ROI. The strength of alpha/beta was computed as sum of magnitude over the bins belonging to 0.5 and 0.9 s and between 12 and 16 Hz TF window, for each ROI. The selection of the time window depended on three factors: (a) significant effect in the previous analysis; (b) not too close to the spike (the duration of the sharp waves is about 200 ms maximum); (c) to avoid border effects of TF decomposition (about 0.1 s at 12 Hz

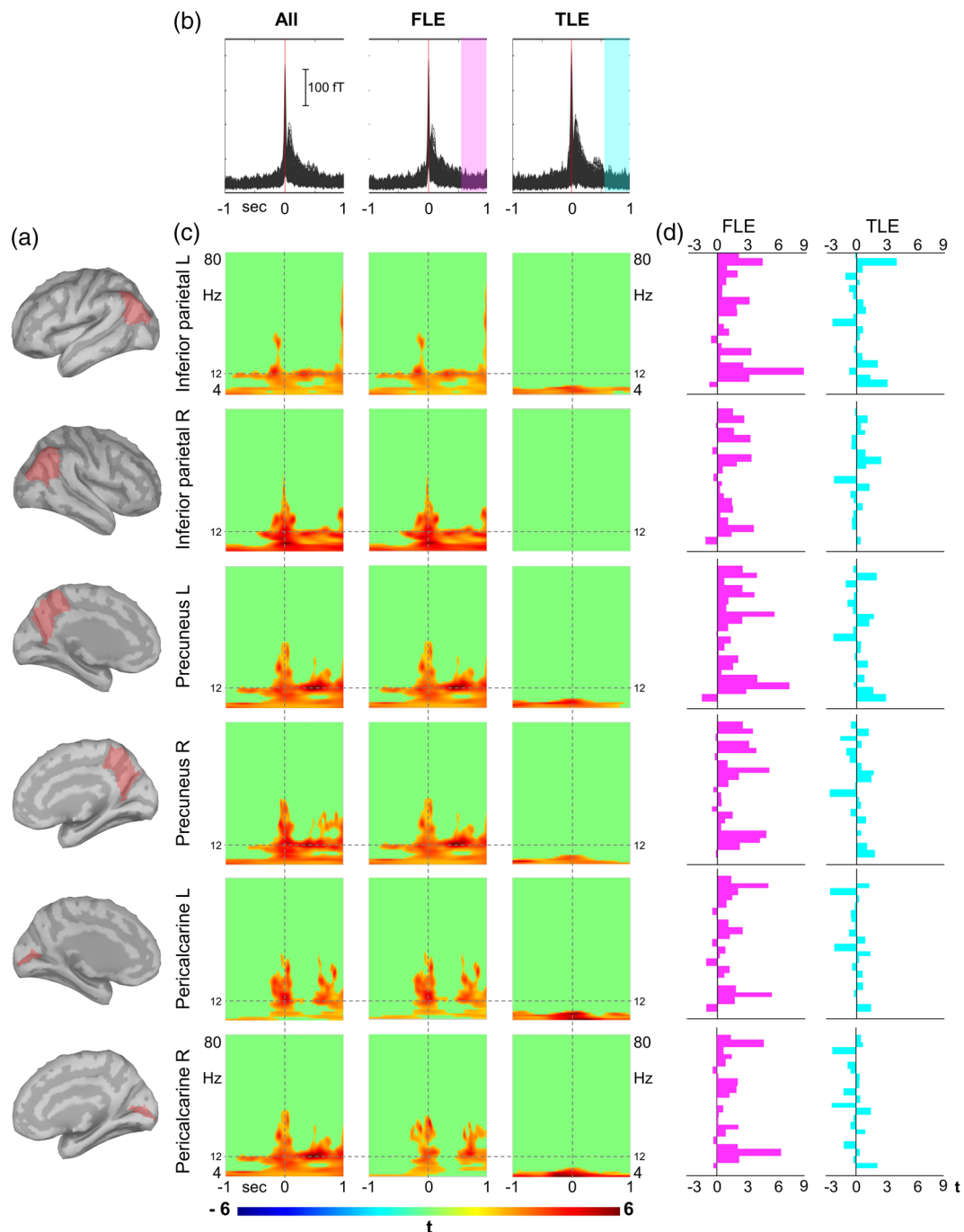


FIGURE 1 Region of interest (ROI)-based analysis: (a) In red the 6 ROIs considered for time-frequency (TF) analysis. (b) Average magnetoencephalography (MEG) interictal epileptiform discharges (IEDs) signal for all patients (left column), frontal lobe epilepsy (FLE) patients (middle column) and mesial temporal lobe epilepsy (TLE) patients (right column). To avoid cancelation phenomena, the absolute value of MEG signal was extracted prior to computing average IEDs. The magenta and cyan bands refer to the time window considered in (d). (c) Statistical maps of IEDs effect, with the color scale indicating the magnitude of the group-level t value. The maps have been thresholded and only report significant clusters after permutation statistics ($p < .05$). Each row refers to the corresponding ROI in (a), each column refers to the patients' group indicated in (b). TF analysis was centered around IEDs (from -1 to 1 s) and from 5 to 80 Hz. IEDs triggered alpha-beta oscillations in the posterior head regions, with a maximum at about 12 – 16 Hz and a duration up to 1 s after IEDs. This effect was appreciated in the entire cohort (left column), was very similar for FLE patients and absent in TLE patients. (d) Patients' specific t values for oscillations triggered at 12 – 16 Hz and between 0.5 and 0.9 s after IEDs versus control markers, computed at the ROI level (as indicated in [a]), for both groups. Each bar corresponds to one patient. Magenta bars (frontal patients) consistently show positive t values. Cyan bars (temporal patients) fluctuate around zero

with the wavelet parameters considered in this analysis). The TF values were normalized over the baseline, before averaging them by group (IEDs and controls) and computing the “IEDs TF–control TF” difference, which corresponded to the patient's IEDs-triggered oscillation increase as compared to controls.

2.7.2 | IEDs amplitude

