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Display of consistent ictal networks in refractory mesial temporal lobe epilepsy

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Abstract

Objective—Exploration of emergent ictal networks was performed in homogeneous subjects with refractory medial temporal lobe epilepsy.

Methods—Maximal Synchrony Index (SI) values were calculated for all electrode pairs for each second during 25 seizures and displayed as connectivity animations. Consistent temporal patterns of SI value and spatial connectivity were observed across seizures and subjects, and used to define a sequence of network stages.

Results—Highest SI values were found in electrodes within the area of surgical resection. Analysis of these electrodes by network stage demonstrated lateral temporal cortex dominance at seizure initiation, giving way to hippocampal synchrony during the major portion of the seizure, with lateral temporal regions re-emerging as the seizure terminated. SI values also corresponded to behavioral severity of seizures, and lower SI values were associated with post-surgical seizure freedom.

Conclusion—SI based methods of network characterization consistently display the intrinsic MTLE ictal network and may be sensitive to clinical features.

Significance—Consistency of EEG-derived network patterns is an important step as network features are applied towards improvement of clinical management. These data confirm consistency of network patterns within and across subjects and support the potential for these methods to distinguish relevant clinical variables.

Keywords

Epilepsy; Hippocampus; Synchrony; Temporal lobectomy; Seizure; EEG; Quantitative EEG

1. Introduction

One hypothesis to account for the third of patients with refractory mesial temporal lobe epilepsy (MTLE) with continued seizures after epilepsy surgery (Wiebe et al., 2001; Spencer et al., 2005; Barbaro et al., 2009) is that surgery may merely interrupt an epileptic network rather than eliminate a discrete “epileptic focus” (Bear et al., 1996; Bragin et al., 2000; Spencer 2002; Bertram, 2003; Bettus et al., 2009). Understanding emergent network behavior may allow improved treatment selection for individual patients.

Analysis of synchronization of EEG patterns among brain regions is one method for examination of epileptic networks (Iasemidis et al., 1990; Valton et al., 2008; Wendling et al., 2010; Kramer et al., 2010; Ossadtchi et al., 2010). For example, high synchrony has been shown in structures important to seizure initiation (Ding et al., 2006; Warren et al., 2010; Bartolomei et al., 2010; Van Mierlo et al., 2011) and in the context of seizure termination (Schindler et al., 2007; Kramer et al., 2010). Other results suggest that interactions between mesial structures and neocortex are critical to seizure initiation (Moran et al., 2001; Wennberg et al., 2002; Bettus et al., 2008; Cadotte et al., 2009; Jiruska et al., 2010).

An important assumption in studies of this type is that there exists an intrinsic ictal network that is consistently demonstrable. Confirmation of this assumption is critical to enabling use of network features for parcellation of individual patients into clinically relevant groups. Consistent features of ictal functional networks have been previously reported in groups of heterogeneous subjects (Kramer et al., 2010) providing insight into principles of ictal physiology but limited in their anatomical interpretation. Evaluation of a more homogenous group, with nearly identical localization and etiology of epilepsy, addresses this issue. The purposes of this study were (1) to identify consistent ictal network spatial patterns within- and across-subjects in a highly selected sample of patients with MTLE with histopathologically-confirmed hippocampal sclerosis and known surgical outcomes and (2) evaluate whether features of these network patterns correspond to relevant clinical variables in this specific population.

2. Methods

2.1. Subjects and seizures

This retrospective, IRB-approved study evaluated patients with pre-operative diagnosis of medically-intractable MTLE who required intracranial monitoring because of insufficient localization after standardized, noninvasive presurgical evaluation including inpatient scalp video-EEG, MRI, neuropsychological battery, and interictal and ictal single-positron emission computerized tomography. Three of four patients had evidence of unilateral hippocampal sclerosis on MRI and all had post-operative histopathological confirmation. All had anterior temporal lobectomy and were followed for at least 2 years.

