RESEARCH ARTICLE

Relationship Between Brain Activity and Impaired Consciousness in Frontal Lobe Seizures

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Abstract

Background and Objectives

Impaired consciousness in epilepsy negatively affects quality of life. Previous work has focused on temporal lobe seizures, where cortical slow waves are associated with depressed subcortical arousal and impaired consciousness. However, it is unknown whether frontal lobe seizures also show cortical slow waves or a different activity pattern with impaired consciousness.

Methods

Intracranial EEG (icEEG) recordings from patients at 3 centers were retrospectively assessed to identify seizures originating in the frontal lobe. Seizures were classified as focal preserved consciousness (FPC), focal impaired consciousness (FIC), or focal to bilateral tonic-clonic (FBTC) based on video review. Changes in icEEG power from preictal baseline were calculated in different cortical regions and across frequency ranges in these 3 seizure categories.

Results

Sixty-five seizures in 30 patients (mean age 27.7 years, 43% female) were analyzed. Frontal lobe FPC seizures showed approximately 40% icEEG power increases in the frontal lobe of onset across frequency ranges, with smaller changes in other regions. Frontal lobe FIC seizures showed approximately 50% power increases, not significantly different from FPC seizures in the lobe of onset ($p = 0.519$, 95% CI −25.8 to 50.4), but with significantly greater power increase in other widespread cortical regions ($p < 0.001$, 95% CI 14.1–45.3). It is important to note that the widespread icEEG power increases in FIC seizures occurred not just in the slow-wave frequency range, but broadly across other frequencies including fast activity. However, the widespread power increases in FIC seizures differed from those of FBTC seizures where icEEG power increases were much greater at approximately 600%, significantly greater than in FIC seizures in both the frontal lobe of onset and other cortical regions ($p < 0.001$, 95% CI 330.1–781.9 and 375.3–818.2, respectively).

Discussion

The widespread power increases across frequencies in frontal lobe FIC seizures contrast with those in focal temporal lobe epilepsy, where impaired consciousness is associated with cortical slow waves. These findings suggest that different focal seizure types produce impaired consciousness by affecting widespread cortical regions but through different physiologic mechanisms. Insights gained by studying the physiology of impaired consciousness may be the first step toward developing novel treatments to prevent this significant negative consequence of epilepsy and improve quality of life.

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Supplementary Material

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Glossary

3D = 3-dimensional; **FBTC** = focal to bilateral tonic-clonic; **FIC** = focal impaired consciousness; **FLE** = frontal lobe epilepsy; **FPC** = focal preserved consciousness; **icEEG** = intracranial EEG; **TLE** = temporal lobe epilepsy.

Introduction

Consciousness is essential to normal human life. Both impaired consciousness and normal consciousness have their anatomical basis in widespread regions of the association cortex regulated by subcortical arousal systems.[1,2] Impaired consciousness is a serious clinical manifestation in epilepsy, affecting quality of life, safety, and emotional health. In recent decades, several studies have investigated mechanism of impaired consciousness during generalized and focal seizures, with many investigations on temporal lobe epilepsy (TLE), the most common type of focal epilepsy.[3-6] Despite these advances, there is limited information on mechanisms of impaired consciousness in frontal lobe epilepsy (FLE), the second most common focal epilepsy type.

Studies in TLE suggest that at least 2 nonmutually exclusive mechanisms may contribute to impaired consciousness. One mechanism, based on the global neuronal workspace theory, posits abnormal cortical-cortical and cortical-thalamic synchrony.[3,4,7] Specifically, this theory suggests that loss of consciousness results from the propagation of low-complexity, hypersynchronous seizure activity from the focal onset zone into the global neuronal workspace, particularly involving frontoparietal association cortices, leading to a collapse in cortical complexity and pathologic hyperconnectivity.[8,9] A second mechanism, the network inhibition hypothesis, posits that focal TLE seizures inhibit subcortical arousal systems, leading to cortical slow waves and impaired consciousness.[5,10,11] Indeed, intracranial EEG (icEEG) studies of TLE seizures with impaired consciousness have shown prominent delta frequency (1–4 Hz) slow waves in widespread areas of the association cortex.[5,10] The network inhibition hypothesis is further supported by animal models where decreased subcortical arousal leads to cortical slow waves and impaired consciousness in focal hippocampal seizures.[12-14] Studies based on both proposed mechanisms of impaired consciousness in TLE have contributed to the development of novel neurostimulation therapies aimed at restoring consciousness during and after seizures.[15-17]

FLE differs from TLE, as FLE exhibits greater clinical and behavioral heterogeneity ranging from paroxysmal emotional outbursts, or unilateral elementary motor signs, to large-amplitude bilateral hyperkinetic movements. Some of the electroclinical heterogeneity in FLE may be attributed to the large anatomical representation and variegated functions of the frontal lobes.[18,19] Investigation of the mechanisms of impaired consciousness in FLE has so far been limited to 1 systematic study, which showed increased frontoparietal synchrony correlated with impaired consciousness, in keeping with the global workspace theory.[20] However, it is not known whether additional mechanisms may also contribute to impaired consciousness. For example, an important question is whether impaired consciousness in FLE, like TLE, is accompanied by widespread cortical slow-wave activity outside the region of seizure onset, or whether a different activity pattern may be present in FLE.

Therefore, our goal was to investigate icEEG patterns across a range of frequencies in a relatively large sample of frontal lobe seizures with and without impaired consciousness. We defined focal preserved consciousness (FPC) and focal impaired consciousness (FIC) seizures based on behavioral review. We found that frontal lobe FIC seizures had abnormal increased activity in widespread brain regions in contrast to FPC seizures where increased activity was confined mainly to the frontal lobe of seizure onset. It is important to note that the increased activity in frontal lobe FIC seizures occurred across a broad range of frequencies, not just slow waves, therefore differing from TLE. Finally, we differentiated frontal lobe FIC seizures from focal to bilateral tonic-clonic (FBTC) seizures, by demonstrating that, although FBTC seizures also involve widespread brain areas across a range of frequencies, the increases in FBTC seizures were over 10 times greater than in frontal lobe FIC seizures.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

All procedures were in accordance with the institutional review boards for human studies at Yale University School of Medicine, NYU Grossman School of Medicine, and Icahn School of Medicine at Mount Sinai. Informed consent was obtained from all participants according to the Declaration of Helsinki.

Patients and Seizures

Patient and seizure selection criteria, along with a flow diagram, and clinical and demographic information of all included patients are provided in eMethods, eFigure 1, and eTable 1.

