FULL-LENGTH ORIGINAL RESEARCH

Reactivation of seizure-related changes to interictal spike shape and synchrony during postseizure sleep in patients

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Summary

Objective: Local field potentials (LFPs) arise from synchronous activation of millions of neurons, producing seemingly consistent waveform shapes and relative synchrony across electrodes. Interictal spikes (IISs) are LFPs associated with epilepsy that are commonly used to guide surgical resection. Recently, changes in neuronal firing patterns observed in the minutes preceding seizure onset were found to be reactivated during postseizure sleep, a process called seizure-related consolidation (SRC), due to similarities with learning-related consolidation. Because IISs arise from summed neural activity, we hypothesized that changes in IIS shape and relative synchrony would be observed in the minutes preceding seizure onset and would be reactivated preferentially during postseizure slow-wave sleep (SWS).

Methods: Scalp and intracranial recordings were obtained continuously across multiple days from clinical macroelectrodes implanted in patients undergoing treatment for intractable epilepsy. Data from scalp electrodes were used to stage sleep. Data from intracranial electrodes were used to detect IISs using a previously established algorithm. Partial correlations were computed for sleep and wake periods before and after seizures as a function of correlations observed in the minutes preceding seizures. Magnetic resonance imaging (MRI) and computed tomography (CT) scans were co-registered with electroencephalography (EEG) to determine the location of the seizure-onset zone (SOZ).

Results: Changes in IIS shape and relative synchrony were observed on a subset of macroelectrodes minutes before seizure onset, and these changes were reactivated preferentially during postseizure SWS. Changes in synchrony were greatest for pairs of electrodes where at least one electrode was located in the SOZ.

Significance: These data suggest preseizure changes in neural activity and their subsequent reactivation occur across a broad spatiotemporal scale: from single neurons to LFPs, both within and outside the SOZ. The preferential reactivation of seizure-related changes in IISs during postseizure SWS adds to a growing body of literature suggesting that pathologic neural processes may utilize physiologic mechanisms of synaptic plasticity.

KEY WORDS: Seizure, Interictal spike, EEG, Neural plasticity.

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Local field potentials (LFPs) display seemingly stereotyped waveform shapes (e.g., sharp-wave/ripples or K-complexes) that may be involved in different aspects of neural computation.[1] LFPs arise from the summed synaptic and axonal activity of large numbers of neurons, and are known to organize neural activity[2,3] and other LFPs.[4] Physiologic LFPs have been shown to undergo subtle changes following spatial learning, such that spatial location can be decoded from changes in hippocampal theta[5] and sharp-wave/

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Key Points

- The shape and relative synchrony of IISs change in the minutes preceding seizure onset
- These changes are reactivated during postseizure SWS, consistent with consolidation theory
- Reactivation of correlations is strongest when at least one macroelectrode is located within the SOZ

ripples,[6] but it is unclear whether these changes are associated with permanent changes to neural circuitry.

Interictal spikes (IISs) are pathological LFPs associated with epilepsy.[7] Although mechanisms underlying IIS generation remain unclear, generation of IISs is thought to involve a paroxysmal depolarizing shift (PDS) during the initial, rapid rise of the spike, followed by a longer hyperpolarization phase.[8,9] This theory has been augmented to include observation of changes in neural activity preceding IIS onset by hundreds of milliseconds,[10–13] but mechanisms by which single neuron activity generated locally or propagated through brain tissue contributes to IIS shape remain unclear.[14,15] Although a rich literature has established a correlation between IISs and seizure-generating brain regions,[10,16–18] and IISs often serve as biomarkers for tissue resection,[7,19] little is known about how various shapes of IISs arise. IISs recorded from individual electrodes may display multiple clusters of shapes that could arise from dynamic changes in local circuitry,[20] but within each cluster the shape and relative synchrony of IISs remain fixed during interictal epochs.

Recently, seizures have been shown to activate sparse, specific neuronal populations, including regions outside the seizure-onset zone (SOZ) in rodents[21] and humans.[22] Seizure-related activity changes have been observed again during postseizure slow-wave sleep (SWS), even when seizure and sleep epochs are separated by hours,[23] suggesting persistent alteration of neural circuitry. This phenomenon has been labeled seizure-related consolidation (SRC), because of similarities to cellular consolidation[24,25] observed through ensemble reactivation during postbehavioral SWS. Reactivation describes the reemergence of coordinated activity first observed during a behavioral task (e.g., running a maze). Reactivation is measured by the use of partial correlation analysis, which describes changes in correlation following a behavioral event given preexisting correlations. Reactivation is a population phenomenon; changes observed in individual neurons can be subtle, whereas effects across a population can be substantial.[24] Because these changes persist after cessation of the original behavior, cellular consolidation is thought to be involved in the formation of long-term memories.[24–26]

Because IISs arise from summed synaptic and axonal currents,[27,28] seizure-related changes in neuronal activity could alter IISs. Although learning has been shown to change spectral power in theta,[29] persistent changes in in vivo waveform morphology or synchrony of temporally discrete LFP associated with prior experience have not been reported. Changes in the relative rates of different types of IISs have been linked to epileptogenesis[30,31]; however, seizure-dependent changes in IIS shape and synchrony have not. Seizure-related changes in single neuron activity prior to and following seizures (SRC) provide a plausible mechanism by which such changes could occur, namely, by "hijacking" learning-related neural mechanisms.[32] We therefore hypothesized that changes in IIS shape and synchrony should be observable prior to seizures and reactivated during postseizure SWS.