2.2. Intracranial EEG recording

Patients were implanted with bilateral, eight contact depth electrodes with 1 cm spacing (Adtech, Racine, WI) inserted occipitally, extending through the hippocampus and terminating in the entorhinal cortex. Bilateral subdural strips with 4–8 contacts, spaced 1 cm apart, were placed across anterior, lateral, and posterior frontal lobes and anterior, inferior and lateral temporal lobe regions (Supplementary Fig. S1A). Continuous video-EEG (Grass/Telefactor, Warwick, RI) was recorded at 200 Hz (60 Hz notch filter, high pass 1 Hz, low pass 70 Hz) using a distant, uninvolved subdural electrode as reference (Korzeniewska et al., 2011). All seizures were visually reviewed by a board certified neurophysiologist (GM or MQ) for motion, muscle, or electrical artifact. For each seizure, time and location of electrographic seizure onset and offset, clinical seizure onset time and severity [simple partial (SPS), complex partial (CPS) or secondarily generalized (GTC)], and behavioral state (sleep/wake) were determined. Processed EEG segments began one minute prior to electrographic seizure onset and ended 20 s after seizure termination. Only electrodes targeting similar anatomical regions among all patients were included for quantitative analysis.

2.3. Synchrony Index analysis and display of connectivity animations

The Synchrony Index (SI), a previously described measure of the strength of oscillator coupling (Kiss et al., 2007, 2008), has shown increased values during seizures, maximal in the area of seizure onset (Martz et al., 2008). The value incorporates both the local amplitude coherence of neuronal activity underlying a single electrode and the phase relationships of neuronal activities underlying different electrodes. The SI unifies symmetric, nondirectional, local neuronal coherence at two distinct sites, and the synchronization of their signals, to quantify the induced order between the two regions. Such a combined approach is promising for the identification within EEG data of distinct states driven by inter-regional synchronization changes (Mormann et al., 2005; Kiss et al., 2008).

Coherence of the neurons underlying an electrode, denoted by r , is calculated from the amplitude of the EEG signal at that electrode (relative to a common, uninvolved reference). Phase synchronization between distinct electrodes, denoted σ , is derived using the Hilbert transformation of the full band signal from each electrode. SI is calculated for two electrodes, k and l , as:

$$SI_{k,l} = \sigma_{k,l} \frac{(r_k + r_l)}{2}$$

where r_k and r_l are the average amplitudes of the respective signals, representing the local coherence, and $\sigma_{k,l}$ is the phase synchronization between the signals (Tass et al., 1998) for a specific time window. Further details on the theory and calculation of SI can be found in a previous study (Kiss et al., 2008).

Customized Matlab (R2009b/ Natick, MA) software was used to calculate SI values over the entire frequency band (1–70 Hz) in non-overlapping one second time bins for every possible pair of electrodes in an iterative fashion. Since the number of interactions among all

electrode pairs is large (total = $n(n-1)/2$), we determined in preliminary studies that an efficient method of displaying SI connectivity was through “connectivity animations” that allowed direct observation of time-dependent changes across the electrode array (Akiyama et al., 2010). For each electrode at each second, the highest SI value pair was plotted, indicating electrode pairing and magnitude, upon a brain schematic (Supplementary Fig. S1B), thus yielding an animated map of the highest connectivity for each electrode at each second. To demonstrate relative values of SI among electrode pairs, and to highlight statistically significant outlier electrodes, SI amplitude was represented on a normalized 255-bit color scale from low to high (red = highest 5% of SI values) (see representative connectivity animation movies; Supplementary videos S1–S4).

Connectivity animations from every seizure from all patients underwent blinded review. Standard EEG terminology was avoided to distinguish animation from EEG interpretations. “*focality*” was defined as 1–2 electrodes that featured visually increased SI amplitude for 3 s. Changes in SI amplitude occurring simultaneously in >80% of electrodes were considered “*global*”. A “*hub*” was defined as a spatial array in which 20% of electrodes were all maximally connected to a single electrode for 3 s.

This process led to the description of “stages” of SI connectivity based on empiric patterns of SI amplitude and spatial connectivity that were agreed upon by mutual subsequent review by the research group. Stages were correlated with standard visual analysis of EEG, using time zero as the seizure onset as determined by standard EEG analysis. Stage durations were analyzed as per cent time (%*T*), calculated by dividing each stage duration by the total duration of the connectivity animation/EEG sample (= 1 min + seizure + 20 s).

2.4. Statistical analysis

To enable inter-seizure and inter-subject statistical comparisons, several steps were performed for normalization of the maximum SI values used in connectivity animations.

