Epilepsia

Neocortical and medial temporal seizures have distinct impacts on brain responsiveness

Simone Russo[1,2,3] | Ezequiel Mikulan[1] | Flavia Maria Zauli[1,3,4] | Ivana Sartori[4] |
Michela Solbiati[1] | Giulia Furregoni[1] | Marta Porro[1,3] | Martina Revay[4] |
Mario Rosanova[1] | Olivier David[5] | Marcello Massimini[1,6,7] | Laura Tassi[4] |
Andrea Pigorini[4,8] [iD]

[1]Department of Biomedical and Clinical Sciences "L. Sacco", University of Milan, Milan, Italy

[2]Allen Institute for Brain Science, Seattle, Washington, USA

[3]Department of Philosophy 'Piero Martinetti', University of Milan, Milan, Italy

[4]"Claudio Munari" Epilepsy Surgery Centre, Azienda Socio Sanitaria Territoriale Grande Ospedale Metropolitano Niguarda, Milan, Italy

[5]Inserm, INS, Institut de Neurosciences des Systèmes, Aix Marseille Université, Marseille, France

[6]Azrieli Program in Brain, Mind and Consciousness, Canadian Institute for Advanced Research, Toronto, Ontario, Canada

[7]IRCCS, Fondazione Don Carlo Gnocchi, Milan, Italy

[8]Department of Biomedical, Surgical and Dental Sciences, University of Milano, Milan, Italy

Correspondence
Andrea Pigorini, Department of Biomedical, Surgical and Dental Sciences, University of Milano, Milan, Italy.
Email: andrea.pigorini@unimi.it

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Abstract

Focal epileptic seizures are characterized by abnormal neuronal discharges that can spread to other cortical areas and interfere with brain activity, thereby altering the patient's experience and behavior. The origin of these pathological neuronal discharges encompasses various mechanisms that converge toward similar clinical manifestations. Recent studies have suggested that medial temporal lobe (MTL) and neocortical (NC) seizures are often underpinned by two characteristic onset patterns, which, respectively, affect and spare synaptic transmission in cortical slices. However, these synaptic alterations and their effects have never been confirmed or studied in intact human brains. To fill this gap, we here evaluate whether responsiveness of MTL and NC are differentially affected by focal seizures, using a unique data set of cortico-cortical evoked potentials (CCEPs) collected during seizures triggered by single-pulse electrical stimulation (SPES). We find that responsiveness is abruptly reduced by the onset of MTL seizures, despite increased spontaneous activity, whereas it is preserved in the case of NC seizures. The present results provide an extreme example of dissociation between responsiveness and activity and show that brain networks are diversely affected by the onset of MTL and NC seizures, thus extending at the whole brain level the evidence of synaptic alteration found in vitro.

1 | INTRODUCTION

Focal epileptic seizures are periods of abnormally excessive and/or synchronous neuronal activity in the brain that originate in a circumscribed region and spread throughout a network of connected areas, impairing brain and cognitive functions.[1]

This broad definition of focal seizures encompasses a heterogenous group of neurological disorders caused by different alterations. In particular, a current hypothesis is that medial temporal lobe (MTL) and neocortical (NC; both temporal and extratemporal) seizures are underpinned by different mechanisms, as reflected by their distinctive clinical features,[2] seizure thresholds,[3] anatomic features (archicortex vs neocortex), and seizure-onset patterns.[4] Specifically, MTL seizures are hypothesized to be triggered by an enhancement of either excitatory or γ-aminobutyric acid (GABA) activity, whereas NC seizures are thought to be triggered by an increase of the extracellular potassium concentration.[4] Although these two mechanisms have been characterized extensively at the cellular and synaptic levels with in vitro and in vivo models,[5,6] their consequences at the network level as well as their generalization to humans remain elusive.

Cortico-cortical evoked potentials (CCEPs) have been employed to characterize the local excitability of epileptogenic areas,[7] to compare early and late seizure propagation patterns,[8] and to identify regions showing epileptic responses.[9] Notably, CCEPs have proved to be effective in capturing fast plastic changes before seizure onset[10] and have also been suggested as a proxy to characterize acute alterations of synaptic transmission across different ictal-onset patterns.[4]

In the present work, we employed CCEPs to evaluate the impact of MTL and NC seizures on the responsiveness and connectivity of the epileptogenic area. To this aim, we collected stereo-electroencephalography (SEEG) recordings during seizures triggered by single-pulse electrical stimulation (SPES) of either MTL or NC structures,[11,12] and compared the CCEPs collected immediately before and after the seizure onset.