Behavioral Analysis

Onset and offset times of all seizures (defined in EEG Analysis) were provided to a reviewer (E.S.) of seizure videos blinded to the EEG recordings. Behavioral analysis proceeded in 2 stages: In the first stage, seizures were screened for exclusion criteria (mentioned in eMethods), and FBTC seizures

were identified by typical behavioral features, with the time of the onset of generalization determined behaviorally based on head or eye version, vocalization, or asymmetric tonic facial contraction, as in previous studies.[21-24] In the second stage, consciousness was assessed as follows:

1. For each seizure, all stimuli that would elicit a response in a normal awake individual and the associated responses were documented in detail.
2. Responses were scored as impaired or spared by the following criteria:
   - No response at all = impaired.
   - Eye and/or head orientation toward the stimulus as the only response = impaired.
   - Purposeless limb movements and/or unintelligible sounds in response to stimuli = impaired. Sounds or movements that were typical seizure manifestations were not listed as responses.
   - Appropriate, meaningful response = spared.
3. Next, overall behavior during the seizure was rated as follows:
   - All responses during the seizure spared = spared seizure.
   - All responses during the seizure impaired = impaired seizure.
   - Some responses during the seizure spared but others impaired = inconclusive. If the reviewer was uncertain whether a stimulus/response was impaired, then the entire seizure was reviewed by 2 additional reviewers (A.V., H.B.) to decide on final ratings by consensus. If consensus could not be reached, the seizure was rated as inconclusive. As mentioned in the eMethods, inconclusive seizures were relatively uncommon and were excluded from the analysis.
4. Finally, seizures were categorized into 3 groups: (i) FPC, focal seizures with spared behavioral responses as per criteria above; (ii) FIC, focal seizures with impaired behavioral responses; (iii) FBTC. Rationale for using responsiveness rather than awareness (recall of experiences during seizures) for classification of FPC and FIC is mentioned in eMethods. All FBTC seizures had impaired behavioral responses.

Anatomic Localization of Electrode Positions

Electrode locations were determined based on clinical factors, and therefore were not standardized. However, because electrodes were placed at a time when grid electrodes were historically more common, we obtained relatively extensive cortical coverage. Of the 30 patients, 24 patients received a combination of subdural grid, strip, and depth electrodes while 6 received depth electrodes only. Seventeen implants were bilateral, 5 left hemisphere only, and 8 right hemisphere only.

Electrodes were localized as follows:

1. At Yale, postoperative CT scans were used to identify electrode locations. The postoperative CT scan was first coregistered to the postoperative MRI for each patient, which was then coregistered to the preoperative MRI, as described previously.[25,26]
2. At Mount Sinai, the postimplantation CT was coregistered to the preoperative MRI.
3. At NYU, electrodes were localized using postoperative MRI. Subsequently, the postimplantation MRI was coregistered to the preimplantation MRI, as described previously.[26,27]

Electrode contacts for each patient were assigned to regions defined previously,[10] with the Rolandic region split along the central sulcus into frontal and parietal regions, to obtain the following locations:

1. Ipsilateral frontal—medial, lateral, and orbital frontal electrodes in the hemisphere of seizure onset.
2. Ipsilateral extrafrontal—occipital, parietal, and temporal electrodes in the hemisphere of seizure onset.
3. Contralateral frontal—medial, lateral, and orbital frontal electrodes in the hemisphere contralateral to seizure onset.
4. Contralateral extrafrontal—occipital, parietal, and temporal electrodes in the hemisphere contralateral to seizure onset.

icEEG and Video Recordings

At Yale, icEEG signals were recorded using either Bio-Logic (Bio-Logic Systems Corp., Mundelein, IL) [before 2011] or NATUS/Neuroworks (Natus Medical Incorporated, Middleton, WI) [after 2011] systems with sampling rates of 256 and 1,024 Hz, respectively. At NYU, icEEG signals were acquired using either the BMSI 5000/6000 EEG system (Nicolet Biomedical, Inc., Madison, WI) or NATUS/Neuroworks with a sampling rate of 512 Hz. At Mount Sinai Center, icEEG signals were acquired through NATUS/Neuroworks with sampling rates of 500, 512, and 1,000 Hz.

Signals were recorded relative to a reference electrode chosen by the clinical team to minimize visible noise artifact on the EEG in all 3 centers. Reference electrodes could include skull pegs affixed to the bone, white matter contacts, mastoid process scalp contacts, or inverted intracranial electrode strips with the insulated side facing the brain surface and the conducting side facing the skull.

EEG Analysis

Time of electrographic seizure onset and end and the electrodes involved in seizure onset were first identified by expert EEG readers (A.V., E.S.) by visual inspection. This information was used in the exclusion criteria already described and in subsequent analysis. Artifacts were also delineated for each channel by visual inspection and removed from the analysis. EEG data were then processed using fast Fourier transform in MATLAB R2018b (Mathworks, Natick, MA) in 1-second nonoverlapping data segments for each electrode, and the average signal power was calculated within the

following frequency bands: delta (0.5–<4 Hz), theta (4–<8 Hz), alpha (8–<13 Hz), beta (13–<25 Hz), and gamma (25–≤50 Hz). We normalized power within each frequency band by calculating percent change in power for each 1-second time segment relative to 30 seconds of baseline power just before electrographic seizure onset. Thus, percent change in power was expressed as ([EEG signal power − baseline power]/baseline power) × 100% for each frequency band.

As noted above, for calculations of percent change in power, the baseline for all 3 seizure types was defined as 30 seconds before electrographic seizure onset. However, for temporal alignment of percent change time courses across seizures, FPC and FIC seizures were aligned to onset ($t = 0$) defined as electrographic seizure onset while FBTC seizures were aligned to behavioral onset of generalization. We used the onset of generalization as $t = 0$ for group data alignment of FBTC seizures rather than electrographic seizure onset because the time between onset and generalization for different FBTC seizures was variable (mean 108.21 seconds, range 0–737 seconds). Therefore, aligning FBTC seizures to onset of generalization provided more consistent time courses for power changes. Percent change in power was then pooled by averaging across electrodes within each of the 4 analysis regions (ipsilateral frontal, ipsilateral extrafrontal, contralateral frontal, and contralateral extrafrontal) for each seizure. Finally, mean values and statistics were calculated across seizures within each group for analysis: FIC, FPC, and FBTC.

Group data time courses were plotted as mean ± SEM percent change in power over time in nonoverlapping 10-second bins. For calculation of overall percent change in power during seizures vs baseline for use in summary histograms, tables, and group statistics, we used the mean for each seizure from onset ($t = 0$, as defined above) to electrographic offset, except for seizures lasting longer than 180 seconds, for which only the first 180 seconds of seizure data were analyzed. For calculating average power changes across all frequency bands for use in 3-dimensional (3D) color brain surface maps, summary tables, and group statistics, we first normalized power to baseline by calculating percent change from baseline within each frequency band and then averaged percent change values across frequency bands for each seizure. All aforementioned analyses were performed using in-house scripts in MATLAB.

To ensure robustness of our findings, we replicated the results by recomputing signal power using the same pipeline but with bipolar montages using adjacent electrodes (eTables 2 and 3).