Materials and Methods

Patients

Informed consent was obtained from patients undergoing intracranial electroencephalography (iEEG) monitoring for drug-resistant mesial temporal lobe epilepsy (MTLE) in this Mayo Clinic Internal Review Board–approved research protocol. Hybrid, polyurethane depth electrodes (diameter 1.3 mm, AD-Tech Medical Instrument Corp., Racine, WI, U.S.A.) containing platinum-iridium clinical macroelectrodes (4 or 8 contact, 2.3 mm long, 5 or 10 mm spacing, 200–500 Ω) and research microelectrodes (9 or 18 oriented radially along the shaft between macro contacts and a bundle of 9 extending from the tip, 40 μm diameter, 500–1,000 kΩ) were placed stereotactically into the mesial temporal lobe using an occipital or lateral approach. For both posterior and lateral approaches, the number, location, trajectory, and depth of electrodes placed were similar across patients (one per hippocampus for posterior approach; three per hippocampus for lateral approach). Longitudinal electrodes were placed under imaging guidance (Stealth, Medtronic, Inc., Minneapolis, MN, U.S.A.) to avoid vasculature. Following surgery, scalp electrodes were placed in a modified configuration (described below) to avoid the craniotomy used for intracranial electrodes.

Data acquisition

Scalp and intracranial macroelectrodes were sampled at 32 kHz by a Neuralynx (Bozeman, MT) Cheetah recording system and then filtered offline (10 kHz low-pass digital filter) and down-sampled to 5 kHz for analysis. Unlike the previous study,[23] only continuous EEG obtained from clinical macroelectrodes were analyzed. In all cases, a referential montage was used, with reference to a subgaleal strip macroelectrode.

Sleep scoring and identification of seizures and behavioral epochs

Scalp recordings were obtained from all patients for use in sleep scoring. Visual, manual sleep scoring was

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performed by a neurologist (EKS) board certified in sleep medicine (ABSM and ABMS/ABPN) and electroencephalography (ABCN and ABMS/ABPN CNP) in accordance with standard methods,[33,34] with modification for omission of electrooculography (EOG) recording in some patients. Stage W (Wake) was determined by the presence of eye blinks and rapid eye movements visualized in EOG on frontal scalp electrodes, FP1 and FP2, accompanied by posteriorly dominant alpha (8–13 Hz) frequency rhythms with eyes closed, and comprising >50% of the epoch (i.e., ≥16 s within a 30 s epoch). N3 (slow wave) sleep was scored when high voltage (>75 μV) delta (0.5–2.0 Hz) frequency EEG activity was seen in at least 20% of the epoch (i.e., at least 6 s within a 30 s epoch) in the frontal scalp derivations, using conventional International 10–20 System scalp electrode placements at FP1, FP2, FZ, F3, F4, CZ, C3, C4, O1, O2, and Oz, referenced to a subgaleal strip electrode. Behavioral epochs were the same as identified previously[23] as continuous epochs of either SWS or Wake lasting at least 3 min within 2 h before a seizure (the "Pre" epoch) or within 6 h after a seizure (the "Post" epoch) (Fig. 1A,B), as well as the 5 min preceding seizure onset, called the "Near-Onset" epoch. Control epochs were identified according to the same criteria as above, but for a time-shifted centering point four hours before each seizure.

Identification of interictal spike (IIS) detection and preprocessing

All data used for analysis other than sleep scoring were obtained from intracranial macroelectrodes. All pre processing was done using Matlab. IISs were detected objectively using an automated detection described previously.[35] Continuous, iEEG data were low-pass filtered (200 Hz), windowed, and centered on the peak energy of identified IISs. The window for IISs extended ±50 msec around the peak energy time (Fig. 1C). For each IIS detection, the following parameters describing waveform morphology were computed: peak amplitude (the most negative voltage value in the 100 msec window), valley amplitude (the most positive voltage value in the 100 msec event), energy (square root of the sum of the squared amplitude), and absolute peak amplitude (the maximum absolute value). For each IIS detection, the correlation coefficient (Matlab 'corrcoef', Eqn. 1) was computed across all macroelectrodes, regardless of whether an IIS was detected on the other macroelectrodes, and the results were stored to a MySQL database:

$$r = \frac{n\sum xy - (\sum x)(\sum y)}{\sqrt{\left[n\sum x^2 - (\sum x)^2\right]\left[n\sum y^2 - (\sum y)^2\right]}} \quad (1)$$

