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Ictal and Preictal Power Changes Outside of the Seizure Focus Correlate with Seizure Generalization

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Summary

Objective—The treatment of focal epilepsies is largely predicated on the concept that there is a “focus” from which the seizure emanates. Yet, the physiological context that determines if and how ictal activity starts and propagates remains poorly understood. To delineate these phenomena more completely, we studied activity outside the seizure onset zone prior to and during seizure initiation.

Methods—Stereotactic depth electrodes were implanted in 17 patients with longstanding pharmaco-resistant epilepsy for lateralization and localization of the seizure onset zone. Only seizures with focal onset in mesial temporal structures were used for analysis. Spectral analyses were used to quantify changes in delta, theta, alpha, beta, gamma, and high gamma frequency power, in regions inside and outside the area of seizure onset during both preictal and seizure initiation periods.

Results—In the 78 seizures examined, an average of 9.26% of the electrode contacts outside of the seizure focus demonstrated changes in power at seizure onset. Interestingly, seizures that secondarily generalized, on average, showed power changes in a greater number of extra-focus electrode contacts at seizure onset (16.7%) compared to seizures that remained focal (3.8%). The majority of these extra-focus changes occupied the delta and theta bands in electrodes placed in the ipsilateral, lateral temporal lobe. Preictally, we observed extra-focal high frequency power decrements, which also correlated with seizure spread.

Significance—This widespread activity at and prior to the seizure onset time further extends the notion of the ictogenic focus and its relationship to seizure spread. Further understanding of these extra-focus, peri-ictal changes might help identify the neuronal dynamics underlying the initiation of seizures and how therapies can be devised to control seizure activity.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Keywords

temporal lobe epilepsy; intracranial EEG; partial seizure; epileptogenic zone; epileptogenesis

Introduction

Epilepsy impacts approximately one percent of the population, with focal epilepsy being the most common type^{1–3}. Focal seizures are considered to be focal because of their localized onset, with mesial temporal lobe seizures being a paradigmatic example⁴. Identification of the seizure onset zone (cortex from which clinical seizures are generated) is critically important for localizing the epileptogenic zone (cortex absolutely necessary for seizure generation)⁵. However, in many patients, resection of the seizure onset zone does not guarantee seizure freedom^{6,7}. For this, and other reasons, our concept of the seizure focus, a term analogous to the seizure onset zone, is increasingly being questioned^{8,9}. Microelectrode recordings^{10–12}, decreases of extra-focal cortical GABA_A¹³, preictal vasoconstriction of blood vessels¹⁴, and fMRI findings¹⁵ have all suggested that there may be phenomena occurring outside the traditionally defined seizure onset zone at or before ictal initiation. In addition, a wide variety of studies, particularly in the efforts to predict seizures, have indicated that the transition to seizure activity is often gradual and involves subtle metabolic and electrical changes before overt clinical or electrographic evidence of the seizure^{16–18}. Using machine learning techniques, some patients' seizures can be predicted up to 25 minutes prior to seizure initiation^{19–22} while other studies using spatio-temporal frequency analysis indicate that there are immediate preictal changes, occurring 8 seconds prior to start, outside of the clinically defined onset zone; it is suggested that such changes may even be ictal changes²³. Using *in vitro* methods, Jiruska *et al.* showed a global preictal buildup of high frequency activity characterized by the interplay between pyramidal and interneuron cell firing¹⁰. Together, these and other studies force us to reexamine our notion of what is focal and extra-focal and how extra-focal activity impacts seizure dynamics including onset and, particularly, generalization.

To better understand how neuronal activity at the time of seizure onset affects seizure spread and impacts our concept of the focus, we explored neural activity occurring outside of the seizure onset zone. We addressed three questions: (1) At the time of seizure onset, are there changes in neuronal activity that occur outside of the seizure focus? (2) In the preictal period, are there changes in neuronal activity that occur outside of the seizure focus? And finally, (3) how do these changes relate to the extent to which the seizure propagates outside the typically defined seizure focus? To answer these questions, we investigated spatio-temporal-frequency changes in intracranial EEG recordings in both intra- and extra-focal onset zones in patients with intractable mesial temporal lobe epilepsy.