To visualize overall power changes anatomically, we generated 3D color map representations of average percent change in EEG power across all 5 frequency bands for 1 representative seizure each from the FPC, FIC, and FBTC groups using methods described previously.[5,28-30] In brief, each electrode contact was localized with Bioimage Suite[26,31] and electrode coordinates were imported into MATLAB. The pial surface was reconstructed by Bioimage Suite as a triangular mesh model using the patient's preoperative T1-weighted MRI, and the triangular mesh model was imported into MATLAB. Percent change in power during seizure vs baseline was averaged across the 5 analyzed frequency bands for each electrode contact, using the methods previously described ([(EEG signal power − baseline power)/baseline power] × 100%, averaged across frequencies over the entire seizure). To display changes on the brain surface, we colored the faces of the triangular mesh based on the power magnitude of the closest electrode contact, applying a linear fade to zero over the radius from 1 to 15 mm surrounding each electrode.

Statistical Analysis

Statistical tests were performed using SPSS 28 (IBM Corp., Armonk, NY). Percent change in power for statistical results shown in the tables was analyzed in the ipsilateral frontal regions and in all other cortical regions combined. We compared percent change in power during FPC vs FIC seizures and FIC vs FBTC seizures using independent 2-sample t tests, followed by Holm-Bonferroni correction, with significance assessed at 2-tailed $p < 0.05$. All values are presented as mean ± SEM.

Data Availability

All codes generated for data analysis have been deposited in Github (github.com) and are available at https://github.com/BlumenfeldLab/SalarDini-et-al_2025. Anonymized icEEG data for this study may be shared at the request of any qualified investigator for purposes of replicating procedures and results.

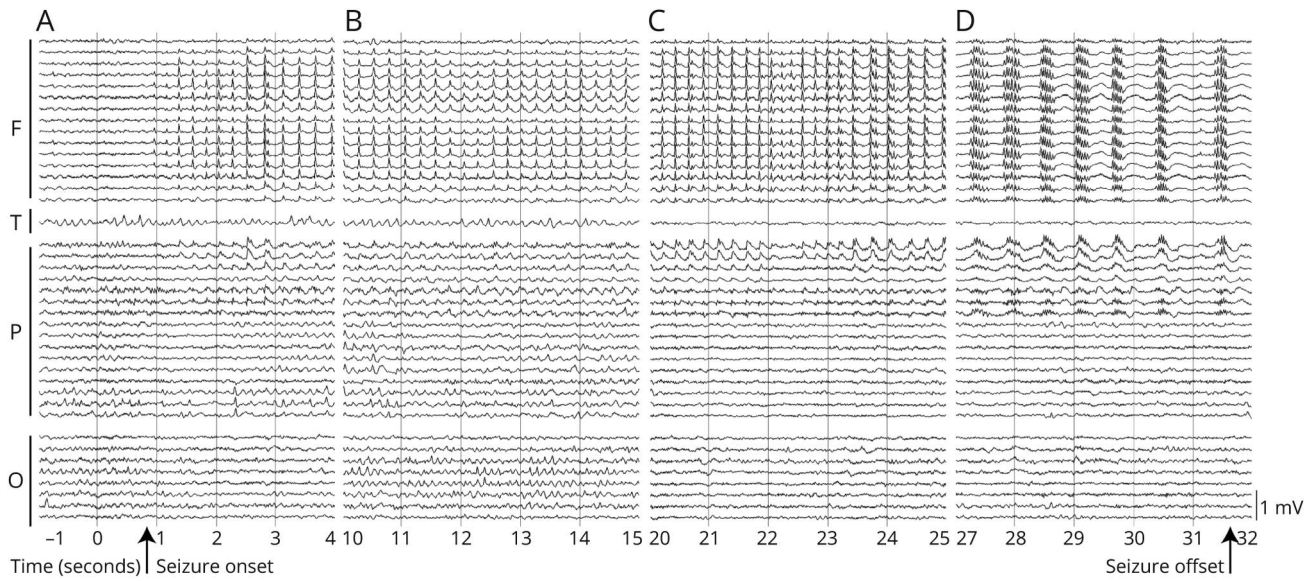
Results

We studied continuous video-icEEG recordings of 65 seizures (24 FPC, 27 FIC, and 14 FBTC) in 30 patients. Thirteen patients were female and 17 male, with a mean age of 27.7 years (range 9–51 years). Twenty-one patients were right-handed, 8 left-handed, and 1 ambidextrous. Additional demographic and clinical information is given in eTable 1. The mean duration of FPC seizures was 43.2 ± 5.5 seconds, FIC seizures 56.0 ± 7.6 seconds, and FBTC seizures 228.6 ± 77.4 seconds.

Greater Power in FIC vs FPC Seizures in Widespread Cortical Regions and Frequency Bands

We found that FPC seizures showed increased icEEG power mainly in the frontal lobe of onset while FIC seizures showed increased power across frequency bands and in widespread cortical regions, both ipsilateral and contralateral to the side of onset. A representative FPC seizure shows localized onset of rhythmic spikes in the frontal lobe (Figure 1, A and B) and later partial spread to the ipsilateral parietal lobe (Figure 1, C and D). By contrast, a typical FIC seizure has onset in the frontal lobe (Figure 2A) but then evolves to show ictal activity of mixed frequencies in widespread cortical regions (Figure 2, B–D, same scale as Figure 1).

Figure 1 Example of Frontal Lobe Focal Preserved Consciousness Seizure: Intracranial EEG Changes Are Mainly Localized to the Frontal Lobe of Onset



(A) Seizure onset shown by the arrow, with periodic spikes in the frontal electrodes. (B) Continuation of seizure as periodic spikes in frontal electrodes and spread of rhythmic activity to some parietal electrodes. (C) Evolution in morphology to polyspike-and-wave discharges and spread within the frontal and parietal electrodes. (D) Seizure offset shown by the arrow at 32nd second as 1-Hz polyspikes in the frontal and parietal electrodes. The montage is referential to the electrode in bone. The calibration bar on the right represents 1 mV. The horizontal axis shows time in seconds relative to the time interval of seizure onset (0–1 second). Illustrative 5-second time epochs are shown from seizure onset to offset. This is a unilateral (left-sided) implantation with a combination of grid, strip, and depth electrodes. Bars on the left show representative electrodes from each lobe. F = frontal; O = occipital; P = parietal; T = temporal.