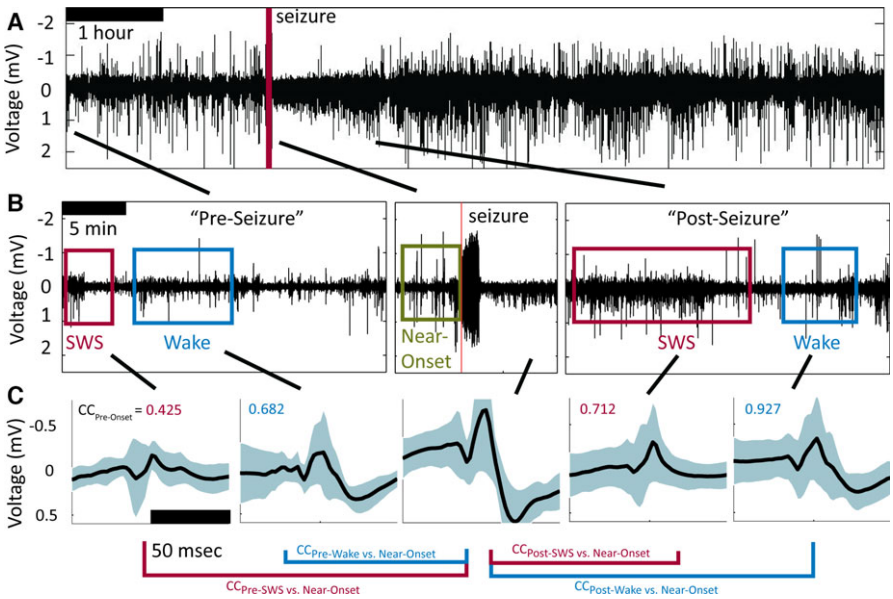

Figure 1.
Interictal spikes (IISs) within identified behavioral epochs during long-duration, continuous recordings around a spontaneous seizure. (**A**) Low-pass filtered intracranial EEG (iEEG) data from −2 h to +6 h around a seizure. (**B**) Behavioral epochs identified from scalp EEG ("Wake" [blue box] and "SWS," Slow-wave sleep [red box]) that occurred close to one another in time, along with the Near-Onset behavioral window (green box). (**C**) Average IISs identified objectively by an established algorithm[35] for each of the five epochs for an electrode located in the SOZ. Solid black line shows the mean waveform and cyan bands show one standard deviation from the mean. Text in upper-left corner of each panel shows the correlation coefficient (CC) for the average waveform during that behavioral epoch with respect to that observed on the same macroelectrode during the Near-Onset epoch.
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where n is the number of IISs and x and y are the mean waveforms on each macroelectrode. As an additional measure of wave shape similarity, the Mahalanobis distance (Matlab Statistics and Machine Learning Toolbox 'mahal' Eqn. 2) was computed between IISs across behavioral epochs:

$$D_m(x) = \sqrt{(x-\mu)^T S^{-1}(x-\mu)} \quad (2)$$

where x is the matrix of all waveforms, μ is the mean waveform, and S is the covariance of x. The Mahalanobis distance is a unitless quantity (similar to a z-score) describing the number of standard deviations between two waveforms, weighted by the variance in each dimension; decreasing distance is associated with increasing similarity between waveforms.

Data analysis

All data analysis, statistics, and figure generation were done in R (http://www.R-project.org/) and Matlab (Matlab R2011b, The MathWorks Inc., Natick, MA, U.S.A.). Because correlation coefficients (CCs) from macroelectrode pairs are bounded on [−1 1], partial correlations were computed using beta (or standardized) regression to determine statistical significance when comparing CCs from different behavioral epochs ('betareg' in R).[36] The result is an estimate of the strength of the predictor variable on the dependent variable, which is measured as a z-score (i.e., in terms of standard deviations).

Results

Data were acquired from nine seizures in six patients (one seizure in three patients and two seizures in the remaining three patients). Using data obtained from scalp electrodes, a total of 279 min of behaviorally consistent windows were identified for five conditions: before seizures (the "Pre" epoch) for SWS (57 min) and Wake (64 min), after seizures (the "Post" epoch) for SWS (75 min) and Wake (83 min), and for 30 min prior to each seizure onset (the "Near-Onset" epoch). Using data obtained from intracranial macroelectrodes, 14,407 IISs were detected during the identified epochs (for individual patients: N = 2,751; 5,429; 631; 535; 1,381; and 3,680).

Changes in IIS shape are sparse and subtle

IIS shapes during the Near-Onset and Post epochs on some electrodes often appeared to be more similar to one another than those observed before the seizure, even though hours often intervened between the seizure and the subsequent behavioral epoch (Fig. 1C). Changes in IIS shape were subtle and observed only on a subset of macroelectrodes following a given seizure and appeared to be continuous, as opposed to all-or-none. Even in the SOZ, examples could be found where IIS shape was unchanged during Near-Onset and Post epochs compared to IISs during the Pre epochs (Fig. 2A). Consistent IIS shape following seizures was observed for macroelectrodes both within hippocampus (Fig. 2A) and outside hippocampus (Fig. 2B). Yet, when changes in IIS shape across epochs were observed during the Near-Onset epoch (Fig. 2C, SWS $p = 0.024$, t-test, Wake $p = 0.006$, t-test), similar changes in IIS shape were observed during the Post epoch. When changes in IIS shape were observed during Near-Onset and Post epochs on one macroelectrode (Fig. 2C), changes were not necessarily observed on neighboring macroelectrodes (Fig. 2B), suggesting that the observed changes in IIS shape did not arise from electrode movement or extracerebral artifacts.