Materials and Methods

Patients

Local Institutional Review Boards (Partners Human Research Committee) granted approval for this study. For inclusion in this study, each patient was required to meet the following

criteria: (1) intractable mesial temporal lobe epilepsy determined at the conclusion of all clinical evaluations; (2) implantation of intracranial depth electrodes; (3) at least 1 focal seizure recorded with intracranial EEG correlate; and (4) electrographic start occurred prior to clinical manifestation. For patients with multifocal or bitemporal epilepsy, we only included seizures that had a unilateral start in the mesial temporal lobe. We note that three patient's resected pathology contains gliosis in the hippocampus and the extended temporal lobe cortex, which may not definitively demarcate classical mesial temporal lobe epilepsy (Table 1). However, these pathologies are only one piece in the clinical puzzle, and based on the EEG recordings themselves, the clinical expertise from epileptologists, and the absence of another pathology contradictory to mesial temporal lobe epilepsy, their inclusion in this study is still valuable. Seventeen patients (mean age 41.0 $\pm$ 11.2, 10 men) fulfilled these criteria and were included in the study.

Intracranial EEG Recordings

Depth electrodes were implanted stereotactically in all patients using Ad-Tech (Ad-Tech Medical Corp., Racine, Wisconsin) 8 contact arrays with 5mm-8mm center to center distance and 2.4 mm contacts with 0.86mm diameter. The iEEG recording was monitored using Natus's XLTEK acquisition system (Natus Medical Incorporated, San Carlos, CA) and sampled at 500 Hz for the first ten chronologically implanted patients and 512 Hz for the subsequent seven patients. Patients were recorded continuously for variable durations depending on seizure frequency and at the discretion of the clinical team. An external reference on the back of the neck at the level of the CII vertebra was used for all recordings.

Seizures

All patients in this study had a seizure onset zone defined as occurring within the mesial temporal lobe, based on clinical interpretation of the data by electroencephalographers. Seizure onset time was also identified by electroencephalographers as the first electrographic change on a mesial temporal lobe electrode contact. All seizures analyzed had a focal start and were separated in time by more than an hour from a previous seizure²⁴. Seizures that remained focal were identified as the absence of a tonic-clonic clinical correlate. In most instances the seizure did not spread outside in the mesial temporal lobe. An example of such a seizure is shown in Fig. 1, where raw activity and spectral power at an electrode contact in the seizure focus (Fig. 1 -Left) and outside the focus (Fig. 1 -Right) are highlighted at the seizure start. Seizures were considered to secondarily generalize if the patient demonstrated tonic-clonic activity⁴. Fig. 2 illustrates intra- and extra-focus activity in seizures that secondarily generalize in the same patient and contacts as Fig. 1. Seventy-eight focal temporal lobe seizures were analyzed; 59 seizures remained focal and 19 seizures secondarily generalized.

EEG Analysis

EEG analysis was conducted using a referential montage, and a subset of contacts was analyzed in each patient. An average of 4.18 ($\pm$ 0.73) contacts per patient were selected from the ipsilateral mesial temporal lobe, while an average of 22.1 ($\pm$ 4.8) contacts were selected outside of this region, which we have deemed the extra-focus (electrode locations of one patient displayed in Supplementary Fig. 1). Contacts were excluded if they were non-

functional, contained artifact, or were thought to be in cerebrospinal fluid, as was the case for some of the most lateral contacts.

Contacts were grouped into six discrete regions: ipsilateral mesial temporal, ipsilateral lateral temporal, ipsilateral frontal, contralateral mesial temporal, contralateral lateral temporal, contralateral frontal. The ipsilateral mesial temporal region was the clinically assigned seizure onset zone for all patients, while the other five regions were considered outside the focus.

A Fast Fourier Transform spectral analysis in Matlab version 2011b (Mathworks, Natick, MA) was used to quantify the power during the seizure initiation (defined in this study as the first second of the seizure, [0s 1s]), during the preictal period [−35s −5s]²³, and during the baseline [−1000s −300s] in the delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), gamma (30–70 Hz), and high gamma (70–120 Hz) frequency bands. This spectral analysis was performed on 1s intervals with 0.5s overlap in the preictal and baseline periods, and a Hamming taper was applied to each interval before spectral analysis. Power in the 58–62 Hz (and all multiples of 20Hz $\pm$ 2Hz) was excluded from the analysis to remove electrical interference. For each contact, we first computed the power spectrum during the baseline in 1s windows, creating a distribution of power over time, and the power spectrum during the seizure initiation, also 1s. We averaged the power over frequencies in the aforementioned bands and compared this band specific average power at seizure initiation to the average power baseline distribution to obtain a percentile equal to the percentage of the baseline intervals that had less average power than the seizure initiation.