Group analysis also showed that icEEG power increases in FPC seizures were confined mainly to the frontal lobe of onset, with some spread to ipsilateral extrafrontal regions (Figure 3, A and C). By contrast, FIC seizures demonstrated power increases in widespread regions outside the lobe of seizure onset and across multiple frequency bands (Figure 3, B and D). We performed statistical analyses comparing FIC and FPC seizures in the frontal lobe of onset and in all other brain regions combined (ipsilateral extrafrontal, contralateral frontal, contralateral extrafrontal). Cortical power in other regions outside the lobe of onset was significantly greater in FIC vs FPC seizures (Table 1, right columns). This was true for the average power across all frequency bands, as well as for most frequency bands individually, with the exception of theta frequency. Power across all these regions and frequency bands increased by 40.4% ± 7.4% during FIC seizures, but only by 10.7% ± 2.6% during FPC seizures ($p < 0.001$, 95% CI 14.1–45.3; Table 1, bottom right entry). By contrast, in the frontal lobe ipsilateral to onset, icEEG power did not differ between FPC and FIC seizures, except at higher frequencies where gamma power was significantly greater in FIC seizures than in FPC seizures (Table 1, left columns). To ensure that these findings were not driven by use of a referential montage, we recomputed signal power using a bipolar montage with contiguous contacts. The results were consistent with the original analysis (eTable 2).

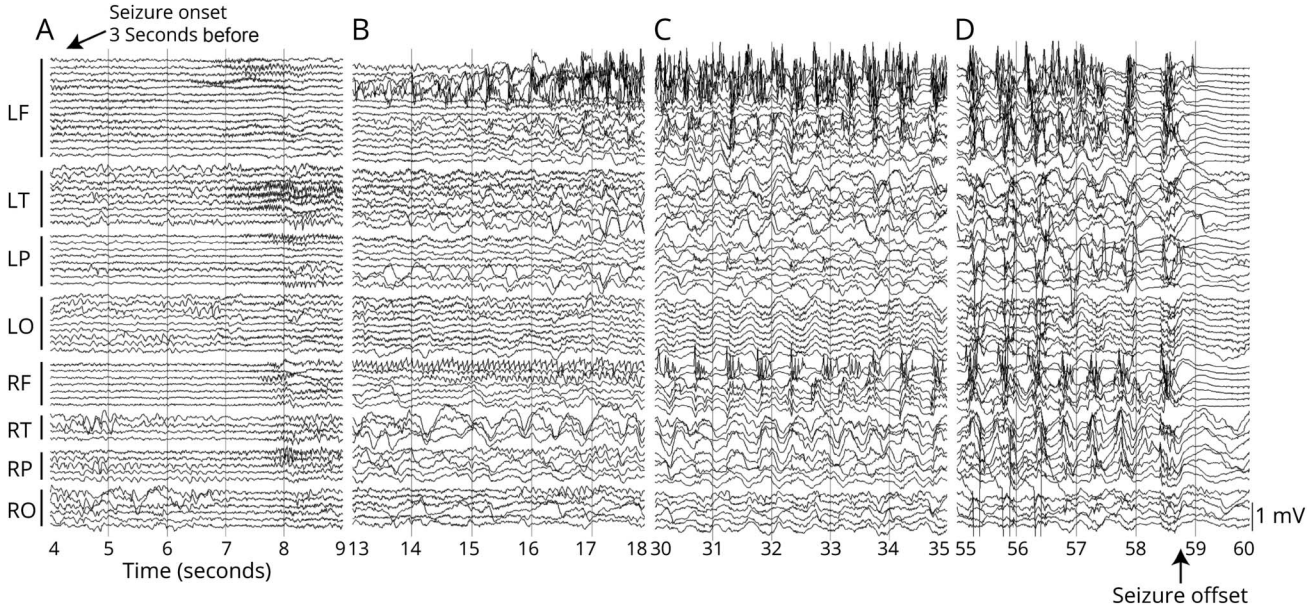
To visualize the anatomical distribution of seizure activity, we created 3D color maps of average power changes across frequency bands for representative FPC and FIC seizures (Figure 3E and F, respectively). These maps show a large increase in average power across frequencies in all recorded regions in the FIC seizure (Figure 3F) while the FPC seizure shows greatest power increases localized to the left frontal lobe of onset, with relatively smaller increases in other brain regions (Figure 3E).

Much Greater Power in FBTC vs FIC Seizures Across All Cortical Areas and Frequencies

The increased icEEG power across frequencies in widespread cortical areas observed in FIC seizures (Figure 3) raises the question of how frontal lobe FIC seizures differ from FBTC seizures, also known to involve widespread areas of the cortex. FBTC seizures were distinguished clinically by typical behavioral manifestations including head or eye version, vocalization, tonic facial contraction, and tonic evolving to bilateral clonic limb movements, as in previous studies.[21,22] We found that FBTC seizures showed much greater icEEG power throughout the cortex and across frequency bands compared with FIC seizures. A typical FBTC seizure shows an initial burst of high-amplitude polyspikes in the ipsilateral frontal lobe (Figure 4A), followed by rapid high-amplitude extrafrontal spread (Figure 4B), evolving to diffuse high-amplitude irregular polyspikes (Figure 4C) and rhythmic polyspike-wave discharges before seizure termination (Figure 4D, note the difference in scale bar vs Figures 1 and 2).

Group analysis confirmed the large-amplitude icEEG power increases across cortical regions and frequencies in FBTC

Figure 2 Example of Frontal Lobe Focal Impaired Consciousness Seizure: Intracranial EEG Changes Extend Widely Beyond the Frontal Lobe of Onset



(A) Seizure onset indicated by arrow with low-voltage fast activity beginning 3 seconds before this time epoch (not visible because of very focal poorly discernible pattern at these settings), evolving as low-voltage fast activity (beta, gamma) in the left frontal contacts with spread to the left temporal, left parietal, and right hemispheric contacts. (B) Further seizure evolution as irregular polyspikes with embedded faster frequencies in the ipsilateral (left) frontal electrodes, sharply contoured rhythmic alpha in the contralateral (right) frontal electrodes, and other widespread changes. (C) Seizure continues as irregular polyspikes in bifrontal regions with additional changes in extrafrontal regions bilaterally. (D) Widespread 1–2 Hz polyspike-and-wave discharges in bilateral hemispheres terminate with seizure offset shown by the arrow at the 59th second. The montage is referential to the electrode in bone. The calibration bar on the right represents 1 mV (same scale as in Figure 1). The horizontal axis shows time in seconds relative to seizure onset. Illustrative 5-second time epochs are shown. This is a bilateral implantation with a combination of grid, strip, and depth electrodes. Bars on the left show representative electrodes from each lobe. LF = left frontal; LO = left occipital; LP = left parietal; LT = left temporal; RF = right frontal; RO = right occipital; RP = right parietal; RT = right temporal.