Since sensor-level MEG data amplitude is influenced by the distance between cortical surface and the sensors, we decided to assess the amplitude at the source level according to the following procedure: (a) For each epoch, the 20 cortical vertices ($\sim 4.5 \text{ cm}^2$) exhibiting the maximum absolute source value at the time of the IED peak (0 s) were extracted and their values were averaged; (b) for each epoch, the absolute values over the baseline signal reconstruction for the same selected vertices were also averaged; (c) the amplitude of each epoch was normalized over the baseline (ratio); (d) normalized amplitudes were then averaged by trial groups (IEDs and Controls); (e) the difference “IEDs amplitude minus control amplitude” was estimated for each patient, which corresponded to a subject-specific estimation of the IEDs amplitude in the source space.

Pearson's correlation coefficients were computed for each ROIs between the source level IEDs' amplitude (one value per ROI per patient) and TF strength (one value per ROI per patient, as described earlier). The relationship between amplitude and strength of oscillations was finally controlled for IEDs number by applying partial correlation tests.

2.8 | Relationship between alpha-beta oscillations and cognition

This study was restricted to FLE patients only, as no significant posterior oscillations around the IEDs were found for TLE patients. In order to estimate the relationship between alpha-beta oscillations and cognition, we relied on a data-driven approach and applied the following procedure: (a) The independent variable corresponded to individual TF t-maps, generated computing a vertex-wise paired t-score between normalized IEDs and control maps; (b) the dependent variable corresponded to the global cognitive performance score, ranging between 1, which corresponded to extremely impaired cognitive profile, and 7, which corresponded to superior cognitive profile. One value was assigned to each patient; (c) Spermann's Rho correlation coefficients were computed over patients between the cognitive score and each element TF t-map (three dimensions: time, frequency, space); (d) the matrix with the Spermann's Rho coefficients (same size as TF t-map) was r-to-z transformed for each cortical vertex, to approximate gaussianity. Clusters of significant association with the cognitive score were tested with the cluster-based permutation approach available in fieldtrip (`ft_statfun_correlationT`) (Maris & Oostenveld, 2007). The confidence level alpha was set to .05. The statistical test was two-tailed.