To control for different awake states, behavioral changes, and epiphenomena, we compared the percentile with a distribution of percentiles obtained from 1000 random surrogate epochs, each lasting 1001 seconds. These surrogate epochs were chosen randomly to include a variety of mental, physical, and awake states during the patient's continuously recorded implantation. To do this, we first removed all epochs from the each patient's continuous recording that consisted of nonphysiological data. The surrogate data contained overlap, the degree of which depended on the duration of the patient's recording, but regardless, all patients had 1000 surrogate epochs. Each surrogate epoch was composed of a surrogate baseline [−1000s −300s] and a surrogate seizure initiation [0s 1s]. Identical to the analysis applied to the actual baseline-seizure epoch, we calculated the power in the six frequency bands and compared the surrogate seizure start to the surrogate baseline for each of the 1000 epochs. Finally, we compared the percentile determined from the actual baseline-seizures to the 1000 percentiles determined from the surrogate baseline-seizures.

For seizure onset analysis, we used an alpha of 0.05 coupled with a Bonferroni correction to adjust for the multiple comparisons across the six frequency bands to assess the number of contacts showing significant changes at seizure initiation for each seizure. We averaged the number of electrodes that contained spectral changes across seizures within each patient, and then compared across patients, brain regions, and prevalence of seizure spread. The mean and standard error across all patients was used to quantify the percent of electrodes that showed significant changes in power. The same analysis was conducted for the preictal period: for each contact, we calculated the mean power, averaged across the 30 preictal

windows of 1s duration (0.5s overlap, as above), to reduce the number of multiple comparisons.

Results

78 seizures, all originating from the mesial temporal lobe, were analyzed in 17 patients (mean age 41.0 $\pm$ 11.2, 10 men) with 59 seizures remaining focal and 19 seizures secondarily generalizing (Table 1). The average number of seizures per patient was 4.59 ($\pm$ 2.94). Six of the patients had both seizures that remained focal and seizures that generalized, seven patients had only seizures that remained focal, and four patients had only seizures with secondary generalization.

Intra-focal activity during seizure initiation

We examined the range of activity present both inside and outside of the seizure focus during a 1s window beginning at seizure onset. As defined, electrodes inside the focus (the ipsilateral mesial temporal region) showed broadband and frequency specific increases in power at the time of onset (Fig. 3). Not surprisingly, the proportion of contacts in the ipsilateral mesial temporal region that showed significant power increases is not 100% because, although this is the onset zone, most seizures have an unequivocal start on only one or two contacts. 38.6% of contacts in the ipsilateral mesial temporal region increased power at the time of onset, consistent with one or two of the hippocampal contacts in the mesial temporal region exhibiting a significant increase in power (Fig. 3 A). We note that 14.1 % of seizures did not exhibit increased power in the seizure onset zone, although every seizure start was confirmed by electroencephalographers. This is an indication that although there are visual changes on the intracranial EEG, these changes do not always reach statistical certainty and, in reviewing the analysis, we attribute this to the stringency of our procedure to define significant changes in power.

To address the possibility of seizure-onset subjectivity we explored what happens if we redefine the start time for each of the seizures. We jittered the start back in time to the first high amplitude, low frequency component of the electrographic start (mean from original start time = -0.436s $\pm$ 0.534s). Separately, we jittered the start forward in time to the first high frequency component which was also accompanied by an electrical decrement (mean from original start time = 2.342s $\pm$ 2.370s) (Supplementary Fig. 2). In most cases, one of these neo-starts was the same as the original start. When we compared these two starts, we actually found that it did not affect our findings. Similarly, we categorized the seizure onset as (1) low frequency fast, (2) sharp activity < 13 Hz, (3) spike and wave, and (4) low frequency high-amp periodic spikes²⁵. Again the frequency used to define the seizure start had no impact on any of our results.