2 | MATERIALS AND METHODS

2.1 | Participants, SPES, and data acquisition

As shown in Figure S1, we screened patients affected by focal drug-resistant epilepsy who underwent SEEG investigations at the "C. Munari" Epilepsy Surgery Center between January 2017 and October 2020. Patients were selected based on the following inclusion criteria: (1) >18 years of age, (2) at least one seizure evoked by SPES, and (3) at least five SPES pulses (out of 15) delivered before and after the seizure onset. We included only seizures showing both electrical and clinical (video-recorded ictal exam) manifestations. Each patient signed the informed consent to participate in the study, which has been approved by the local ethics committee (ID.348–24062020, Comitato Etico Milano Area 3). Data were acquired through a Nihon Kohden Neurofax 1200 EEG Amplifier with a sampling rate of 1000 Hz. Bipolar SPES pulses (15 square biphasic pulses; intensity: 3–5 mA; duration: 0.5–1 ms) were delivered at rest between two contiguous SEEG contacts pertaining to the same electrode at 1 Hz frequency. Each stimulation session was classified as MTL or NC, according to the stimulated area (hippocampus/parahippocampus or neocortex, respectively). As a control group, we also included 12 recording sessions (from 11 patients) during which SPES of the MTL did not induce any seizure.

2.2 | Seizure characterization

All seizures included in the current study were elicited by SPES at the site of stimulation during video-SEEG monitoring. Behavioral and electrical evaluation of seizures as well as the identification of their onset were performed online and reviewed retrospectively based on SEEG recordings by trained neurologists and neurophysiologists (FZ, IS, and LT). Seizure-onset time was determined as the first sign of epileptic activity on any channel.

2.3 | Imaging analysis

Magnetic resonance imaging (MRI) sequences and computed tomography (CT) scans were acquired before and after the implantation of SEEG electrodes and coregistered.[13] Localization of SEEG contacts was automatically extracted using Freesurfer and SEEG Assistant, and then manually fine-tuned by a trained neurophysiologist (EM). Anatomic labels for each contact were obtained employing the Desikan-Killany atlas and verified by a trained neurosurgeon (MRe).

2.4 | CCEP preprocessing and quantification

The SEEG data were analyzed employing custom-made MATLAB scripts. The stimulation artifact was removed through a Tukey filter; then the signal was high-pass filtered (third-order Butterworth; cutoff: 1 Hz), split in epochs (from −300 to 700 ms), baseline corrected (from −290 to −10 ms), and visually inspected by a trained neurophysiologist (SR) to exclude electrical artifacts from further analyses. Finally, the activity of each contact was z-scored with respect to the mean and standard deviation (SD) of the concatenated baselines of all trials (ictal and interictal).

The quantifications on the elicited CCEPs were performed between 10 and 150 ms to focus mainly on direct cortico-cortical connectivity. Contacts showing CCEPs exceeding 6 SD from the baseline—in at least one condition—were considered as responsive to SPES[14] and used for further analyses. For these contacts we quantified the power of the response in each condition as the average square of the CCEP within the 10–150 ms time-window.

The power of spontaneous activity in the baseline in the gamma band was calculated by applying a high-pass filtered (>20 Hz, third-order Butterworth) and by averaging across trials.

Statistical analyses were performed using a mixed-effects model and post hoc comparisons were obtained using estimated marginal means.