3 | RESULTS

3.1 | Patients' characterization

Forty-one patients were included in this study. The number of subjects and IEDs was comparable across groups, sides, and hemispheres (Table 1 and Table 2).

3.2 | ROI-based analysis

The results of ROI analysis are summarized in Figure 1. Panel (c) reports the statistical maps of differences between IEDs and corresponding control oscillations. An increase in alpha-beta oscillations was found for all ROIs (identified in panel [a]). These oscillations occurred after IEDs, remarkably at 12–16 Hz, and lasted up to 1 s. After separating patients by group, increased oscillatory patterns were found in FLE patients, but not in TLE patients. This suggests that FLE and TLE groups behave very differently with respect to triggering alpha-beta oscillations in distant cortical regions. To be noted, the IEDs-triggered oscillations showed group specificity (only frontal and not temporal patients), frequency specificity (alpha and beta) and time specificity (occurring largely after the IEDs). Panel (d) reports the single-patient *t* values (for visualization purpose only) for 12–16 Hz within the time window 500–900 ms: as opposed to TLE, almost all FLE patients exhibited an increase of oscillations at the single subject level.

All patients had a significantly higher amount of theta activity before and after IEDs, confirmed by a supplementary analysis with a wavelet tuned for this specific frequency range (data not shown, see Supporting Information). This effect is consistent with the knowledge that IEDs occur more often during hypersynchronous cortical activity, such as when there is somnolence. As expected, there was a broad-band increase of power at the time of the IEDs. IEDs did not significantly impact gamma oscillations. Temporal IEDs did not significantly affect the oscillatory patterns of contralateral temporal structures (Supporting Information).

3.3 | Topographical distribution of alpha/beta oscillations

In order to map the topographical distribution of alpha/beta oscillations triggered in the posterior head regions, we then performed a vertex-wise analysis restricted to the frequency range 12–16 Hz, as this was the frequency range exhibited most significant results at the ROI level. The results are summarized in Figure 2. Panel (c) shows the statistical maps thresholded after spatio-temporal cluster-permutation analysis ($p < .05$). Alpha-beta oscillations were broadly triggered in the posterior head regions for FLE patients. No significant effects were found for TLE patients.

TABLE 1 Subjects and IEDs included in the analysis

		All	Frontal	Temporal	Left hem	Right hem	Left frontal	Right frontal
	Number of subjects	41	21	20	18	23	10	11
IEDs	Total number	3,749	1,945	1,803	1,962	1,786	791	1,154
	Average/subject	91	93	90	109	78	79	105
	Median/subject	67	69	55	70	57	68	126
	Maximum/subject	413	239	413	413	203	239	203
	Minimum/subject	10	19	10	14	10	19	20

Note: The number of subjects and spikes was comparable across groups, sides, hemispheres.
Abbreviation: IEDs, interictal epileptiform discharges.