Extra-focal activity at seizure initiation

Intriguingly, there were also changes in neural activity outside of the seizure focus (Fig. 3 A). Outside of the seizure focus, i.e. all regions excluding the ipsilateral mesial temporal lobe, an average of 9.26% of contacts per seizure showed a significant power increase in at least one of the examined frequency bands at the time of seizure onset. The majority of these

changes, 66.87%, occurred in the ipsilateral lateral temporal and ipsilateral frontal regions. We then looked within the different frequency bands to further identify specific changes (Fig. 3 B). In the ipsilateral lateral temporal region, an average of 6.7% contacts in the delta band and 8.7% contacts significantly increased in theta band power. In the ipsilateral frontal region, 6.3% of contacts significantly increased in theta band power. In contrast, there were minimal changes in the alpha, beta, gamma, and high gamma bands. We also tested for the number of contacts with significant power decreases but the number, both intra- and extra-focally, was marginal although existing changes occurred contralaterally to the seizure start.

Extra-focal activity at seizure initiation is correlated with generalization

Interestingly, we found that extra-focal neuronal activity at seizure onset differed between seizures that remained focal and those that secondarily generalized. We first looked at the 6 patients who exhibited both types of seizures. We found that in the ipsilateral lateral temporal region, significantly more electrode contacts showed an increase in power in seizures that generalized (t-test with $df = 5$, $p = 0.046$),

Given the low number of patients that had both seizure types, we then compared the two seizure propagation patterns across all patients. Seizures that generalized showed a significantly larger percentage of contacts with increased power in the ipsilateral lateral temporal (t-test with $df = 21$, $p = 0.01$) and the ipsilateral frontal (t-test with $df = 21$, $p = 0.01$) regions, compared to seizures that remained focal, (Fig. 4 A). For seizures that remained focal ($n = 59$), we found only an average of 3.8% of contacts per seizure outside of the seizure focus showed significant increases in any of the frequency bands at the time of seizure onset (Fig. 4 B). In contrast, 16.7% of contacts outside of the seizure focus in generalizing seizures ($n = 19$) showed significant increases at the moment of onset. Most notably, we found these changes were significant in the delta and theta frequency bands of the ipsilateral lateral temporal electrode contacts and theta band of the ipsilateral frontal contacts (Fig. 4 C). These findings are consistent with visualization of the raw signal (Fig. 1 – Fig. 2) at the seizure start, highlighting increased low frequency power outside of the seizure focus in seizures that generalize and fewer changes in those that remain focal. The contralateral frontal (t-test with $df = 16$, $p = 0.12$) region showed similar trends, but did not reach statistical significance.

Preictal extra-focal activity precedes generalization

We measured the number of electrode contacts that showed increased preictal power [–35s –5s] outside of the seizure focus and found that power increases were evident in the low frequency bands, similar to the changes identified at the seizure onset. To test this, we analyzed the 30s preictal epoch by computing the mean power over the preictal time windows and then performing the same analysis as discussed above (e.g. with respect to seizure onset).

Again, we first quantified the increase in preictal power in the subset of patients ($n = 6$) who had both types of seizure spread (21 remained focal; 8 secondarily generalized) in the six frequency bands, allowing for a matched pairs comparison between seizures that remained focal and those that went on to generalize. Small changes were evident globally but in no

specific region was there a statistically significant difference across the six frequency bands between preictal periods of seizures that went on to generalize and of those that remained focal (Fig. 5 A). This was likely a consequence of the relatively small number of patients with both types of seizure propagation. These results identified preictal changes in the low frequencies, particularly in the delta and theta bands of the ipsilateral region and the alpha band of the bilateral frontal regions (Fig. 5 B–C).

Similarly, we examined preictal power decrements over these same 6 patients. Again, small changes were evident globally but in no specific region was there a statistically significant difference in seizures that went on to generalize and of those that remained focal (Fig. 5 D). However, when we aggregated all of the contacts outside of the seizure onset, thus collapsing spatial information, we did find that significantly more contacts showed preictal changes across the six frequency bands in seizures that remained focal (t-test, $p = 0.01$, $df = 27$). This significance held true when we also incorporated the seizure focus itself in the grouping (t-test, $p = 0.03$, $df = 32$). These changes are mainly occurring in the higher frequency bands (gamma and high gamma) in both seizure types (Fig. 5 E–F).