To determine whether average IIS parameters were changed across all electrodes during time epochs (Pre vs. Post seizures) or behavioral epochs (Sleep vs. Wake), IIS shape parameters (waveform peak amplitude, energy, valley amplitude, and maximum absolute amplitude) and rates were computed for each channel and within-subject means were compared. No changes in average parameters were observed in any parameters for Pre and Post epochs relative to the Near-Onset epoch (Fig. 3). No change was observed in rate or absolute maximum amplitude, and there was no change observed in mean waveform CCs for a multifactor comparison (Wake vs. Sleep $p = 0.641$; Pre vs. Post $p = 0.495$; interaction $p = 0.370$; analysis of variance [ANOVA]). These results suggest that although specific instances of seizure-related changes in IISs were observed (Fig. 2C), little change was observed across the population of observed IISs; that is, IISs changed on only a subset of macroelectrodes.

Changes in and reactivation of IIS relative synchrony

The observation of sparse, subtle changes in IIS shape during Near-Onset that persisted into Post-SWS, even hours following a seizure was reminiscent of changes that were observed previously on a similar timescale and spatial distribution: seizure-related changes in single neuron activity.[23] Because IISs arise from the summed activation of single neurons, we hypothesized that increased single neuron correlations during the Near-Onset and Post-SWS epochs[23] alter IISs in a manner consistent with reactivation observed in single neuron activity.[23,24] To determine whether behavior-specific changes in IIS synchrony occurred, differences in CCs were computed for Post compared to Pre epochs and found to differ for SWS (0.036 ± 0.011; $p = 0.0486$; paired t-test), but not for Wake (-0.053 ± 0.084; $p = 0.559$; paired t-test). To determine whether these changes were consistent with reactivation, CCs were also computed for the Near-Onset epoch and partial regression computed for the Pre/Post epochs. After accounting for Pre-seizure CCs, Post-seizure CC changes were correlated to Near-Onset CCs, but only during SWS

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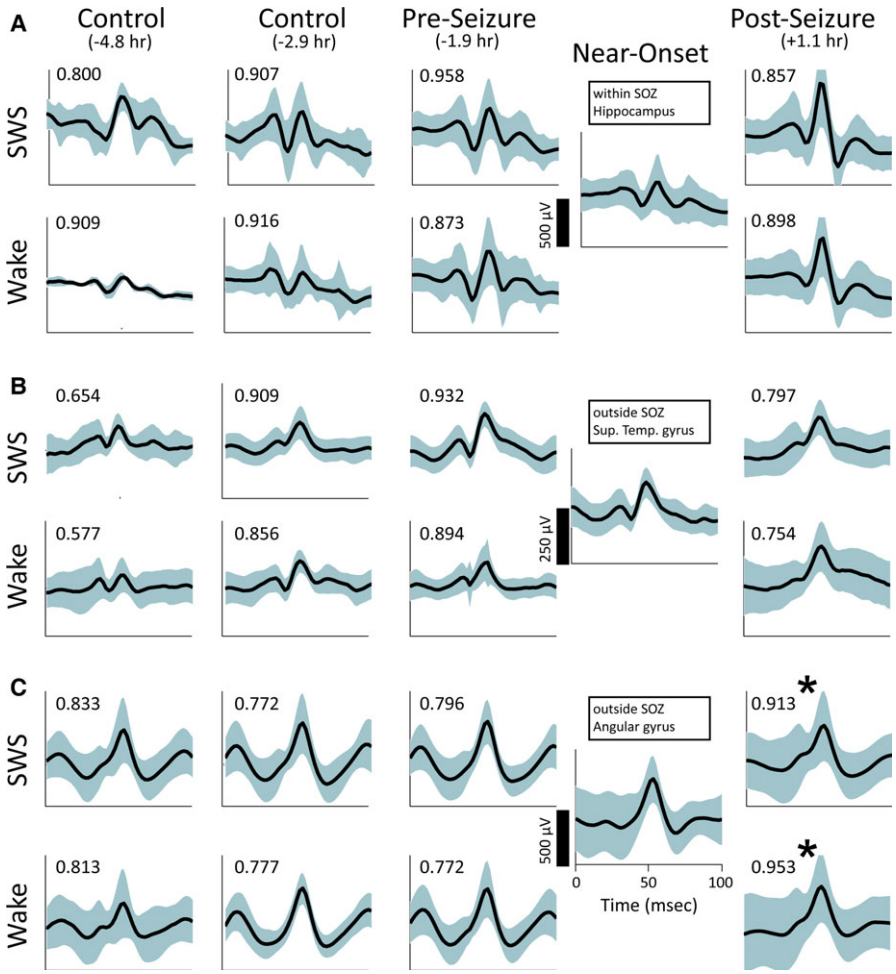