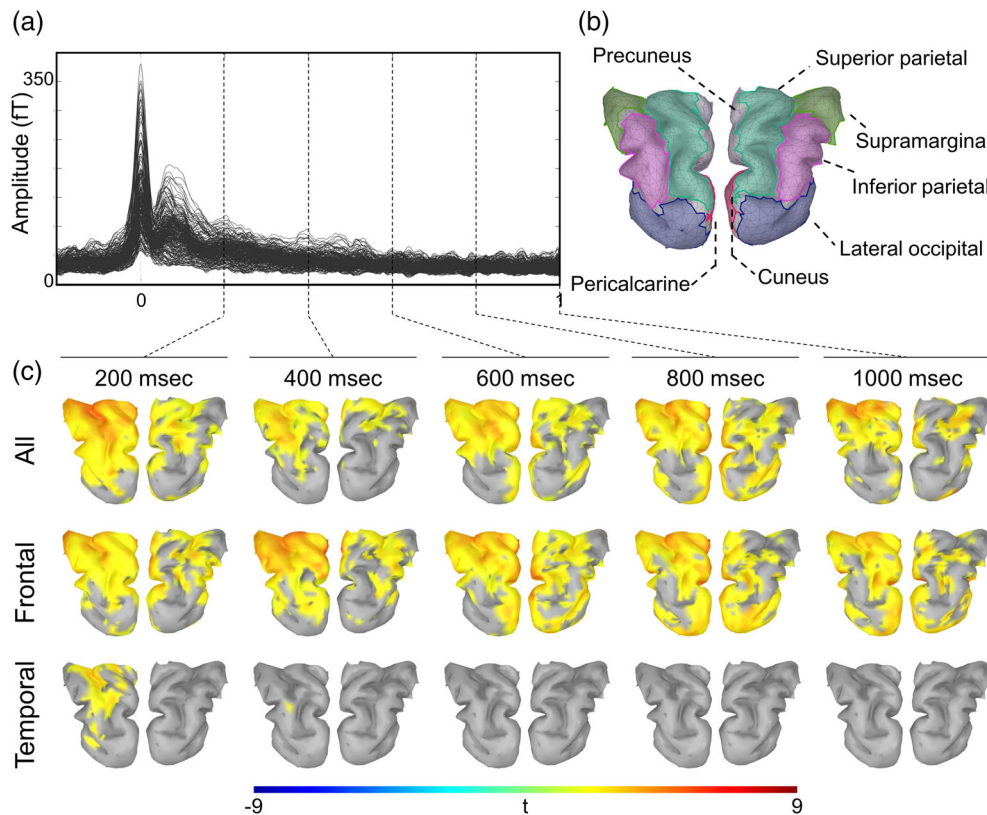


FIGURE 2 (a) Average spike across all patients. Absolute values of magnetoencephalography (MEG) signal were extracted prior to computing the group level average spike. (b) Time-frequency analysis was restricted to the posterior head region, as highlighted in different color-coded regions of interest, to avoid potential volume conduction effects with the main generators of the interictal epileptiform discharges (IEDs). (c) Statistical maps showing the distribution of significant increases in alpha/beta oscillations (12–16 Hz range) in the posterior head regions at different time points along the IEDs, for the entire cohort (first row), frontal lobe epilepsy (FLE) patients (second row) and mesial temporal lobe epilepsy (TLE) patients (third row). Cortical surface has been inflated to improve visibility of represented sources. Note that the FLE group showed a significant, sustained and quite widespread increase of alpha/beta oscillations in bilateral posterior cerebral cortices

3.4 | Relationship between IEDs amplitude and number and alpha/beta oscillations

No significant correlation between the number of IEDs and posterior changes in alpha-beta oscillations was found ($p > .200$ consistently). In contrast, IED amplitude positively correlated with the strength of induced oscillations, for all ROIs in FLE patients (Inferior parietal left: $R = .711$, $p < .001$; Inferior parietal right: $R = .711$, $p = .001$; Precuneus left: $R = .555$, $p = .009$; Precuneus right: $R = .500$, $p = .021$; Pericalcarine left: $R = .482$, $p = .027$; Pericalcarine right: $R = .583$,

$p = .006$). This relationship was robust when controlling for the number of IEDs, as assessed using partial correlation coefficients results.

3.5 | Relationship between alpha-beta oscillations and cognition

A cluster of significant and positive correlation was found between IEDs-triggered oscillations in the posterior head regions and global cognitive performance in FLE patients, suggesting that stronger