3 | RESULTS

We retrospectively screened a database of 130 patients (see Figure S1) and found 12 patients fulfilling the inclusion criteria—mainly because SPES rarely elicits seizures. From these 12 patients we retrieved 19 seizures evoked by SPES. Specifically, 12 seizures were elicited by SPES
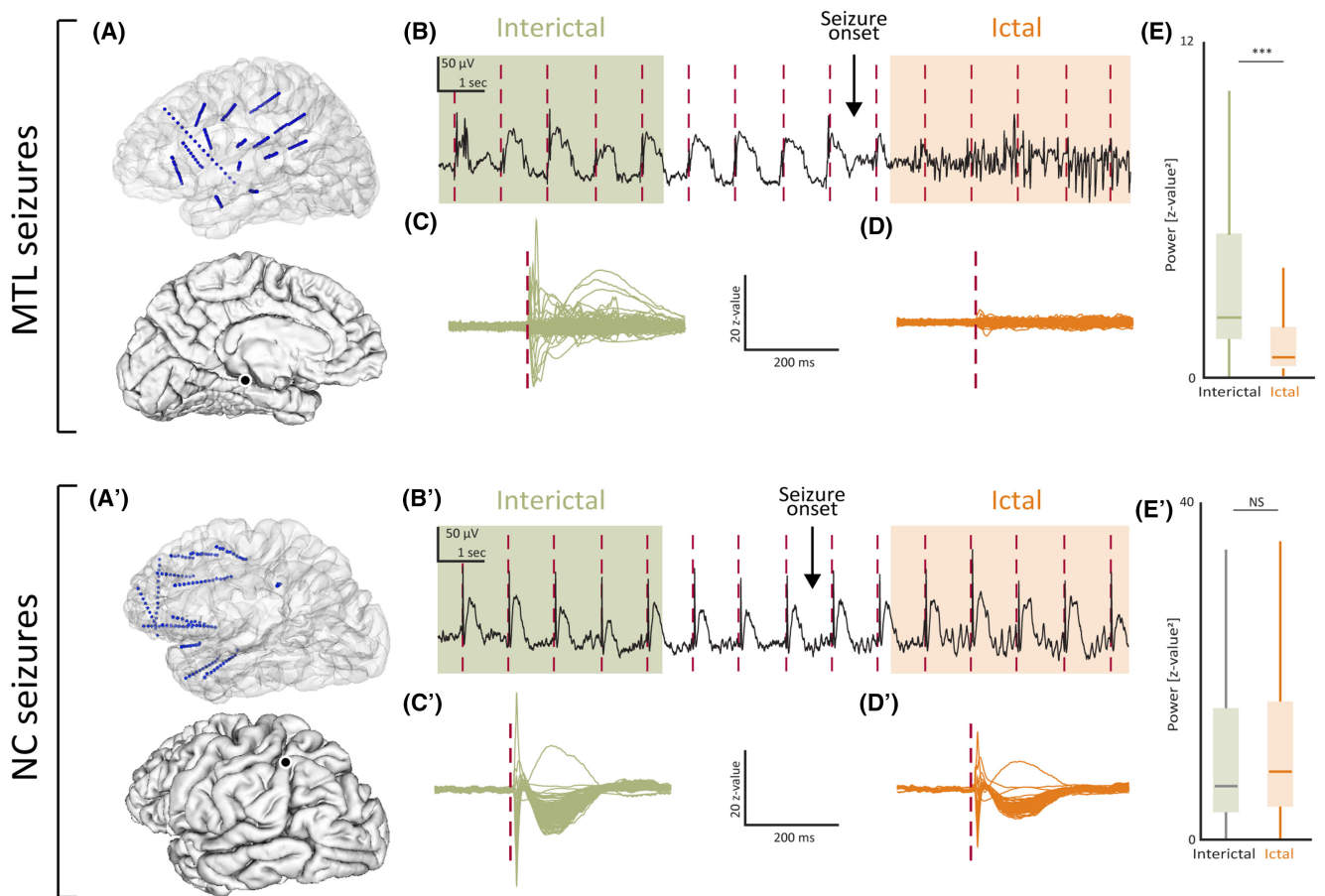

FIGURE 1 Upper panels refer to MTL seizures; bottom panels refer to NC seizures. In both cases, A shows the location of the recording contacts (upper section, blue dots) and stimulating contacts (lower section, black dots) in the 3D reconstruction of the subject's brain surface. The activity of a responding contact is shown in B, together with the highlight on the interictal (gray) and ictal (red) period. C and D show the CCEP obtained from all SEEG contacts by averaging interictal trials and ictal trials, respectively. E illustrates the associated broadband CCEPs (p: *** <.001; NS, nonsignificant; outliers not shown). CCEPs, cortico-cortical evoked potentials; MTL, medial temporal lobe; NC, neocortical.

TABLE 1 Demographic and clinical details for each patient.