We recognize that only 10 of these patients had temporal lobectomies with 6 of these patients having Engel Scores of 1a/1b (Table 1). Even though the seizures of the other 11 patients were clinically determined to have originated in the mesial temporal lobe, we wanted to more thoroughly examine those patients with a successful clinical outcome (Engel score of 1a/1b) to ensure that the results were not biased. The intra and extra-focus results at seizure onset were just as robust when we eliminated these 11 patients. Extra-focally, we found an average of 4.5% contacts in focal seizures increased in power compared with 28.0% of generalizing seizures, meaning a clearer mesial temporal lobe etiology only strengthened our results.

Discussion

In order to more completely explore the networks of human brain regions that are responsible for seizure initiation and spread, we focused on spatiotemporal neuronal activity of mesial temporal lobe seizures and transient changes in intracranial EEG that occur at and before the electrographically defined seizure onset time. Spatially distributed significant increases in power outside of the onset zone were identified at the seizure start, predominantly occurring in lateral contacts of the temporal and frontal lobes ipsilateral to the seizure onset. These changes were most prominent in the delta and theta bands and involved significantly more electrode contacts in those seizures that went on to secondarily generalize. Moreover, prior to the start of the seizure, high frequency power decrements were observed globally prior to seizure start, particularly in seizures that remained focal.

To our knowledge, this is the first study to examine focal seizures with particular attention paid to analysis of activity outside the seizure onset zone and its relationship with the degree of subsequent seizure spread. At the onset time, changes were found predominantly in low frequency bands of extra-focal electrode contacts and these low frequency power increases were correlated with seizure generalization. Post-onset neocortical slowing particular in the frontal regions has been identified²⁶ but our study is the first to demonstrate preictal and

seizure onset extra-focal slowing. These changes may reflect the association between low frequencies and global, distant cortical structure synchronization or communication, while higher frequencies typically remain local^{27,28}. Our results also suggest that most of these extra-focal changes occur in the lateral ipsilateral temporal region which supplements research suggesting that ictal spread to this region precedes seizure generalization²⁹. However, our study is the first to demonstrate that changes in this area are evident not only prior to seizure spread but also prior to seizure initiation.

Not only are these extra-focal changes associated with generalization, but their mere presence suggests that seizure initiation may involve network interactions among disparate brain regions. During the 35 second preictal epoch, there were trending power increases in the frontal and temporal lobe regions outside of the seizure onset zone between seizures that spread and those that remained focal suggesting that these regions play a role in seizure initiation and spread. This was concordant with global high frequency power decreases. This idea of a more generalized start, or that the electrographic focus is not (always) the true seizure start, is consistent with many other studies^{10–13,15,17,18,30,31}.

There are three main possibilities consistent with these findings. The first is that the start of seizures, specifically those that eventually generalize, actually involve widespread changes in activity that are both necessary and sufficient to induce electrographic and clinical seizure activity. Only the seizure onset zone meets our criteria for what constitutes a seizure from an electrographic sense, but the physiology of the outlying regions may still be part and parcel of the mechanisms involved in seizure initiation. An alternative (albeit somewhat overlapping) construct is that the activity changes that we observe outside of the seizure onset zone reflect the presence of a permissive state. They are, in essence, necessary for seizure activity to commence but not sufficient. Thus, these increases in low frequency and decreases in high frequency power across a number of cortical structures may be non-specific and non-ictal with only the pathological region likely to “convert” these changes in activity into epileptic seizures. A different perspective on this concept is that the activity changes that we observe outside the seizure onset zone may reflect distal effects of the beginning of the seizure – a beginning which is effectively a hidden state based on our current recording capabilities. This idea dovetails with the notion that there is a preictal state in which physiological changes are leading to overt seizure activity. More fine-grained analysis of the temporal ordering of these changes in neuronal activity is needed to select between these or other possibilities and to help extend and refine our understanding of focality in localization related epilepsy.

These findings are predicated on our designation of the seizure start. To control for this subjectivity, we used a 1s seizure initiation window, minimizing the effects of propagated activity from the seizure focus. Furthermore, our preictal analysis excludes the five seconds immediately preceding the seizure start to conservatively account for inaccuracies in identifying the seizure onset and reduce biases as a result of such variances. Also, we chose patients with mesial temporal lobe epilepsy not only because this is a common form of epilepsy³² but precisely because it provides one of the cleanest situations in which to test hypotheses about the focal nature of localization related epilepsy.