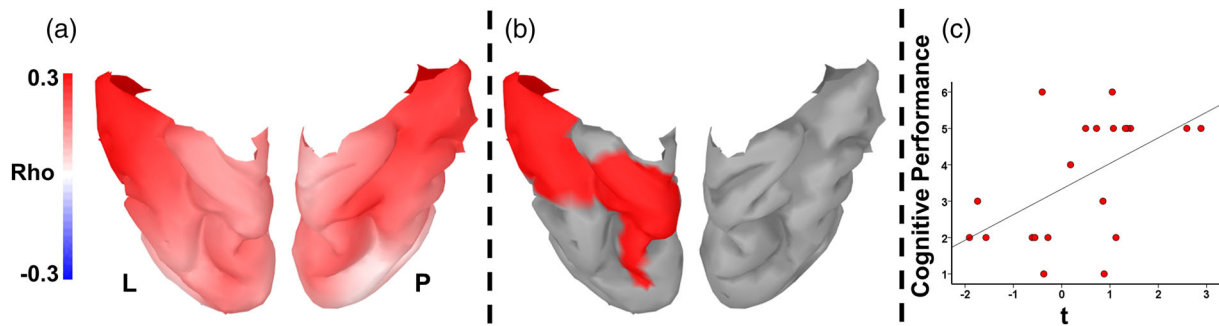


FIGURE 3 (a) Average map of the correlation between alpha/beta oscillations generated in the posterior head regions and cognitive performance. Red indicates positive relationship, with more alpha/beta corresponding to better cognitive performance. L = Left, P = Posterior. (b) Map of the cluster with a significant relationship ($p = .037$) between alpha/beta oscillation and cognition after correction for multiple comparisons with cluster-based permutation approach. (c) Scatterplot of the correlation of data extracted from the cluster reported in (b)

oscillations generated in the posterior head regions pair with better cognitive status. The cluster with the largest t values (corresponding to lower p values and larger R values) occurred after the IEDs in a frequency range between 16 and 21 Hz (Figure 3). The topographical mapping of the correlation in the posterior head regions confirmed this effect (Figure 3).

4 | DISCUSSION

We demonstrated that in FLE patients, alpha-beta oscillations are generated in the posterior head regions in response to IEDs, with stronger oscillations following larger amplitude spikes. More intense alpha-beta oscillations were linked to a better cognitive profile in these patients.

The idea that IEDs could induce a response in distant brain regions is not new, with the concept of “auto-evoked potentials” dating back to 40 years ago. The focus was however mainly on the direct propagation of IEDs rather than on the “reaction” of distant cortical region, and the dynamic of the responses was never fully characterized (Sidrup, 1981). More recently, a pediatric EEG study failed to detect changes in brain activity linked to IEDs (Nair, Morse, Mott, Burroughs, & Holmes, 2014), whereas an intracranial EEG study demonstrated a decrease of gamma activity and an increase of oscillations below 30 Hz in the default mode network (Fahoum, Zelman, Tyvaert, Dubeau, & Gotman, 2013).

This hypothesis that cortical regions at a distance from the epileptic focus may react to IEDs by generating inhibitory activity is supported by multiple arguments. First, diffuse cortical networks exhibit variable degrees of resilience to the effects of IEDs. The higher is the resilience the better is the cognitive profile. Although the mechanisms which determine the degree of resilience remain unknown, they must involve the inhibition of the effects of IEDs (Ibrahim et al., 2014; Lee et al., 2018).

Second, cortical inhibition is known to occur both locally and remotely from the epileptic focus. IEDs are followed by massive local inhibition -supposedly a safety mechanism to protect cerebral cortex

and prevent transition to seizure (De Curtis & Avanzini, 2001; Dorn & Witte, 1995). Cortical excitability is broadly suppressed in patients with epilepsy (Cincotta, Borgheresi, Lori, Fabbri, & Zaccara, 1998), with higher cortical inhibition being linked to better seizure control (Badawy, Macdonell, Berkovic, Newton, & Jackson, 2010).

Third, the depolarization of a large parcel of cortical tissue—as it happens for IEDs—typically triggers oscillatory activity reverberating over other cortical regions (Engel & Fries, 2010; Fuggetta, Fiaschi, & Manganotti, 2005; Mouthaan et al., 2016; Rosanova et al., 2009). For instance, animal studies have demonstrated that IEDs generated in the mesial temporal structures induce oscillations in the frontal lobe and by doing so have a direct effect on cognition (Gelinas, Khodagholi, Thesen, Devinsky, & Buzsáki, 2016).

Fourth, oscillatory activity is a prominent mechanism to tune neuronal firing, to coordinate information transfer across brain regions, and to regulate spike-timing dependent plasticity (Buzsáki & Draguhn, 2004). The functional value of oscillations is largely determined by their frequency (da Silva, 2013), with alpha and beta oscillations having remarkable inhibitory effects (see Section 1).