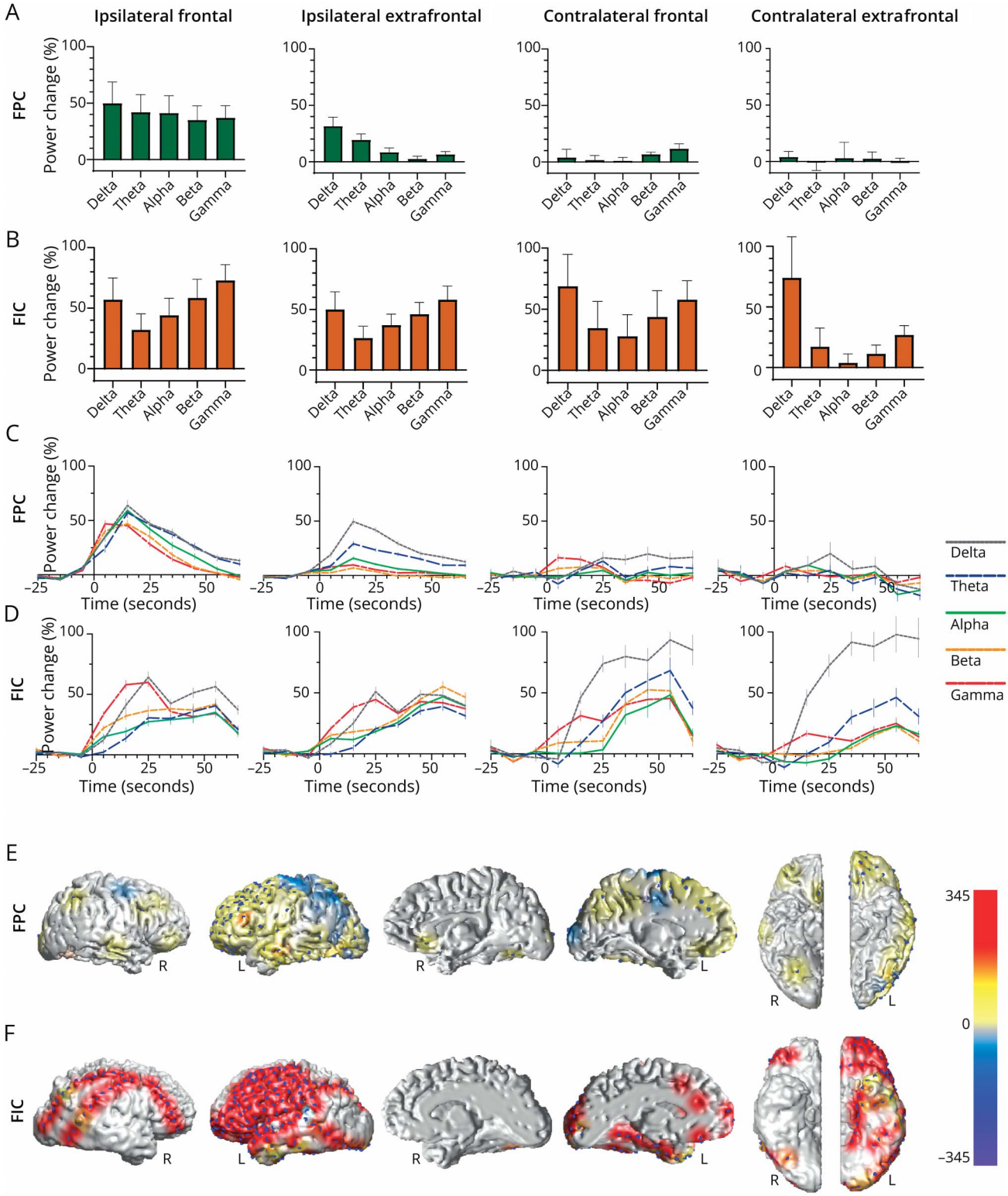
seizures (Figure 5, A and B). Statistical analyses demonstrated that FBTC seizures had much greater icEEG power compared with FIC seizures in all brain regions and across all frequency bands (Table 2). In summary, the power increase averaged across frequency bands in the frontal lobe of onset was 52.9% ± 13.4% for FIC seizures and 608.9% ± 104% for FBTC seizures ($p < 0.001$, 95% CI 330.1–781.9); the power across frequency bands in other cortical regions was 40.4% ± 7.4% for FIC seizures and 637.2% ± 107.1% for FBTC seizures ($p < 0.001$, 95% CI 375.3–818.2; Table 2, bottom row). Again, to ensure that these findings were not driven by use of a referential montage, we recomputed signal power using a bipolar

Table 1 Intracranial EEG Power in Frontal Lobe Focal Preserved vs Focal Impaired Consciousness Seizures

	Ipsilateral frontal power			Other cortical power		
Frequency range	**FPC**	**FIC**	**FPC vs FIC**	**FPC**	**FIC**	**FPC vs FIC**
Delta	49.9 ± 18.8	57.0 ± 17.8	T (48.4) = 0.28, p = 0.784	22.9 ± 6.1	60.2 ± 12.4	T (72.1) = 2.70, p = 0.016[a]
Theta	42.0 ± 15.5	32.0 ± 13.1	T (46.6) = 0.49, p = 0.627	13.7 ± 4.0	26.4 ± 8.0	T (72.8) = 1.42, p = 0.320
Alpha	41.3 ± 15.2	44.1 ± 13.9	T (47.9) = 0.14, p = 0.891	6.3 ± 2.9	27.1 ± 6.8	T (67.5) = 2.81, p = 0.012[a]
Beta	35.0 ± 12.6	58.4 ± 15.3	T (48.1) = 1.18, p = 0.243	3.6 ± 1.7	37.5 ± 7.6	T (56.0) = 4.34, p < 0.001[a]
Gamma	36.9 ± 10.7	72.9 ± 12.9	T (46.7) = 2.15, p = 0.036[a]	7.0 ± 2.0	50.9 ± 7.3	T (58.3) = 5.82, p < 0.001[a]
All	40.6 ± 13.4	52.9 ± 13.4	T (48.8) = 0.65, p = 0.519	10.7 ± 2.6	40.4 ± 7.4	T (63.0) = 3.80, p < 0.001[a]