Figure 2.
Comparison of postseizure changes in IISs from macroelectrodes on a single depth electrode. In each panel, IISs are shown for slow-wave sleep (SWS) on the top row and Wake on the bottom row. Each column shows data from a specific behavioral epoch (left-to-right: Control epoch before a time-shifted seizure, Control epoch after a time-shifted seizure, Pre epoch before the actual seizure, Near-Onset before the seizure, and Post epoch after the actual seizure; the average time relative to seizure onset in each case is shown in parentheses.) The black line shows the mean IIS waveform. Cyan bands show one standard deviation above and below the mean. Text in the upper left of each panel shows the CCs for that behavioral epoch relative to the Near-Onset waveform. (**A**) The most distal macroelectrode, which was located in hippocampus and within the SOZ. (**B**) Macroelectrode located in the superior temporal gyrus and outside the SOZ. (**C**) Macroelectrode adjacent to that shown in **B**, but located in angular gyrus and outside the SOZ. IIS during Near-Onset and both SWS and Wake following the seizure differ from those preceding the seizure (*signifies $p < 0.05$, *t*-test).
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and not Wake (Fig. 4A, SWS: $p = 0.027$; Wake: $p = 0.159$; beta regression), consistent with reactivation. Beginning 30 min prior to seizure onset and separating the data into 1 min time bins, postseizure increases in correlation increased for SWS roughly 10 min prior to onset, whereas changes in CCs during Wake were never significant (Fig. 4B). For the control period shifted 4 h prior to seizure onset, differences in CCs for Post-seizure compared to Pre-seizure were not different from zero (SWS: 0.093 ± 0.084, $p = 0.306$; Wake: 0.047 ± 0.091, $p = 0.611$; beta regression). To determine whether selecting high/low Pre-onset CC pairs biased these results, the same analysis was repeated for an alternate measure of waveform separation (Mahalanobis distance) for these same epochs, which produced a similar result: decreases in Mahalanobis distance (i.e., increased similarity) were significant during SWS for pairs with high Pre-onset correlations ($\rho = 0.5591$, $N = 18$, $p = 0.0196$), whereas changes were not significant during SWS for pairs with low Pre-onset correlations ($\rho = 0.4459$, $p = 0.0728$), and changes in Mahalanobis distance were not significant during Wake for either high ($\rho = 0.0751$, $p = 0.7745$) or low ($\rho = -0.0029$, $p = 0.9911$) Near-Onset correlation pairs.

Changes in IIS relative synchrony during the Near-Onset epoch and their preservation in the Post epoch could be observed in the raw data obtained from specific pairs of

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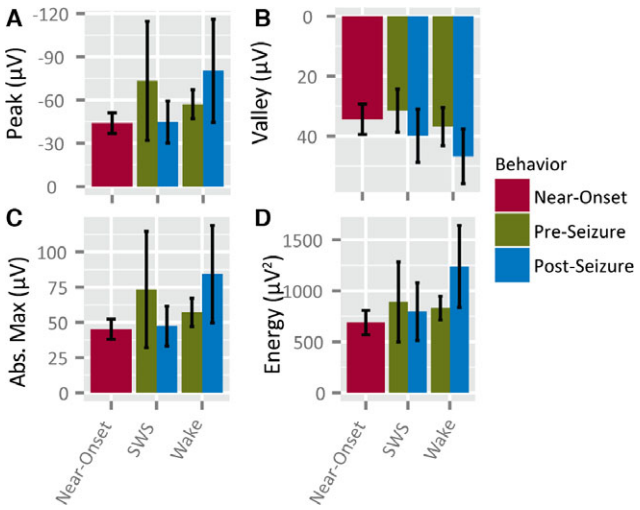

Figure 3.
IIS parameters do not change following seizures. (**A**) Peak voltage, (**B**) valley voltage of IIS, (**C**) absolute peak voltage (both positive- and negative-going voltage peaks), (**D**) energy (amplitude squared) of IIS.
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electrodes. The analysis described earlier provided a means for identifying electrode pairs that showed observable changes. Macroelectrode pairs were selected that had "Low" and "High" Near-Onset cross-correlations where both pairs shared a common electrode. That is, for one electrode, a different electrode was identified that displayed "Low" Near-Onset CCs with the first electrode, whereas a third electrode was identified that displayed "High" Near-Onset CCs with the first electrode. For the pair whose Near-Onset IIS cross-correlation was "Low" (actually anti-correlated; Fig. 5A.1), the CCs between IISs on these electrodes decreased following the seizure both during SWS (Pre: 0.9077; Post: −0.6313) and Wake (Pre: 0.6111, Post: −0.5926). Conversely, for the pair whose IIS cross-correlation was "High" during Near-Onset (Fig. 5B.2), the CC between IISs on these electrodes increased following the seizure during SWS (Pre: 0.9906; Post: 0.9957) and during Wake (Pre: 0.9908, Post: 0.9940). Changes in IISs could be observed as changes both in the shape of IISs on each macroelectrode and the relative timing of IISs between the two macroelectrodes. For the pair with "Low" Near-Onset CC (Fig. 5A.2), the peaks of the two average IIS waveforms shifted away from one another during Near-Onset, and this shift persisted for >2 h until the shift was reactivated following the seizure (Fig. 5A.2 "a"). For the pair with "High" Near-Onset CC, the peaks and valleys of the two average IIS waveforms shifted toward one another, and this shift persisted for >2 h following the seizure (Fig. 5B.2 "b" and "c"). Such changes in average IIS shape and synchrony were not observed between interictal control periods, regardless of behavior or time epoch (Fig. 4), suggesting that these