Our data demonstrates time specific, frequency specific (alpha/beta), and patient specific (only FLE) oscillations in the posterior head regions linked to anterior IEDs (Figure 1). The occurrence of oscillations after IEDs, suggests that they are triggered by the spikes. The specificity for alpha and beta band agrees with our hypothesis of an inhibitory response to interictal transients (Bologna et al., 2019; Engel & Fries, 2010; Gilbertson et al., 2005; Händel et al., 2011; Jensen & Mazaheri, 2010; Joundi et al., 2012; Kelly et al., 2006; Klimesch et al., 2007; Pogosyan et al., 2009; Romei et al., 2007; Sauseng et al., 2009; Swann et al., 2009; Tinkhauser et al., 2017; Waldhauser et al., 2012; Worden et al., 2000). In addition, recent evidence suggests a strong link between the fluctuations of alpha/beta amplitude, the activity of resting state networks (Hipp, Hawellek, Corbetta, Siegel, & Engel, 2012) and post-surgical outcome in patients with drug-resistant epilepsy (Aydin et al., 2020).

A parallel could be drawn between the transient neuronal depolarization due to IEDs and the depolarization that can be experimentally achieved with pulses of transcranial magnetic stimulation (TMS)

TABLE 2 Patients' clinical features

ID	Epilepsy classification	Focus side	Age (years)	Seizures preferentially during sleep	MRI findings	AEDs
1	Frontal	Left	27	Yes	Left orbitofrontal encephalocele	LEV, LTG
2	Frontal	Left	24		Left frontal parasagittal FCD	LTG
3	Frontal	Left	31		Left frontal PMG	CBZ, LEV, CLB
4	Frontal	Left	35	Yes	Left orbitofrontal FCD	LCM, PHT
5	Frontal	Left	19	Yes	Left frontal opercular FCD	CBZ, CLB
6	Frontal	Left	30	Yes	Left frontal FCD	PHT, LTG
7	Frontal	Left	35	Yes	No MRI lesion	LEV, LTG
8	Frontal	Left	28		Left anterior cingulate FCD	CBZ, LCM, CLB
9	Frontal	Left	52		No MRI lesion	LTG, CBZ
10	Frontal	Left	30		No MRI lesion	PHT, LCM
11	Frontal	Right	32		Right hemimegalencephaly	LEV, OXC, CLB
12	Frontal	Right	15		Right frontal FCD	CBZ, CLB
13	Frontal	Right	15	Yes	Right frontal FCD	OXC, CLB
14	Frontal	Right	20	Yes	Right frontal FCD	CBZ, CLB
15	Frontal	Right	32		Right hemimegalencephaly	LEV, OXC, CLB
16	Frontal	Right	41	Yes	No MRI lesion	PB, LEV, CLB
17	Frontal	Right	22		Right frontal FCD	VPA, LTG
18	Frontal	Right	34	Yes	Right frontal FCD	LEV, PB, GBP
19	Frontal	Right	29	Yes	Right frontal FCD	VPA, OXC
20	Frontal	Right	21	Yes	No MRI lesion	PHT, CBZ, LTG, CLB
21	Frontal	Right	35	Yes	No MRI lesion	CBZ, LEV
22	Temporal	Left	42		Left hippocampal atrophy	PHT, LTG, TPM
23	Temporal	Left	29		Left hippocampal atrophy	CBZ
24	Temporal	Left	29		Left amygdala signal abnormality	LEV, CLB
25	Temporal	Left	13	Yes	Left hippocampal malrotation	LEV, TPM, PHT
26	Temporal	Left	38		Left hippocampus malrotation	LEV
27	Temporal	Left	33		Left hippocampal atrophy	OXC, LTG
28	Temporal	Left	46		Left hippocampal atrophy	CBZ, OXC, TPM, LCM
29	Temporal	Left	23		Left hippocampal atrophy	CBZ
30	Temporal	Right	40		Right hippocampal atrophy	LEV
31	Temporal	Right	58		Right hippocampal atrophy	OXC, CLB
32	Temporal	Right	31		Right hippocampal atrophy	CBZ, CLB
33	Temporal	Right	19		Right hippocampal atrophy	LEV
34	Temporal	Right	34		Right hippocampal atrophy	LTG, TPM, CBZ
35	Temporal	Right	23		Right hippocampal atrophy	CBZ, LTG, TPM
36	Temporal	Right	23		Right hippocampal atrophy	CBZ
37	Temporal	Right	39		Right hippocampal atrophy	LEV, CBZ
38	Temporal	Right	32		Right hippocampal atrophy	LAM
39	Temporal	Right	19		Right hippocampal atrophy	GBP, CLB
40	Temporal	Right	25		Right hippocampal atrophy	OXC, LTG
41	Temporal	Right	55		Right hippocampal atrophy	OXC, CLB, LEV