Normalized maximal SI (nMaxSI) = for each electrode at all time points, the maximum SI value (regardless of which other electrode was paired with it for that value at that second) was divided by the largest observed maximum SI score of any electrode within that seizure and subject. The resultant nMaxSI ranged from 0 to 1 (see Supplementary Fig. S3).

Average nMaxSI = the mean value of nMaxSI of a specific electrode confined within an explicitly stated parameter (e.g., seizure, subject, stage or electrode).

Global average SI = mean nMaxSI across multiple explicitly stated parameters (e.g., average nMaxSI of all electrodes over all seizures for one subject, during a specific stage).

Differences in nMaxSI for each stage and electrode, and for stage by electrode interaction, were evaluated using generalized linear mixed models (GLMMs) within and across subjects, treating seizure as a random effect. For statistical comparison of SI distributions of electrodes, SI values for a theoretical average electrode were generated using the mean nMaxSI of all electrodes at each second in time. Contrasts exploring differences between electrodes and stages were conducted via comparisons to the theoretical average electrode

value. Associations between nMaxSI and clinical variables (surgical outcome, seizure severity, side of surgery, gender and behavioral state) were similarly explored. The Tukey–Kramer method was used to adjust for multiple comparisons (Kramer 1956). A GLMM was used to compare stage durations (%*T*) across subjects. All analyses were conducted using SAS 9.2 (SAS Institute, Cary NC).

3. Results

3.1. Seizures and subjects

Four subjects met criteria, with 25 of 26 seizures artifact-free (Table 1). Three subjects had simple partial and complex partial, while one had complex partial and secondarily generalized seizures. Clinically determined seizure onset zones (SOZ) were ipsilateral with MRI abnormality and with subsequent temporal lobectomy. Notably, seizures from subject B consistently had brief right hippo-campal onset, followed by predominantly left hippocampal representation on intracranial EEG, and this subject underwent right temporal lobectomy. The other three subjects had more typical uni-lateral temporal lobe seizure onsets. Two subjects were Engel Class 1a outcome at 2 years, while two were Engel Class 1d (see Table 1).

3.2. SI connectivity animations and network stages

Connectivity animations revealed six distinct stages, defined by consistent, stage specific, SI amplitude and spatial patterns (see Section 2). Stages were monotonic and evident in the majority of seizures from all subjects (Fig. 1). Please see representative connectivity animation movies (Supplementary videos S1–S4).

Stage 1: Baseline (Fig. 1, column 1): The baseline, preictal stage was marked by diffuse, randomly distributed, low amplitude SI connections. No dominant spatial pattern was observed, though there were brief episodes of focality in the SOZ rarely persisting more than one second in duration.

Stage 2: Early focality (Fig. 1, column 2): Within a mean latency of 3.8%*T* (SD 10.8, range (–34)–24) after seizure onset, *focalities* emerged with durations between 2 and 4 s. The majority were located in cortical regions not within the clinically determined SOZ. These occurred on an unchanged background of low SI values elsewhere across the array and the spatial pattern remained disorganized. This stage lasted a mean of 10.6%*T* (SD 11.7, range 2–48).

Stage 3: Pre-hub (Fig. 1, column 3): This stage was often characterized by a shift in the location of the *focality* to electrodes within the SOZ. Typically as the second focality emerged the initial focality attenuated. Despite this change in focality location, the baseline pattern persisted across the rest of the electrode array. This stage began at a mean of 14.8%*T* (SD 10.2, range 4–38) and lasted a mean of 7.6%*T* (SD 5.1, range 2–17).

Stage 4: Hub (Fig. 1, column 4): The random spatial connectivity pattern seen in earlier stages abruptly coalesced to a dramatic *hub* pattern, with nearly all electrodes sharing their maximal SI connection to a single electrode that had been part of the pre-hub *focality*. The

hub emerged at a mean latency of 22.3%*T* (SD 11.5, range 9–49) and dominated the array for an average of 25.7%*T* (SD 12.5, range 3–67). In 22/25 seizures, the *hub* center corresponded to the SOZ (correlations detailed below).