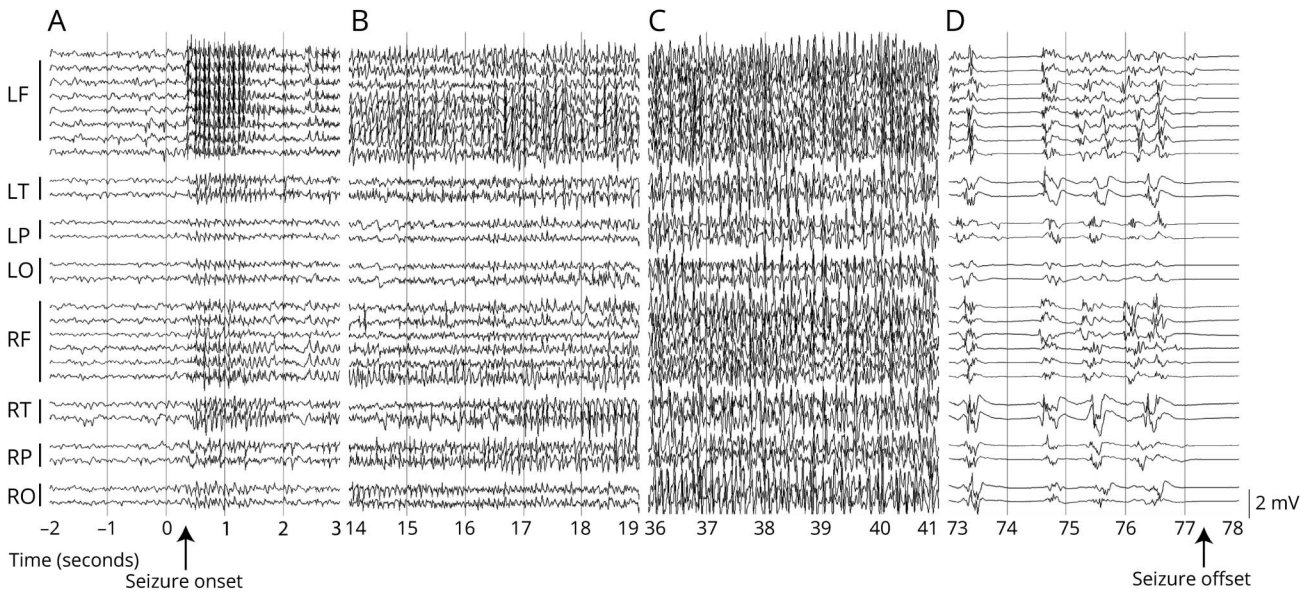
Abbreviations: FIC = focal impaired consciousness; FPC = focal preserved consciousness.
Values represent overall mean ± standard error percent change in EEG power during seizure vs 30-second preseizure baseline. Ipsilateral frontal power is from the frontal lobe on the side of seizure onset. Other cortical power is from all other cortical regions (ipsilateral extrafrontal, contralateral frontal, and contralateral extrafrontal in Figure 3, A and B). All is the average change in EEG power across frequency bands (each power band is first normalized to its own baseline before averaging across frequency bands). T values and degrees of freedom (in parenthesis) are shown. p Values are Holm-Bonferroni corrected, from a 2-tailed t test. Data are from 24 FPC seizures in 11 patients and 27 FIC seizures in 16 patients.
[a] $p < 0.05$.

Figure 3 Group Analysis and Surface Maps of icEEG Changes During Frontal Lobe Focal Preserved and Focal Impaired Consciousness Seizures



(A, B) Mean percent change in power in (A) focal preserved consciousness (FPC) seizures and (B) focal impaired consciousness (FIC) seizures compared with 30-second preseizure baseline. (C, D) Time course plots of intracranial EEG (icEEG) percent changes in power during FPC seizures (C) and FIC seizures (D) compared with 30-second preseizure baseline binned every 10 seconds. Electrographic seizure onset is indicated as time = 0. (A–D) Data are from 24 FPC seizures in 11 patients and 27 FIC seizures in 16 patients. Error bars are SEM. Delta = 0.5–<4 Hz; theta = 4–<8 Hz; alpha = 8–<13 Hz; beta = 13–<25 Hz; and gamma = 25–≤50 Hz. (E, F) Three-dimensional color maps showing the mean percent changes in power (color scale ±345%) across all 5 frequency bands during the entire seizure vs 30-seconds preseizure baseline in examples of a FPC seizure with left frontal onset (E) and a FIC seizure with left frontal onset (F) (details of percent change calculations in Methods).

Figure 4 Example of Focal to Bilateral Tonic-Clonic Seizure of Frontal Onset: Intracranial EEG Changes Are Widespread and Large Amplitude



(A) Seizure onset indicated by arrow, with burst of high-amplitude polyspikes, followed by rapid bilateral and extrafrontal spread. (B) Seizure evolution as irregular polyspikes with embedded faster frequencies in ipsilateral (left) frontal and temporal electrodes, followed by spread to the extrafrontal ipsilateral and contralateral regions by the end of the panel. (C) Tonic phase of the seizure seen on EEG as high-amplitude polyspikes with admixed mixed frequencies, showing widespread bilateral cortical involvement. (D) Clonic phase of the seizure shown as irregular polyspike-wave discharges of approximately 1 Hz, with seizure offset indicated by the arrow at the 78th second. The montage is referential to the electrode in bone. The calibration bar on the right represents 2 mV (note the scale difference in Figures 1 and 2). The horizontal axis shows time in seconds relative to the time interval of seizure onset (0–1 second). Illustrative 5-second time epochs are shown. This is a bilateral implantation with a combination of grid, strips, and depth electrodes. Bars on the left show representative electrodes from each lobe. LF = left frontal; LO = left occipital; LP = left parietal; LT = left temporal; RF = right frontal; RP = right parietal; RO = right occipital; RT = right temporal.

montage with contiguous contacts, and the results were consistent with the original analysis (eTable 3).

To illustrate these large-magnitude and widespread changes for FBTC seizures, we again created 3D color maps of average power changes across frequencies for a typical FBTC seizure (Figure 5C). This showed a large increase in power across all recorded regions, considerably larger in scale compared with typical FPC or FIC seizures (Figure 3, E and F).