Abbreviations: CBZ, carbamazepine; CLB, clobazam; FCD, focal cortical dysplasia; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PMG, polymicrogyria; VPA, valproic acid.

(Giambattistelli et al., 2014). Combined TMS and EEG studies demonstrate that transient and focal cortical depolarizations trigger distant oscillatory effects, largely centered in alpha and beta band (Fuggetta et al., 2005; Paus, Sipila, & Strafella, 2001; Rosanova et al., 2009). Interestingly, and in agreement with our findings, more intense TMS pulses (i.e., stronger cortical depolarization) trigger stronger oscillations (Fuggetta et al., 2005; Paus et al., 2001).

No significant alpha-beta oscillations were found in TLE patients. It should be noted that MEG has low sensitivity for pure mesial temporal lobe IEDs (Pellegrino, Hedrich, et al., 2018) and IEDs recorded in patients with TLE typically correspond to a mixture of IEDs generated in mesial temporal structures propagated to neocortex (Baumgartner et al., 1995; Sutherling & Barth, 1989) and IEDs primarily generated in temporal neocortex (Alarcon et al., 1994; Wennberg, Valiante, & Cheyne, 2011). As temporal IEDs tend to interact with the homologous contralateral regions and with frontal regions (Emerson, Turner, Pedley, Walczak, & Forgiione, 1995; Gelinis et al., 2016), we performed a dedicated supplementary analysis addressing this aspect. Although no significant effects were found, these results should be taken with caution given the small sample size.

We also observed a steady increase in theta activity, for both TLE and FLE patients, in the period around the IEDs (Figure 1c). Because of their temporal dynamic, which covers the entire 2s (IEDs -1 s to IEDs $+1$ s) time window, theta oscillations do not appear as “reactive” to IEDs. In contrast, they may indicate a state of relax and drowsiness which would have facilitated spikes occurrence (Ferrillo et al., 2000; Frauscher et al., 2015). We performed a supplementary analysis showing a transient increase of theta-delta activity over the course of the recording, which might be compatible with drowsiness. Nonetheless, it cannot be ruled out that slow activity depends on different mechanisms, such as deep IEDs (Tao et al., 2011), cortical dysfunction (Gloor, Ball, & Schaul, 1977), medications (Pellegrino et al., 2018), attention (Cona et al., 2020) or cortical plasticity (Assenza, Pellegrino, Tombini, Di Pino, & Di Lazzaro, 2015; Pellegrino et al., 2017). Similarly, the increase in alpha activity observed in Figure 1 (as early as 0.8 s before the onset of IEDs) might be related to a less engaged state (i.e., lack of alpha-beta desynchronization) susceptible to the generation of epileptiform activity (Pfurtscheller et al., 2003).

A previous small case series reporting on intracranial EEG oscillatory pattern at the time of IEDs (Fahoum et al., 2013) detected an increase of activity below 30 Hz, in agreement with this study, but also a decrease of gamma oscillations in regions of the default mode network. We performed a dedicated analysis for gamma frequency up to 80 Hz, but we did not unveil any significant effect. This is not surprising considering that MEG has far lower sensitivity than invasive EEG in detecting fast activity generated by small and deep generators (Hedrich, Pellegrino, Kobayashi, Lina, & Grova, 2017).