Stage 5: Global SI increase (Fig. 1, column 5): This stage manifested as an abrupt increase in SI values across the entire array (mean latency 46.8%*T* (SD 20.5, range 12–98)), such that nearly every electrode simultaneously surpassed the 95th percentile threshold. Despite this marked increase in SI values, the spatial connectivity pattern – the *hub* – persisted. This stage comprised the majority of each seizure duration (49.5%*T* (SD 18.6, range 14–79)).

Stage 6: Late focality (Fig. 1, column 6): Near seizure termination (mean latency 96.0%*T* (SD 17.4, range 37–115); duration 19.6%*T* (SD 14.6, range 1–62)), the spatial connectivity pattern again became diffuse, and the SI values of the majority of the electrode connections decreased to nearly baseline levels, leaving focality primarily in the *hub* region.

The durations and sequences of SI connectivity stages were highly consistent within and among patients with a few exceptions. Five seizures (25%) lacked one SI stage. Absence of an SI stage did not correlate with clinical or EEG characteristics. Two of five seizures from subject B displayed spatial *hub* patterns but had small overall SI amplitude ranges, and thus clear stage transitions could not be visualized. Thus only two atypical seizures, of 25 total, were omitted from further analysis.

Duration (%*T*) of each network stage was similar across subjects (Supplementary Fig. S2). The early focality stage (stage 2) was significantly longer for subject D than for subject C ($p < 0.05$), likely due to (a) two of this subject's three seizures had no discernible pre-*hub* stage (stage 3), such that the early focality lasted until the emergence of the *hub* stage (stage 4) and (b) in one seizure, the early focality stage began nearly a minute before time zero.

3.3. SI characteristics

For each subject, nMaxSI values averaged across all electrodes showed a characteristic temporal profile with lowest values during the baseline stage, rising through pre-*hub* and *hub* stages (stages 3–4), peaking at the Global Maximal SI stage (stage 5), and dropping as late focality occurred (Fig. 2). These average nMaxSI differences by stage were statistically significant ($p = 0.002$).

Analysis of individual electrodes global average nMaxSI across seizures and subjects identified highest values at sites in the hippocampus and lateral temporal cortex, (Fig. 3A). This same distribution was confirmed in every seizure (Fig. 3B). These electrodes were identical to those central to the focalities and *hub* seen during connectivity animations, and were within the SOZ and resected region in 3 of 4 subjects. Conversely, electrodes in the contralateral frontal lobe, far from the SOZ, had significantly lower global average nMaxSI than the rest of the array ($p = 0.05$).

Evaluation of average nMaxSI of individual electrodes during network stages revealed characteristic spatiotemporal patterns during seizures (Fig. 3C). During Baseline and early focality (stages 1–2), lateral temporal electrodes showed highest nMaxSI (not significant).

During pre-hub and hub stages (stages 3–4), ipsilateral hippocampal electrodes had significantly elevated nMaxSI. Lateral temporal electrodes re-emerged with highest nMaxSI during the global increased SI stage (stage 5) and remained elevated through late focality (stage 6) while nMaxSI declined in the hippocampal electrodes (Table 2). Of note, for subject B, average nMaxSI of right hippocampal electrodes, identified as the SOZ by standard visual analysis of EEG, never significantly differed from the mean.

The significant elevation and characteristic temporal behavior of nMaxSI of electrodes within the ipsilateral hippocampus and lateral temporal region was a property consistently found among individual seizures, pooled seizures within individual subjects and across pooled subjects (Table 2). The sole exception was subject D, for whom hippocampal electrode pairs showed trends towards higher values but were not significantly elevated above the theoretical average electrode values (likely underpowered with only three seizures recorded).

3.4. Clinical correlations

SOZ and surgical outcomes: As demonstrated above, nMaxSI and the electrode location of seizure hubs corresponded to the precise electrodes of the SOZ and subsequent surgical location in 3 of 4 subjects. The one subject in whom nMaxSI did not identify the SOZ was Subject B. This subject had brief, focal EEG onset within the right hippocampus with rapid spread and subsequent evolution mainly expressed in the left hippocampus. The SI network topology revealed prominent left hippocampal connectivity in pre-hub and hub stages (stages 3–4) (Table 2). This subject underwent right-sided resection, and was not seizure-free 2 years after surgery. Lack of correspondence between visual analysis and SI methods may relate to subsequent seizure recurrence.