Subject ID	Group	Stimulated area	Sex	Age	Anatomic malformations	Epileptogenic area
1	NC seizures	Left temporal pole	F	32	Negative	Left insula
2	NC seizures	Right parietal opercolum	M	46	Negative	Multifocal
3	NC seizures	Right superiortemporal gyrus	F	32	Negative	Superior temporal gyrus
4	NC seizures	Right superiortemporal gyrus	M	23	Periventricular peritrigonal bilaterl nodular heterotopia	Left nodule
5	NC seizures	Right central sulcus	F	23	Right postcentral malformation	Central sulcus, postcentra gyrus, and motor operculum
6	NC seizures	Left long gyri of insula	F	26	Large perisilvian ischemic lesion	Superior temporal gyrus
7	NC seizures	Left intraparietal sulcus	F	28	Left fronto-insular atrophyand hippocampal sclerosis	Left mesiotemporal structures
1	MTL seizures	Left parahippocampus	F	32	Negative	Left insula
2	MTL seizures	Right hippocampus	M	46	Negative	Multifocal
3	MTL seizures	Left hippocampus	F	32	Negative	Superior temporal gyrus
3	MTL seizures	Right hippocampus	F	32	Negative	Superior temporal gyrus
4	MTL seizures	Left hippocampus	M	23	Periventricular peritrigonal bilateral nodular heterotopia	Left nodule
8	MTL seizures	Left hippocampus	M	50	left parietal-insular ulegirya	Supramarginal gyrus, mesial-temporal strctures, long gyri of insula
9	MTL seizures	Right hippocampus	F	40	Negative	Hippocampus, insula, and superior temporal gyris
9	MTL seizures	Left hippocampus	F	40	Negative	Hippocampus, insula, and superior temporal gyris
9	MTL seizures	Left parahippocampus	F	40	Negative	Hippocampus, insula, and superior temporal gyris
10	MTL seizures	Left parahippocampus	F	45	Negative	Hippocampus, inferior temporal lobe, temporal pole, occipitotemporal gyrus
11	MTL seizures	Left parahippocampus	M	37	Negative	Hippocampus, amygdala, temporal pole, superior temporal gyrus, orbitofrontal cortex
12	MTL controls	Right hippocampus	M	35	Negative	Unknown
13	MTL controls	Right hippocampus	F	25	Negative	Long insular gyri, central operculum, parietal operculum
15	MTL controls	Right parahippocampus	M	24	Double cortex	Unknown

Ictal symptoms (during chocs)	Hemisphere SEEG	Therapy	Outcome
Pulsation of the left hand, confusion	Left	CBZ 1000 mg/day; FBM 1800 mg/day; ESL 400 mg/day	RFTC: III; Surgery: IV
Slight confusion	Bilateral	LEV 2000 mg/day; CBZ 800 mg/day; lorazepam 1 mg/day	Surgery III
Confusion, impared reading, blinking, deviation of the left labial fold, auditory hallucination	Bilateral	CBZ 1200 mg/day; TPM 150 mg/day	Surgery: I
Deviation of the left labial fold, delay in naming objects	Bilateral	LEV 1500 mg/day; LTG 400 mg/day; CLB 10 mg/day	RFTC II
Impaired language and dizziness	Right	VPA 1500 mg/day; LCM 400 mg/day	Surgery: I
Nausea	Left	LEV 1000 mg/day	RFTC III
Dizziness	Left	CBZ 1200 mg/day; CLB 6 mg/day	Surgery: I
Dizziness, nausea, confusion	Left	CBZ 1000 mg/day; FBM 1800 mg/day; ESL 400 mg/day	RFTC: III; Surgery: IV
Altered visus, dizziness	Bilateral	LEV 2000 mg/day; CBZ 800 mg/day; lorazepam 1 mg/day; risperidone 4 mg/day	Surgery: III
Impaired reading; discomfort of mouth and tongue	Bilateral	CBZ 1200 mg/day; TPM 150 mg/day	Surgery: I
Impaired language	Bilateral	CBZ 1200 mg/day; TPM 150 mg/day	Surgery: I
Altered faccial expression	Bilateral	LEV 1500 mg/day; LTG 400 mg/day; CLB 10 mg/day	RFTC II
Epigastric aura	Left	LTG 300 mg/day; LCM 300 mg/day; Triatec 5 mg/day	RFTC: Ib
Epigastric aura, impaired swallowing	Bilateral	LTG 400 mg/day; PMP 8 mg/day	RFTC: III
Epigastric aura	Bilateral	LTG 400 mg/day; PMP 8 mg/day	RFTC: III
Epigastric aura	Bilateral	LTG 400 mg/day; PMP 8 mg/day	RFTC: III
Epigastric aura, altered facial expression	Left	CBZ 600 mg/day	RFTC IV; Surgery: II
Anxiety	Left	BRV 200 mg/day; CBZ 2000 mg/day	RFTC: Ib
none	Right	LAC 200–0 – 300 mg/day; LEV 500–0 – 500 mg/day; TPM 75–0 – 75 mg/day	RFTC: Ia
none	Right	TPM 300 mg/day; LEV 3000 mg/day	RFTC: III; Surgery: II
none	Bilateral	CBZ 800 mg/day; LTG 200 mg/day	RFTC: III; Surgery IV