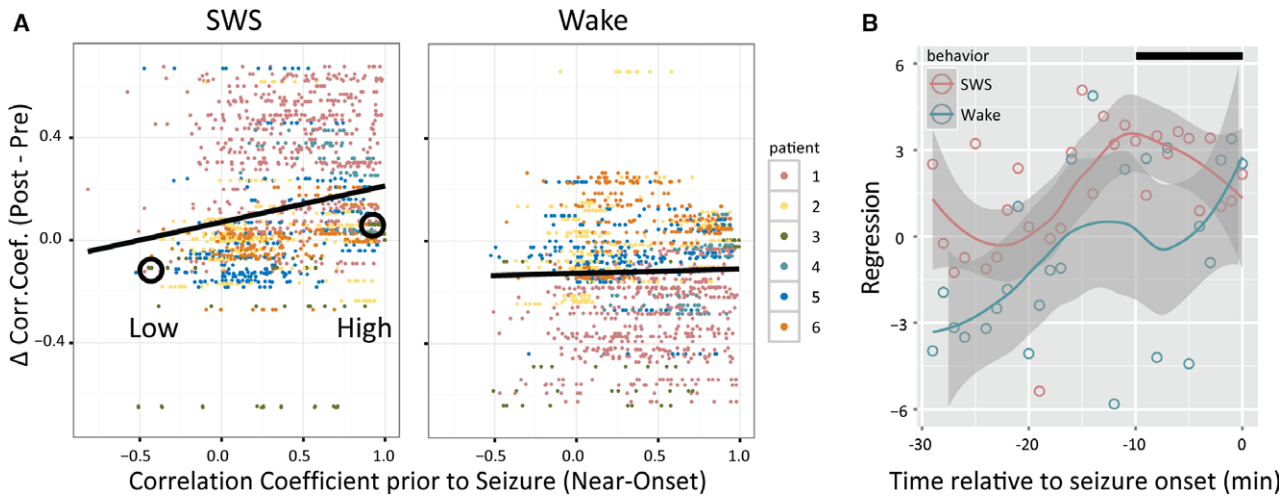

Figure 4.
Correlation coefficient of IISs show seizure-related consolidation (SRC) specific to slow-wave sleep (SWS). (**A**) Each dot shows the difference (during Post epoch minus during Pre epoch) in correlation coefficient (CC) between two macroelectrodes as a function of the CC in the 10 min preceding seizures. Differences in CCs increased during SWS as a function of the magnitude of CC prior to the seizure, but not during Wake (*$p < 0.05$, beta regression). Dot color denotes patient, as shown in the legend at right. (**B**) Beta regression coefficients during SWS and Wake for 1 min "seizure" time bins relative to seizure onset. The Loess confidence interval (gray band) for Wake (cyan) never differs from zero for the entire 30 min window prior to seizure onset. The confidence interval for SWS (magenta), however, is greater than both zero and the Wake confidence interval for most of the 30 min prior to seizure onset, except for the last few minutes prior to onset, when the confidence intervals overlap. The black bar at upper right denotes the 10 min time window used to compute the values shown in panel A. Circles denote macroelectrode pairs that are used as examples in Figure 5.
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changes in IIS shape arose from a different mechanism than that underlying normal, interictal variation in IIS generation.

To determine whether observed changes in IIS were related to the SOZ, the location relative to SOZ of each macroelectrode was established (see Methods) and CC values were grouped according to whether both macroelectrodes were "Inside" or "Outside" the SOZ, or whether the two electrodes were located "Across" the SOZ boundary. Partial regressions were computed for these post hoc groupings. For SWS, all groups showed significant, positive z-scores (Inside $z = 8.66$, $p < 1E\text{-}6$; Across $z = 9.83$, $p < 1E\text{-}6$; Outside $z = 3.21$, $p = 0.00131$, beta regression), whereas for Wake, all groups showed *negative* z-scores, but only the Inside group was significant (Inside $z = -3.50$, $p = 0.00046$, Across $z = -0.788$, $p = 0.431$, Outside $z = -0.513$, $p = 0.608$, beta regression) (Fig. 6).

Discussion

These results show that the shape and relative synchrony of IISs recorded on intracranial macroelectrodes change on a subset of macroelectrodes in the minutes preceding a seizure and that these changes are reactivated hours later.