Potential for prediction of surgical outcome was further suggested by the finding that global average nMaxSI was significantly lower among patients with Engel Class 1a than those with Class 1d ($p = 0.018$). Stage-level analysis demonstrated that this finding was driven by significantly higher SI values ($p < 0.0001$) during the seizure hub stage (stage 4) in subjects with continued post-operative seizures (see Supplementary Fig. S4).

Seizure severity and state: Complex partial seizures (those with impaired consciousness) had higher nMaxSI during the Globally Increased SI stage (stage 5) than did seizures with retained consciousness (SPS) ($p < 0.001$) (Fig. 2). Seizures arising from wake did not differ in SI characteristics from those arising from sleep. Notably, baseline nMaxSI of electrodes within and outside the SOZ did not differ by sleep-wake state.

Other patient characteristics: No SI network properties differed by gender ($p = 0.699$) or side of resection ($p = 0.231$).

4. Conclusions

This study of emergent ictal network patterns among a highly selected sample of subjects with MTLE demonstrated several important properties. (1) The methodology of connectivity animations effectively displayed complex connectivity data allowing visual determination of

distinct stages of maximal network synchrony corresponding to seizure initiation, propagation, and termination. (2) Spatiotemporal ictal features were consistent within- and across-subjects. (3) The measure of normalized maximum SI, calculated iteratively among all electrode pairs, agreed well with seizure localization by traditional clinical interpretation of EEG. (4) SI values differed by severity of seizures, with greater amplitudes of synchrony indicating greater impairment of consciousness. (5) SI values differed by surgical outcome, demonstrating higher values among patients who did not become seizure-free.

The primary limitation of this study is the small sample of highly selected patients; further examination with larger samples is required to confirm the identified clinical and pathophysiological trends. Although the sample is small, it represents a rare group since many patients with hippocampal sclerosis do not require the use of intracranial electrodes in presurgical evaluation. Not only were patients highly uniform in having unilateral MTLE with histopathologically confirmed HS, but electrode locations were broadly distributed (bilateral frontal, temporal, and hippocampal) and highly similar among patients. The homogeneous selection insured that SI findings could be validated in the setting of a well-defined syndrome with known pathophysiology, localization, surgical resections, and outcomes. Subsequent use of SI techniques in a wider population – such as those patients with nonlesional extra-temporal neocortical epilepsy or patients with “dual pathology” (Diehl et al., 2002; Kim et al., 2010) – can therefore be evaluated against a clear clinical reference that this highly selected sample provides. Finally, despite the advantage of highly homogeneous pathophysiology and electrode locations, the size of the sample (both in patients and in seizures) is comparable to other published studies (D’Alessandro et al., 2005; Valton et al., 2008; Wilke et al., 2009; Ossadtchi et al., 2010; Van Mierlo et al., 2011).

The most important observation from this analysis of emergent spatiotemporal SI-derived ictal network patterns was their consistency and reproducibility within a homogenous group of seizures from subjects with unilateral MTLE. Our data persistently revealed increased maximal lateral temporal synchrony around the time of seizure initiation, followed by transition of this synchrony peak to the mesial structures, followed by incorporation of more distant structures into this network linked to the mesial structures as the seizure propagated. Synchrony then increased globally across the brain during the major clinical portion of the seizure. With termination, synchrony once again decreased, leaving a relative peak in the lateral temporal structures as the ictus terminated.

In contrast to our findings, multiple authors have previously reported desynchronization at or before seizure onset both within the onset zone and broadly across the recorded network, perhaps correlating with a peak in gamma power. Most also report steadily increasing synchrony as the seizure continues. (Netoff and Schiff, 2002; Mormann et al., 2003; Wendling et al., 2003; Schindler et al., 2007). This difference is most likely due to methodological differences highlighting different features of the ictal network.

We used a full band EEG signal, whereas other studies focused on the gamma band (60–90 Hz) (Wendling et al., 2003). Although our broadband approach may have limited the detection of seizure onset or subtle shifts in network dynamics (Mormann et al., 2003), it was deemed suitable for this initial investigation of network dynamics, given that our

intention was to evaluate synchronization within the context of whole brain network patterns.