Although it might be suggested that these extra-focal changes may simply represent state changes, such as arousal, that are immaterial to ictal dynamics, we believe that our methods and results support that these changes are related specifically to the occurrence of the seizure itself. First, seizures emerging from both sleep and wake were analyzed – there was no predominance which would have suggested a stereotyped state change that could account for the extra-focal activity observed; 52.5% of the remaining focal seizures occurred during sleep and similarly 42.11% of secondarily generalized seizures originated during sleep. Second, were state changes the root cause, we might expect to see global effects across wide spatial regions as opposed to the more delineated changes involving predominantly the ipsilateral lateral temporal and ipsilateral frontal areas that we observed. Finally, we controlled for this possibility by bootstrapping the data using intra-patient surrogate epochs, which incorporate such variations in neural signal – that is, periods of time in which there were state changes of a wide variety of types were included in the control data used.

By exploring activity outside of the seizure focus, we consider the more holistic idea of seizures as network phenomena, and the effect of this network on seizure propagation. In aggregate these results enhance our working knowledge of brain network dynamics during a seizure. We postulate that changes outside the focus at the seizure start are a continuation of preictal changes outside of the seizure focus, and that with further research we can identify seizure propagation patterns before or at seizure start allowing for advanced clinical treatment. For example, this continuation of increased activity across preictal time coupled with the increased activity at the seizure start outside of the focus may allow for early identification of seizures that will generalize or remain focal, and help to design improved closed-loop interventions. There is also an implication that different surgical strategies may be employed which isolate extra focal network hubs which play a role in seizure initiation and degree of spread. Overall, these new ideas about the spatiotemporal dynamics of seizure initiation and spread require further exploration in hopes of designing more effective treatments for epilepsy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Key Points

- At seizure onset, regions outside of the seizure focus show changes in spectral power, despite showing no ictal electrographic changes.
- At seizure onset, extra-focal increases in delta and theta power, particularly in the ipsilateral lateral temporal lobe, correlate with whether the seizure secondarily generalizes.
- Power decreases in high frequencies are present in periods just preceding the seizure onset.

Seizure that Remains Focal

Fig. 1. IEEG, time-frequency plots, and spectral power in a seizure that remains focal
 (A) Two electrode contact locations superimposed on pre-operative MRI. The left side of the figure represents one contact located inside the seizure focus and the right side of the figure depicts a contact outside the seizure focus. (B) iEEG recording during the onset of a seizure. Both left and right iEEG recording are of the same seizure at the two electrodes indicated in (A). Time scale is same as in (C). The grey line indicates the seizure start interval [0s 1s]. (C) Time-frequency plots during the same time window. (D) Spectral power in the [0s 1s] bin compared to a baseline [-1000s -300s]. The Baseline Confidence here represents a 95%

confidence interval. Outside of the seizure focus, there are no clearly visible frequency bands that exhibit changes in power during the seizure initiation interval.

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Seizure with Secondary Generalization

Fig. 2. IEEG, time-frequency plots, and spectral power at seizure start in a seizure that generalizes

(A)–(D) as in Fig. 1, but for a seizure that generalized. Here we observe increases in power outside of the seizure onset area (D).

Fig. 3. Changes in power occur outside the seizure focus at seizure onset

(A) Percentage of electrode contacts showing a significant increase in power at seizure onset time across different regions. The percent of contacts exhibiting changes is greatest in the ipsilateral mesial temporal region (seizure focus). On average, 38.6% of contacts ($n = 78$ seizures) in the ipsilateral mesial temporal region increased power at the time of onset. (B) Separates the findings by frequency band. Most changes outside of the seizure occur in the delta and theta frequency bands in the ipsilateral lateral temporal and ipsilateral frontal regions. IMT = ipsilateral mesial temporal; ILT = ipsilateral lateral temporal; IF = ipsilateral

frontal; CF = contralateral frontal; CLT = contralateral lateral temporal; CMT = contralateral mesial temporal

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Fig. 4. Extra-focal changes in power at seizure onset occur at low frequencies in ILT and IF regions

(A) Percent of contacts that show significant power increases at seizure initiation in seizures that remain focal ($n = 59$) compared with those that secondarily generalize ($n = 19$). In the ILT and IF regions, the percent of contacts exhibiting changes is significantly higher than in seizures that remain focal. (B) In seizures that remain focal, there are sparse changes outside of the focus. (C) In seizures that generalize, the majority of these changes occur in the delta and theta band. See Figure 3 for definitions of abbreviations.