TABLE 1. Continued

Subject ID	Group	Stimulated area	Sex	Age	Anatomic malformations	Epileptogenic area
16	MTL controls	Left hippocampus	F	43	Negative	Left inferior temporal gyrus, superior temporal gyrus and hippocampus
17	MTL controls	Right hippocampus	M	44	Negative	Hippocampus
18	MTL controls	Left hippocampus	M	44	Negative	Hippocampus
18	MTL controls	Left hippocampus	F	26	Left periventricular nodular heterotopia	Left temporobasal gyrus, temporo-occipital junction, Mesiotemporal structures, Temporal pole, Nodule
19	MTL controls	Right hippocampus	F	29	Right periventricular nodular heterotopia	Right nodule
20	MTL controls	Left hippocampus	F	39	Negative	Left mesiotemporal structures
22	MTL controls	Right hippocampus	F	23	Periventricular nodular heterotopia from temporal pole to occipital horn and temporal-occipital neocortex	Right heterotopia, Inferior temporal gyrus, Temporo-occipital junction, Inferior occipital gyrus
23	MTL controls	Right hippocampus	F	32	Negative	Right temporal neocortex (middle and inferior temporal gyrus), mesiotemporal structures
24	MTL controls	Right hippocampus	M	43	Negative	Right temporal neocortex

Note: Each Subject ID identifies one patient, which could have been stimulated in NC, in MTL, or both. Outcomes are expressed in Engel classes.

Abbreviations: BRV, Brivaracetam; CBZ, carbamazepine; CLB, Clobazam; ESL, Eslicarbazepine; F, female; FBM, Felbamate; LCM, Lacosamide; LEV, Levetiracetam; LTG, Lamotrigine; M, male; MTL, Medial-temporal lobe; NC, Neocortical; OXC, Oxcarbazepine; PB, Phenobarbital; PMP, Perampanel; PRM, Primidone; RFTC, radio-frequency thermo-coagulation; SEEG, stereo-electroencephalography; TPM, Topiramate; VPA, Valproic acid; ZNS, Zonisamide.

delivered to MTL sites (from nine patients), while 7 seizures were induced by NC stimulation (from seven patients). Demographic and clinical information for each subject is reported in Table S1.

When stimulating MTL sites (Figure 1A), we observed that CCEPs—which were clearly visible at the single trial level during the interictal phase—were obliterated by the seizure onset (Figure 1B). This effect comprised all channels (Figure 1C,D) and was statistically significant at the group level, as assessed by a linear mixed-model analysis ($p < .001$ – Figure 1E; see also Table S1 for a complete report of this analysis). Of note, we verified that this phenomenon was specific to ictal events by performing the same analysis on 11 control sessions during which SPES delivered to MTL did not induce seizures. In this case, the comparison between early (first five pulses) and late (last five pulses) CCEPs did not show any significant difference (Figure S2).

At odds with MTL, CCEPs evoked by stimulating NC sites (Figure 1A′, Table 1) were not influenced by the occurrence of seizures (Figure 1B′). Indeed, interictal and ictal CCEPs were similar in terms of overall response, as confirmed by the linear mixed-effect model analysis ($p = .30$ – Figure 1E′, Table S1). It is important to note that for both MTL and NC sessions, similar results were obtained when including in the analysis either only contacts directly involved by the ictal activity (MTL: $p < .001$; NC: $p = .403$) and only contacts not directly involved by the ictal activity (MTL: $p < .001$; NC: $p = .6790$). Furthermore, similar results were obtained when including in the analysis only contacts located at more than 2 cm from the stimulated site (MTL: $p < .001$; NC: $p = .216$).

At odds with reactivity, spontaneous activity, indexed by ongoing gamma power (calculated over the baseline of each trial), showed a significant increase with respect to interictal activity, which was more prominent in the case of MTL as compared to NC seizures. Specifically, while during MTL seizure the increase of gamma power was 103.38% with respect to interictal activity ($p < .001$), during NC seizure the increase of gamma power was 15.94% ($p < .001$).