Another technical issue is that the nMaxSI, which is derived from the normalized single maximal SI value per electrode, may mask decreases in SI values over the range of interelectrode interactions for that same electrode. Despite this limitation, the use of peak values was deemed appropriate given the intention of detecting the dominant interactions across the ictal network, and was seemingly justified by the agreement of the SI findings with the clinical data.

Finally, we used a common reference electrode, which has been reported to most accurately reflect a network of mixed intracerebral and subdural electrodes (Korzeniewska et al., 2011), whereas others have used bipolar nearest neighbor montages (Schindler et al., 2007), which alters the amplitudes and phases of the resulting signals and the relationship of each signal to other more distant signals.

Beyond technical differences, the SI metric may have different properties than previously published measures of synchrony, though it has been reported that different classes of metric behave similarly qualitatively (Quiroga et al., 2002). Compared to correlative, coherence-based or phase-synchrony based measures, the SI performed most similarly to coherence-based measures. Authors reporting desynchronization at seizure onset tend to use correlative measures, often with zero-time lag (Wendling et al., 2003; Mormann et al., 2003; Schindler et al., 2007, 2010). The SI, conversely, is not limited to in-phase relationships because synchronization is calculated throughout phase cycles. Thus, an anticorrelated signal would be considered “synchronized” under our methods and result in an increase of SI. Nonetheless, the timing of the major mid-seizure synchrony increase in our data was remarkably similar to that seen in the correlation-based studies (Wendling et al., 2003; Schindler et al., 2010). Perhaps coherence-based methods are less sensitive to changes at seizure initiation, though our use of only peak SI values was likely also a factor in this difference.

Given the above limitations, a conservative interpretation of the temporal neocortical dominance at onset and termination of seizures is the hypothesis that “limbic seizures” require a cortico-hippocampal interaction for initiation (Fountain et al., 1998; Bertram et al., 1998). In rodents, entorhinal input has been shown to modulate the timing of hippocampal firing (Sullivan et al., 2011). The extent and behavior of the ictal network may impact surgical outcomes. Distinct electrographic signatures have been described for seizures originating in different regions of the limbic network (Spencer and Spencer, 1994; Bonilha et al., 2012), and our results offer a possible method for distinguishing these subtleties.

Synchrony-based techniques appear to yield distinct, consistent stages in progression of ictal networks, allowing visualization of how a region of “seizure onset” interacts with other brain regions in reproducible patterns. Furthermore, we found higher SI values among patients who had recurrent post-operative seizures, though our small sample size prevents firm conclusions regarding this finding. Future work may strengthen these clinical associations, and extend to cognitive and other dysfunction reported during interictal periods

in patients with MTLE (Akanuma et al., 2003). The ultimate purpose of network characterization is to enhance understanding of epilepsy and its treatment, a goal these data suggest may be achievable as these techniques are further refined on larger subject groups.

5. Significance

We conclude that the consistent visual appearance of a hub – centered within the hippocampus and closely coupled to ipsilateral temporal neocortex – is a striking mathematical support of the concept of intrinsic epileptic networks (Bertram et al., 1998; Spencer 2002) in patients with MTLE. Furthermore, these networks may be reliably displayed using EEG-based connectivity measures – the values and localization of which may reflect clinically relevant information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- EEG-derived ictal networks were created among subjects with refractory mesial temporal lobe epilepsy using the previously published Synchrony Index.
- Distinct ictal network stages were identified that were consistent across seizures and subjects.
- Synchrony Index values during specific ictal stages were significantly lower in subjects with post-operative seizure freedom.

Fig. 1.

Seizure network stages manifested by maximal SI connections. (A and B) Raw left hemispheric intracranial EEG tracings for a simple (A) and complex partial seizure (B) from subjects A and C, respectively. Lobar electrode locations are indicated: F = frontal, P = parietal, TC = temporal neocortex, H = hippocampal depth electrodes. Time of corresponding network stage still image is demarcated for each seizure. SzO = seizure onset, EF = early focality, PH = pre-hub, GSI = global SI increase, LF = late focality. (C) Single-second images displaying representative patterns of SI network stages. SI values are shown on schematic brain image (see Supplementary Fig. S1). For each electrode, the maximal SI value pairing is displayed as a line between the paired electrodes. Each electrode and the

line are colored according to the SI value. An electrode involved in more than one connection is colored according to its highest SI value pairing. Color scales are specific to each seizure. Blue indicates low SI value; red indicates high SI with maximum red intensity for values above the 95th percentile. Similar spatiotemporal patterns emerged monotonically during seizures for each subject. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 2.