Fig. 5. Global preictal increases in power occur in the delta, theta, and alpha frequency bands while decreases in power occur in the gamma and high gamma frequency bands

(A) Percent of electrode contacts that show significant power increases in preictal epochs [−35s −5s] of seizures that remain focal compared with those that secondarily generalize in the 6 patients with both types of seizure onset. (B)–(C) Percent of electrodes showing power increase, separated by frequency. This difference is most marked in the delta and theta bands of the ipsilateral regions and the alpha band of the frontal regions of seizures that generalize. (D)–(F) As in Fig. 5 A–C, but for significant power decreases. Most power decreases occur

in gamma and high gamma frequency bands of both seizures that remain focal and that generalize.

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Table 1

Patient Demographics and Seizures

Patient ID	Gender	Age, yrs	Seizure Localization	MRI Findings	Pathology	Engel Score (Follow up period)	# RF	# SG	# Total
1	M	47	Multifocal; including mesial temporal lobe	Normal	No resection		2	0	2
2	F	45	Bitemporal lobe	Normal	No resection		2	3	5
3	M	45	Bitemporal lobe	Normal	No resection		7	1	8
4	M	29	Mesial temporal lobe	Small area of left frontal encephalomalacia	Reactive gliosis temporal lobe structures and hippocampal formation with small infarct	1a* (9yr)	5	1	6
5	F	45	Mesial temporal lobe	Normal	No resection		0	1	1
6	F	65	Multifocal; including mesial temporal lobe	Normal [†]	No resection		1	0	1
7	M	29	Multifocal; including mesial temporal lobe	Normal	Microscopic infarct in white matter hippocampus, hypertensive vasculopathy	4 (8yr)	4	0	4
8	M	35	Bitemporal lobe	Right fronto-temporal atrophy with mild hyperintensity in right hippocampus	Dentate gyrus is thinned	1a (8yr)	10	0	10
9	M	36	Mesial temporal lobe	Normal [§]	No resection		3	0	3
10	F	30	Mesial temporal lobe	Anterior horn of right lateral ventricle consistent with periventricular/subependymal grey matter heterotopia	Hippocampal sclerosis	1a (6yr)	0	2	2
11	F	41	Mesial temporal lobe	T-2 hypersensitivity in posterior limb of internal capsule	Low grade astrocytoma in mesial temporal lobe structures	1a (5yr)	0	4	4
12	M	46	Mesial temporal lobe	Hypersensitivity of left temporal lobe	Mild gliosis of left temporal lobe. Small fragments of white matter in hippocampus	1b (5yr)	11	0	11
13	M	41	Mesial temporal lobe	Unspecific white matter abnormalities	No resection		7	0	7
14	M	47	Mesial temporal lobe	T-2 hypersensitivity left frontal lobe	Temporal lobe and hippocampus gliosis	1b (3yr)	2	1	3

Patient ID	Gender	Age, yrs	Seizure Localization	MRI Findings	Pathology	Engel Score (Follow up period)	# RF	# SG	# Total
15	F	38	Mesial temporal lobe	T-2 hypersensitivity in right precentral and superior frontal gyri	Mild hippocampus sclerosis and small glial scar in hippocampus	4 (3yr)	3	1	4
16	F	59	Mesial temporal lobe	Decreased definition of the laminar architecture of the hippocampus on the left side	Temporal lobe and hippocampus reactive gliosis.	2b [‡]	2	1	3
17	M	19	Mesial temporal lobe	T-2 hypersensitivity in medial temporal lobes; pronounced on right.	Right mesial temporal sclerosis	3a (2yr)	0	4	4
Total	Men = 10	--					59	19	78
Mean +/- Std	--	41.0 +/- 11.20					3.47 +/- 3.45	1.12 +/- 1.36	4.59 +/- 2.94

RF = remains focal; SG = secondarily generalizes

* Patient had one seizure in the setting of missed medications and stress 2 years post resection.

[‡] Arachnoid cyst cerebellar cistern

[§] Hypersensitivity in corona radiata

[‡] Lost to follow up