Ictal symptoms (during chocs)	Hemisphere SEEG	Therapy	Outcome
None	Left	CBZ 2000 mg/day; PRM 1250 mg/day	RFTC: II; Surgery: Ib
None	Right	CBZ 1200 mg/day; PMP 6 mg/day	RFTC: Ia
None	Right	CBZ 1200 mg/day; PMP 6 mg/day	RFTC: Ia
None	Left	LEV 3000; LTG 400 mg/day	Surgery:III
None	Bilateral	LEV 2000 mg/day; CBZ 800 mg/day	RFTC: Ib
None	Left	CBZ 1000 mg/day; LEV 2750 mg/day; CLB 10 mg/day	RFTC Ic
None	Bilateral	LEV 3000 mg/day; OXC 1200 mg/day	RFTC: III
None	Bilateral	CBZ 800 mg/day; ZNS 200 mg/day; CLB 20 mg/day	RFTC Ia
None	Right	CBZ 1400 mg/day; LTG 400 mg/day; PB 100 mg/day	RFTC: Id

4 | DISCUSSION

The aim of the present study was to assess whether seizures originating in different brain regions (medial temporal lobe vs neocortex) diversely impact responsiveness and effective connectivity. To this aim, we compared CCEPs recorded immediately before and after the onset of seizures induced by SPES of either MTL or NC. We showed that seizures triggered by the stimulation of MTL structures led to an immediate reduction of responsiveness whereas NC seizures did not.

MTL seizures can be initiated by the excessive activity of multiple neuronal types (including both excitatory and inhibitory)[15,16] that disrupts the local excitation/inhibition balance. This pathological activity propagates throughout the network, potentially saturating or inhibiting the engaged circuits.[17,18] This can lead to a refractory state during which electrical stimulation fails to engage the network, resulting in the obliteration of CCEPs.

At odds with MTL seizures, Gnatkovski and colleagues showed that the onset of NC seizures in humans is characterized by a sharp, high-amplitude deflection followed by low-voltage fast activity—named P-type pattern.[6] It is important to note that a similar onset pattern has also been found in the guinea pig model of olfactory seizures, suggesting that both cases might be mediated by analogous mechanisms.[4,6] Specifically, the seizure might be initiated by an increase of the extracellular potassium concentration at the synaptic level gradually moving toward the neuronal body.[4] As a consequence, during the early phase of NC seizures (<5 s), synaptic transmission may be preserved and play a crucial role in the initial local propagation of the ictal discharge. In vitro, as soon as this depolarizing wave of extracellular potassium reaches the neuronal axon and body (~10 s), it hampers synaptic transmission.[6] If this is also the case in humans, CCEPs might be reduced during later phases of NC seizures; however, testing this hypothesis would require future studies delivering SPES over a longer time window.

In sum, the observed selective reduction of responsiveness characterizing MTL—but not NC—seizures, is in line with previous in vitro findings on neuronal alterations,[4–6]

and might represent a possible in vivo, macro-scale counterpart of these micro-scale mechanisms.

At the macro-scale level, the most evident consequence of the reduction of responsiveness during MTL seizure is the disruption of effective connectivity—that is, in our data CCEPs are reduced or abolished not only locally, but also at distant sites—despite a remarkable increase in gamma power activity (i.e., neuronal firing). This increase in gamma power is associated with a local neuronal hypersynchronization,[19] which can curtail the inputs and/or the outputs of the stimulated area (i.e., pre-synaptic impairment). Another possibility is that distant cortical sites become unresponsive to the stimulation when engaged by the seizure (i.e., post-synaptic impairment). Both mechanisms can lead to a loss of information transmission from the stimulated area to the rest of the network, thus breaking down effective connectivity. It is important to note that our results indicate that CCEPs are obliterated even in contacts not directly involved by MTL seizures, thus suggesting a pre-synaptic impairment.

Further elucidating the contribution of these mechanisms would require exploring the connectivity of areas other than the stimulated one (i.e., remote sites) by perturbing different sites during both spontaneous and evoked seizures. In this respect, our findings suggest that a perturbational approach—including invasive and non-invasive techniques[20]—constitutes an invaluable tool to investigate the network alterations responsible for the impairment of brain functions during seizures.

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ORCID
Andrea Pigorini https://orcid.org/0000-0002-1856-3413

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SUPPORTING INFORMATION

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