An important observation in our study is the relationship between the alpha-beta oscillations in the posterior head region and cognition: more intense oscillations paired with better cognitive profile. Multiple factors contribute to the chronic cognitive status of focal epilepsy patients and previous literature has provided conflicting results on the possible interaction between IEDs and cognition (Aldenkamp &

Arends, 2004; Binnie, 2003; Kleen et al., 2013; Kleen, Scott, Holmes, & Lenck-Santini, 2010; Krauss, Summerfield, Brandt, Breiter, & Ruchkin, 1997). Rather than weighting the potential negative consequences of IEDs, our results shift the perspective toward the safety mechanisms activated in the “healthy” cortex in response to their occurrence. We speculate that inhibitory oscillations may represent one of the possible mechanisms by which the integrity of functional networks and cognition are preserved (Aldenkamp & Arends, 2004; Ibrahim et al., 2014). In principle, if alpha and beta oscillations have a protective role, they may also be a contributing mechanism for resolved epilepsy (Fisher et al., 2014), but no data is available to support this, warranting future studies.

Previous data demonstrates that, as opposed to TLE, FLE patients do not show a typical and consistent neuropsychology profile, partially because the functions of the frontal lobe are highly difficult to accurately estimate within the context of strictly structured neuropsychological test procedures (Elger, Helmstaedter, & Kurthen, 2004), partially because very often cognitive deficits are not topographically restricted but rather diffuse (Aldenkamp & Arends, 2004; Xiao et al., 2016). Therefore, we opted here for a concise measure of global efficiency, based on the combination of all available information from presurgical neuropsychological assessment. Although such approach prevents us from inferring on the relationship between alpha-beta oscillations and impairment of specific cognitive functions, it provides a reliable estimate of the global cognitive efficiency and of its possible impact on daily life.

For decades there has been a remarkable and unsolved debate on whether antiepileptic medications should be administered to treat IEDs in the attempt to prevent their negative consequences on healthy cortex, especially in children (Aldenkamp & Arends, 2004; Asadi-Pooya, Xiao, & Zhou, 2016; Binnie, 2003; Nordli, Xiao, & Zhou, 2016; Sanchez Fernandez, Loddikenemper, Galanopoulou, & Moshé, 2015; Xiao et al., 2016). If the mechanisms highlighted here could be further validated, new non-pharmacological therapeutic approaches could be attempted to protect “healthy” cortex and to maintain better cognitive performance in persons with epilepsy. Indeed, recent evidence suggests that it is possible to safely modulate oscillations via non-invasive brain stimulation techniques, auditory stimulation and neurofeedback (Bagherzadeh, Baldauf, Pantazis, & Desimone, 2020; Becher et al., 2015; Helfrich et al., 2014; Pellegrino et al., 2019; Sitaram et al., 2017; Thut, Schyns, & Gross, 2011).

In conclusion, our study demonstrated that cerebral cortex protects itself from IEDs with the generation of remote inhibitory alpha/beta oscillations and that this mechanism plays a role in determining the cognitive status of patients with FLE.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Giovanni Pellegrino: Study design, data acquisition, data analysis, data interpretation, manuscript preparation and revision. **Tanguy Hedrich:** Study design, data acquisition and analysis, manuscript revision. **Viviane Sziklas:** Data acquisition, data interpretation, manuscript revision. **Jean Marc Lina:** Data analysis, data interpretation, manuscript revision. **Christophe Grova:** Study design, data acquisition, data analysis, data interpretation, manuscript revision. **Eliane Kobayashi:** Study design, data acquisition, data analysis, data interpretation, manuscript preparation, manuscript revision.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study, as well as the software and/or algorithms essential to the conclusions of this work are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This study was approved by the Research Ethics Board of the Montreal Neurological Institute and Hospital – McGill University Health Center and complies with the Declaration of Helsinki and its later amendments.

PATIENT CONSENT STATEMENT

All participants signed a written informed consent prior to enrollment.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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