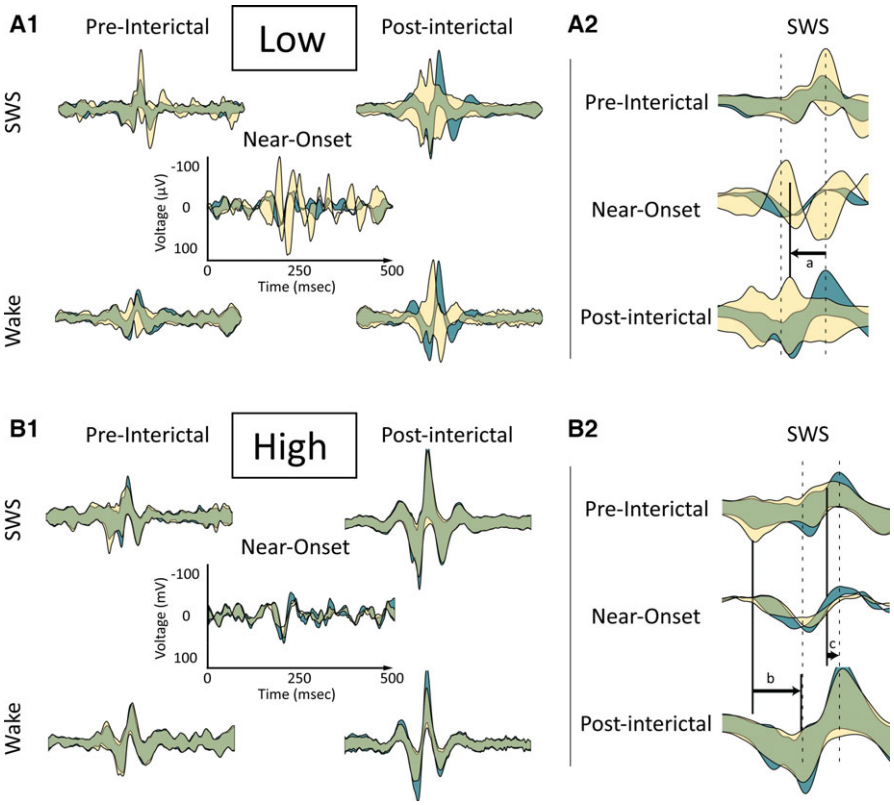

Figure 5.
Examples of IIS synchrony changes following a seizure based on correlation during Near-Onset. (**A**) "Low" Near-Onset correlation pair circled in Figure 4. (**A.1**) Average IISs ± one standard deviation for two macroelectrodes shown in cyan and yellow. IISs on the two macroelectrodes are centered to the peak of IISs recorded on the cyan waveform. Areas of overlap between the two appear as green. **top row:** slow-wave sleep (SWS), **bottom row:** Wake, **left column:** Pre epoch before the seizure; **right column:** Post epoch after the seizure, **middle:** Near-Onset epoch. Time and voltage scales are shown on the Near-Onset panel and are consistent across all panels. The low Near-Onset correlation persists into postseizure SWS and Wake, where the overlap between IISs recorded from the two macroelectrodes decreases (i.e., the yellow and cyan areas are more visible). (**A.2**) Expanded time view around the IIS peak during SWS **(top)** Pre epoch before the seizure, **(middle)** Near-Onset, and **(bottom)** Post epoch after the seizure. Dotted lines show the peak and trough of the Near-Onset average waveform for IIS from the cyan waveform. Changes to IIS synchrony for the yellow waveform after the seizure reflect changes during the Near-Onset. (**a**) The peak of IISs recorded for the yellow waveforms shifts backward relative to IISs recorded from the cyan waveforms. (**B**) "High" Near-Onset correlation pair circled in Figure 4. (**B.1**) Panel arrangement is the same as in **A.1**. The high Near-Onset correlation persists into Post-seizure SWS and Wake, where the overlap between IIS recorded from the two macroelectrodes increases (i.e., the green area signifying overlap increases). (**B.2**) Expanded time view around IIS during SWS, as described in **A.2**. The (**b**) valley and (**c**) peak of IIS recorded for the yellow waveforms shifts forward in time during Near-Onset and Post epoch after the seizure with respect to the cyan IIS waveform.

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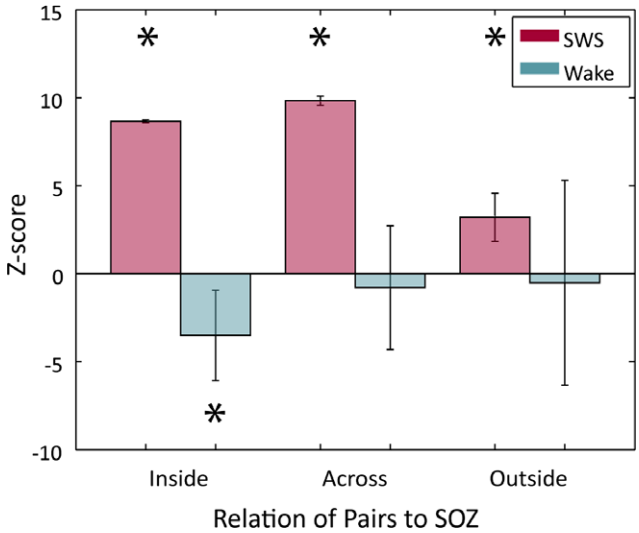

Figure 6.
Seizure-related consolidation of IISs is strongest when at least one electrode is within the SOZ. Across-subject beta regression scores grouped by electrode location relative to SOZ were positive for all groups during SWS (magenta), but were largest for the "Inside" and "Across" groups. Scores during Wake (cyan) only differed from zero when both macroelectrodes were "Inside" SOZ, but then the changes were anticorrelated with Near-Onset activity.
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Postseizure changes in IIS shape and synchrony were behaviorally specific, being greatest during SWS. The magnitude of these modifications was continuous, rather than all-or-none; IIS waveforms on many channels (both within the SOZ and outside of it) changed only slightly or not at all. The changes could differ on a small spatial scale; both increased and decreased correlation changes relative to the same macroelectrode were observed for macro-contacts located on the same physical electrode (Figs 2 and 5), consistent with the "fractured" spatial distribution of changes in multiunit[22] and single-neuron activity[23] observed prior to seizures. The largest changes in IIS synchrony were observed when at least one electrode was located in the SOZ, suggesting that these changes may be related to the spread of the epileptogenic zone.