Discussion

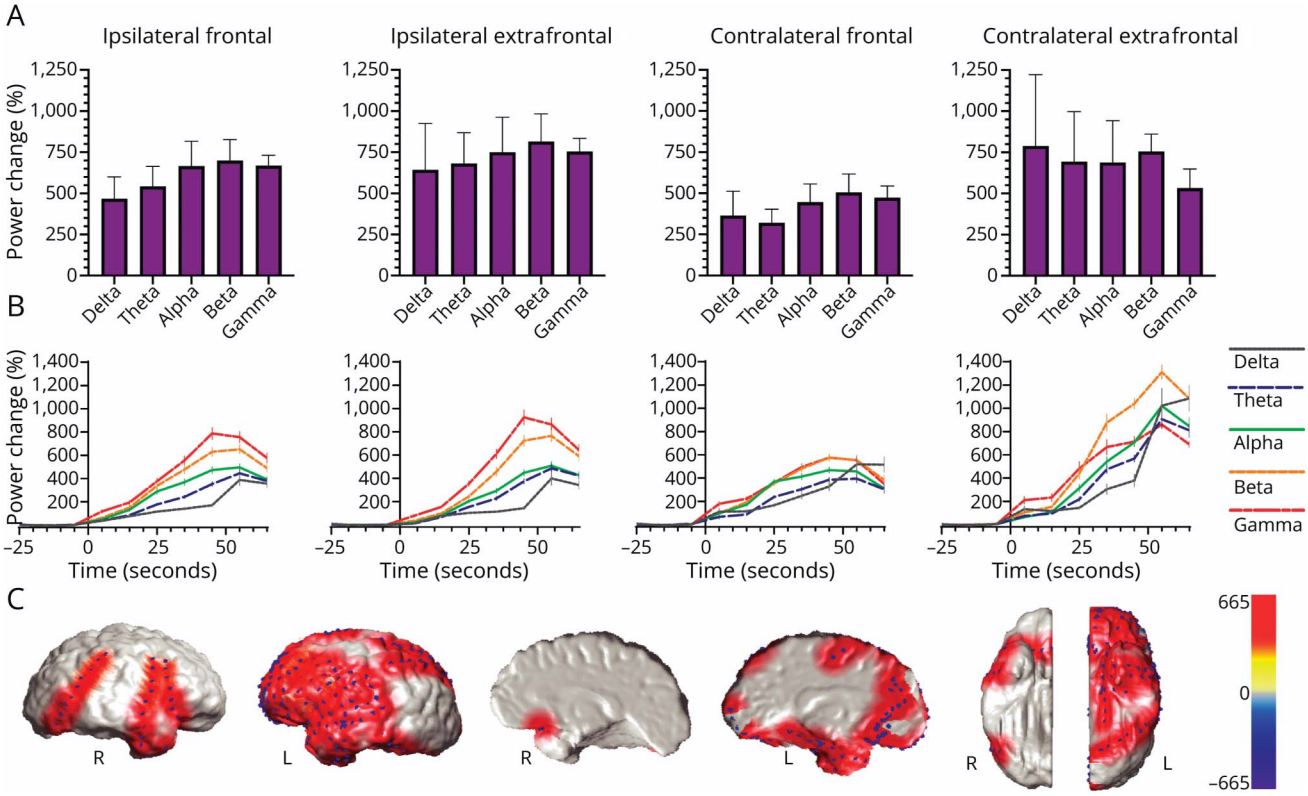
Our goal was to investigate the physiologic basis of impaired consciousness in frontal lobe epilepsy. We found that frontal

Table 2 Intracranial EEG Power in Frontal Lobe Focal Impaired Consciousness vs Focal to Bilateral Tonic-Clonic Seizures

	Ipsilateral frontal power			Other cortical power		
Frequency range	**FIC**	**FBTC**	**FIC vs FBTC**	**FIC**	**FBTC**	**FIC vs FBTC**
Delta	57.0 ± 17.8	467.2 ± 133.0	T (13.5) = 3.0, p = 0.018[a]	60.2 ± 12.4	588.6 ± 173.8	T (24.2) = 3.0, p = 0.012[a]
Theta	32.0 ± 13.1	543.1 ± 121.2	T (13.3) = 4.2, p = 0.002[a]	26.4 ± 8.0	582.6 ± 118.3	T (24.2) = 4.7, p < 0.001[a]
Alpha	44.1 ± 13.9	665.7 ± 150.7	T (13.2) = 4.1, p < 0.002[a]	27.1 ± 6.8	655.3 ± 129.1	T (24.1) = 4.9, p < 0.001[a]
Beta	58.4 ± 15.3	699.2 ± 127.8	T (13.4) = 5.0, p < 0.001[a]	37.5 ± 7.6	719.0 ± 102.1	T (24.3) = 6.7, p < 0.001[a]
Gamma	72.9 ± 12.9	669.2 ± 62.2	T (14.1) = 9.4, p < 0.001[a]	50.9 ± 7.3	640.3 ± 57.1	T (24.8) = 10.2, p < 0.001[a]
All	52.9 ± 13.4	608.9 ± 104.0	T (13.4) = 5.3, p < 0.001[a]	40.4 ± 7.4	637.2 ± 107.1	T (24.2) = 5.6, p < 0.001[a]

Abbreviations: FBTC = focal to bilateral tonic-clonic; FIC = focal impaired consciousness.
Values represent overall mean ± standard error percent change in EEG power during seizure vs 30-second preseizure baseline. Ipsilateral frontal power is from the frontal lobe on the side of seizure onset. Other cortical power is from all other cortical regions (ipsilateral extrafrontal, contralateral frontal, and contralateral extrafrontal in Figures 3B and 5A). All is the average change in EEG power across frequency bands (each power band is first normalized to its own baseline before averaging across frequency bands). Ictal data for FBTC seizures begin with onset of generalization; however, very similar results were obtained if the entire ictal period was used for FBTC seizures (data not shown). T values and degrees of freedom (in parenthesis) are shown. p Values are Holm-Bonferroni corrected, from a 2-tailed t test. Data are from 27 FIC seizures in 16 patients and 14 FBTC seizures in 7 patients.
[a] p < 0.05.

Figure 5 Group Analysis and Surface Maps of icEEG Changes During Focal to Bilateral Tonic-Clonic Seizures of Frontal Onset



(A) Mean percent change in power in focal to bilateral tonic-clonic (FBTC) seizures compared with 30-second preseizure baseline. As described in the Methods, ictal data begin with onset of generalization; however, very similar results were obtained when ictal data began with electrographic seizure onset (data not shown). (B) Time course plots of intracranial EEG (icEEG) percent changes in power during FBTC seizures compared with 30-second preseizure baseline binned every 10 seconds. Data before time = 0 are before electrographic seizure onset; data after time = 0 are after onset of generalization. (A, B) Data are from 14 FBTC seizures in 7 patients. Error bars are SEM. Delta = 0.5–<4 Hz; theta = 4–<8 Hz; alpha = 8–<13 Hz; beta = 13–<25 Hz; and gamma = 25–≤50 Hz. (C) Three-dimensional color maps showing the mean percent changes in power (color scale ±665%) across all 5 frequency bands during the entire seizure vs 30-second preseizure baseline in an example of a FBTC seizure with left frontal onset (details of percent change calculations in Methods).

lobe FIC seizures had greater power increases across frequencies in widespread areas of the cortex while FPC seizures had relatively localized increases in the frontal lobe of onset. In addition, we found that both frontal lobe FIC and FBTC seizures have widespread icEEG activity increases across frequencies and cortical regions, but the increases are much larger during FBTC seizures. These findings in frontal lobe epilepsy contrast with temporal lobe FIC seizures, which show mainly increased slow-wave activity in the cortex, suggesting that different mechanisms produce impaired consciousness in different types of focal seizures.

Impaired consciousness is proposed to arise from abnormal activity in widespread bilateral cortical networks modulated by subcortical arousal systems. One theory of impaired consciousness in focal epilepsy, the global workspace theory,[4] proposes that widespread abnormal synchrony disrupts consciousness in TLE,[3,7] parietal lobe seizures,[32] and FLE.[20] A second theory, the network inhibition hypothesis,[6,11] focuses specifically on TLE and proposes that inhibited subcortical arousal causes encephalopathy-like cortical slow waves and impaired consciousness. Support for the network inhibition hypothesis in TLE comes from icEEG recordings showing significantly larger bilateral frontoparietal slow-wave activity in temporal lobe FIC vs FPC seizures,[5,10] resembling sleep, coma, or encephalopathy.[33,34] Cortical slow waves during FIC seizures in TLE are associated with widespread frontoparietal cerebral blood flow decreases, correlated with abnormal subcortical arousal activity in patients and in animal models.[12,14,35] However, previous work has not investigated whether similar mechanisms of depressed arousal and cortical slow waves contribute to impaired consciousness in focal epilepsy aside from TLE.