Normalized average SI values for each seizure across network stages. For all seizures from each subject, the normalized average maximum SI value across all electrodes is displayed for each network stage. Clinical severity of seizures is indicated by color (SPS = simple partial, CPS = complex partial, GTC = secondary generalized tonic-clonic seizure). Temporal pattern of average SI value was similar for behaviorally similar seizures both within and across subjects. CPS had higher SI values than SPS during global SI increase (stage 5) ($p < 0.001$).

Fig. 3.

Hippocampal and temporal cortical electrodes SI value distributions during seizures.

Electrodes with highest average nMaxSI correlated well with area of seizure manifestation by visual analysis. Electrodes identified at the group level were at the top of the distribution for each individual seizure. Stage analysis revealed that lateral temporal cortex dominates the early and late portions of seizures, while the hippocampus had highest connectivity during the hub stages. (A) Least square means for each electrode across all subjects, seizures, and network stages. Dashed horizontal line represents the global average nMaxSI. Red dots show electrodes with significantly increased SI value, while black dots show those with significantly reduced SI value (adjusted $p < 0.05$). L = left, R = right F: frontal, H: hippocampus, TC: temporal cortex. (B) Average SI value of ipsilateral hippocampal (red) and temporal neocortical (green) electrodes shows them consistently at the top of the distribution for all analyzed seizures. Mean SI value for each seizure in gold. (C) Average nMaxSI across seizures for each electrode at each network stage is plotted for each subject. Hippocampal electrodes (red) show higher connectivity during the hub stages (3 and 4), then recede as seizures terminate. Conversely, lateral temporal electrodes (green) dominate at the onset and termination of seizures (stages 1, 2, 5, 6) with less variability across stages. (For

interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Clinical characteristics of temporal lobe epilepsy subjects.

	Subject A	Subject B	Subject C	Subject D
Sex	Female	Female	Female	Male
Age at onset	36	15	22	<1
Age at surgery	41	54	36	16
Side of surgery	Left	Right	Left	Left
Surgical pathology	HS	HS	HS	HS/FCD
Engel class at 2 years	1d	1d	1a	1a
No of Sz analyzed	4	7	11	3
Average duration (s)	130	170	90	139
Duration range (s)	51-232	135-200	57-203	73-196
SPS	2	2	1	0
SCPS	2	5	10	1
2GTC	0	0	0	2
Ictal EEG Localization	Left	Right to left	Left	Left
IEDs	Left	Right	Bilateral	Left
Interictal slowing	Left temporal	Right	Left	Left
MRI	Normal	Right MTS	Left MTS	Left temporal T2
SPECT	Symmetric	Right	Left	Left

Table 2

Electrodes with higher SI value by stage and subject.

Electrode	Pre-hub	Seizure hub	Global SI	Late focality
LOD01	A, Group	A, B, C, Group		
LOD02	A, Group	A, B, C, Group	C, Group	
LOD03		C, Group		
LOD04		B*, Group*		
LOD05		B, Group*		
LOD06		B		
LTA02			A, C, Group	C, Group*
LTA03			A, C, Group	C
LTA04			C, Group	
LST01		A		

Rows indicate all electrodes that displayed significantly elevated nMaxSI during any stage for any subject. Letters A-C signify individual subjects; "Group" indicates mean nMaxSI across subjects. All p-values were <0.01 (adjusting for multiple comparisons), except where * indicates $0.05 > p\text{-value} > 0.01$. There were no significant electrodes during the baseline or early focality stages. High SI values for individual electrodes indicate these electrodes had disproportionately strong connectivity during that seizure stage. Note the transition from elevated hippocampal electrodes (LOD) during hub stages to lateral temporal electrodes (LTA, LST) during global SI and late focality stages (see Supplementary Fig. S1 for precise electrode labels).