Of interest, our present findings show that unlike TLE, in frontal lobe FIC seizures, there is an increase in icEEG activity across the cortex over a wide range of frequencies, not just in the slow delta frequency range. Therefore, instead of indirect effects of seizures on subcortical arousal, frontal lobe FIC seizures may directly disrupt widespread neocortices in both hemispheres. By contrast, frontal lobe FPC seizures produce relatively localized increases on the side of onset. These findings raised the question of

whether the widespread icEEG changes in frontal lobe FIC seizures are similar to those in FBTC seizures, well known to cause impaired consciousness.[21-23,36] However, we found substantial differences between frontal lobe FIC and FBTC seizures, with significantly larger increases in widespread cortical areas across frequencies in FBTC seizures by a full order of magnitude.

These findings suggest a model in which the behavioral severity of seizures, including degree of impaired consciousness, is related to the physiologic severity of seizure activity and its impact on widespread regions of the cortex. The mechanisms of physiologic disruption may vary in different seizure types and can include a combination of factors such as enhanced synchrony as per the global neuronal workspace theory, increased cortical slow-wave activity as per the network inhibition hypothesis in TLE, increased activity across frequencies in FLE, and other activity patterns in different types of seizures. For example, recent work in absence epilepsy has shown that generalized spike-wave discharges do not always cause impaired consciousness, but that the degree of behavioral impairment is directly related to the physiologic severity of spike-wave EEG amplitude and fMRI signal changes in widespread corticothalamic networks.[37,38] A similar relation between physiologic severity and impaired consciousness may also be present in frontal lobe seizures but through different mechanisms. Thus, frontal lobe FPC seizures with minimal widespread cortical involvement do not impair consciousness, FIC seizures with widespread abnormal cortical involvement across frequencies do impair consciousness, and FTBC seizures with widespread abnormal cortical activity of much greater magnitude also cause impaired consciousness. Of note, previous work has shown that the level of impaired behavioral responsiveness is more severe in FBTC seizures than in FIC seizures.[36]

Future work should investigate several open questions not addressed in this study. For example, one interesting observation is that the increase in delta power in the contralateral extrafrontal regions during FIC seizures seemed especially prominent (Figure 3A), so the possible role of this activity in impaired consciousness should be investigated further. In addition, despite providing a better understanding of electrophysiologic signals associated with decreased consciousness in FLE, our data cannot be used to infer the sequence of events through which abnormal activity spreads throughout the cortex in frontal lobe FIC seizures. There are a few potential circuits, which could play a role in propagation of seizure activity, among which cortico-cortical and cortico-thalamo-cortical circuits stand out.[39] Generally, the intralaminar and medial thalamic nuclei form extensive cortico-thalamo-cortical pathways, proposed to modulate synchrony and large-scale integration of information across multiple cortical circuits. Support for this notion includes robust connections between the intralaminar thalamus and frontoparietal cortex, playing an important role in arousal regulation, and diffusion tractography demonstrating extensive interconnections between the thalamic mediodorsal nuclei and frontal cortex.[1,40] Another thalamic nuclear candidate for cortico-thalamo-cortical propagation is the medial pulvinar, given its crucial role in signal coordination in frontoparietal networks.[41] In addition, frontal connectivity is certainly compatible with the possibility of seizure spread through local cortico-cortical circuits or through long-range connections such as the corpus callosum.[42,43] Furthermore, future studies should investigate whether measures of cortico-cortical synchrony such as collapse in complexity and pathologic hyperconnectivity[8,9] track behavioral severity in frontal lobe seizures as potential markers of impaired consciousness, either independently of or in parallel with the more basic increases in signal power shown here.

Another important future direction will be more localized investigation of the anatomical regions contributing to impaired consciousness in FLE. Despite investigating a relatively large number of patients and seizures across 3 centers, and the presence of many cortical electrodes due to the common use of grids and strips rather than stereo-EEG during the period covered (1997–2020), we did not have sufficient electrode coverage across patients to separately study different lobes in each hemisphere. In particular, fewer recordings were available for the hemisphere contralateral to seizure onset, especially in extrafrontal regions. Future work with even larger samples across centers should enable investigation of smaller subregions within each hemisphere. For example, it would be valuable to further localize verbal and nonverbal deficits in FIC seizures in relation to anatomically and functionally specialized subregions of the frontal lobes. This analysis was not possible in this study because of limited sample sizes and because formal verbal and nonverbal testing was not performed during seizures, although such approaches are available and should be used for future studies.[44-46]

Finally, an important question that cannot be addressed with standard clinical icEEG electrodes is how the spread of ictal icEEG activity we observed in FIC seizures across widespread cortical regions and frequencies relates to underlying neuronal firing. For example, it is not known whether the observed widespread cortical icEEG changes are accompanied by changes in neuronal firing, or whether they instead reflect local field potential changes related to synaptic inputs without changes in firing. Human unit activity recordings have been used to investigate the distinction between changes in neuronal firing and local field potential changes including studies of ictal unconsciousness,[47] and this approach could be applied to frontal lobe FIC seizures as well. Furthermore, just as animal models have been productive for studying underlying neuronal mechanisms of impaired consciousness in absence seizures and TLE,[12,14,48] an animal model of impaired consciousness in FLE would be very useful for future investigation into fundamental mechanisms.

Impaired consciousness has substantial negative impacts on quality of life of patients with epilepsy.[49] For example, impaired consciousness can lead to motor vehicle accidents,

drowning, poor work and school performance, and social stigmatization. Although FLE has not attracted as much attention as TLE because of its less common occurrence, a number of studies of FLE in children have shown that impaired cognitive function and behavior are frequent complications.[50,51] As such, a better appreciation of long-range network effects could help with guiding novel therapeutic strategies to prevent these neocortical consequences and adverse outcomes.

In conclusion, this study provides quantitative evidence of a broad increase in icEEG activity across frequency bands in widespread regions of the cortex associated with impaired consciousness during frontal lobe FIC seizures, whereas FBTC seizures show much larger increases in broadband activity throughout the cortex. These findings contrast with impaired consciousness in focal TLE, where impaired consciousness is associated with widespread cortical slow-wave activity. We can speculate that different types of focal seizures produce impaired consciousness by affecting widespread cortical regions but through different mechanisms. Given that cortical dysfunction affects patients' quality of life, understanding mechanisms underlying this impairment and developing new therapeutic options to prevent altered consciousness remain important goals for helping people with epilepsy.

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