Alternative explanations

Increased IIS rates could lead to spurious increases in CCs,[37,38] but although Post-seizure CCs increased for SWS, Post-seizure IIS rates increased more during Wake than SWS. It is also possible that, following seizures, there is a general increase in IIS correlations, but then it is not clear why IISs during Wake would not be affected (Fig. 3A). Even if such a general increase in overall IIS correlation following seizures were limited to postseizure SWS, it is not clear why changes to IIS shape and synchrony that appeared specifically during the Near-Onset epoch would reappear during sleep (Fig. 2C). Another possibility is that seizure-related movement shifted electrode positions, but this would not explain why the changes in IISs were largest during sleep or why those changes were recorded only on some contacts of a given, physical electrode, but not others (Fig. 2).

Synchronization of both neural activity and field potentials may play multiple roles in epilepsy, including the possibility that increased synchronization of field potentials reflects seizure inhibiting mechanisms.[39] Preictal and ictal states also activate seizure-inhibiting mechanisms (e.g., inhibitory surround) and seizures are thought to terminate when long-range synchronization is established across brain structures.[40–42] Synchronous activity arising from these mechanisms could also be reactivated as part of the consolidation process during postseizure sleep, possibly interfering with the consolidation of synchronous activity associated with the seizure itself. The relationship between possibly pro- and antiepileptogenic consequences of seizure-related synchrony following seizures could also relate to other observations relating interictal spikes to epileptogenesis. Many (but not all) of the changes observed in IIS shape preceding seizures produced increasingly temporally asymmetric waveform shapes (Fig. 1C). Asymmetric IIS shape has been associated with epilepsy pathology.[43] Temporal asymmetry implies underlying nonlinear generators,[44] which in turn have been shown to characterize epileptogenic brain areas.[45,46] One test of whether SRC overall favors pro- or antiepileptogenic mechanisms would involve experiments that interrupt or enhance postseizure sleep. Our observed associations between SWS and reactivated seizure-related interictal spike characteristics imply that state-dependent synaptic homeostatic mechanisms may reactivate and reinforce seizure engrams. Theoretical analyses have shown the importance of preventing saturation of synapses to maximize information storage via neural plasticity mechanisms.[47] The synaptic homeostasis hypothesis holds that an essential function of sleep is the downscaling of synaptic strength to energetically sustainable levels, thereby preventing saturation and impaired information processing and facilitating future learning and space conservation.[65] Targeted disruption of SWS[48,49] provides one approach for testing whether seizure-related consolidation is governed by similar mechanisms.

Mechanisms of IIS modification

The change in IIS shapes following seizures was much larger than the variability of the shape of IIS observed during interictal periods, suggesting a permanent alteration in the underlying neural circuitry generating the IISs (Fig. 4). The finding that changes in partial correlation were strongest for electrode pairs across SOZ boundaries raises the possibility that these alterations play a role in epileptogenesis, recruiting neural circuits during seizures and then capturing them via physiologic, learning-related mechanisms during postseizure SWS.[32] Changes in shape and synchrony of IISs from only some macroelectrodes following a single

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seizure suggests either the emergence of new IIS generators or the introduction of a relative temporal shift between different generators. The observation that changes in single neuron activity can precede IIS by hundreds of milliseconds suggests the existence of a broad repertoire of neural mechanisms that could be altered following a single seizure.[11,12] This is supported by the observation of more than a dozen types or classes of IIS waveform shapes,[10,12,14] suggesting that IIS waveforms reflect a diversity of neural generators. This would also be consistent with the development of pathologic interconnected networks ("PINs") of neurons being strengthened over repeated seizures,[50] particularly if only specific subassemblies of those PINs were activated selectively during any given seizure.[23] Because IISs can activate different specific neural circuits on each spike,[20] the parallel development of multiple PINs in the same tissue could provide the necessary variability in underlying neural generators to produce modified IIS shapes following individual seizures.

Comparison to multiple, single neuron studies

The temporal and spatial dimensions IIS changes during Near-Onset and Post-SWS were similar to seizure-related changes observed in patterned, single neuron activity. Changes in the firing rates of individual neurons in the minutes preceding seizure onset are reactivated during postseizure SWS.[23] Changes occur for some neurons recorded on a single microwire, but not for other neurons recorded on the same microwire (i.e., the network activated by the seizure is sparse), and changes can occur for neurons located outside the SOZ and even the opposite hemisphere (i.e., the network is distributed). Not all microwires within the SOZ record changes in seizure-related neural activity, giving the appearance of a spatially fragmented or "fractured" pattern of activation.[22] In animals, seizure-related changes in neural activity show a similar sparse, distributed and fractured pattern,[21] which shares similarities to neuronal activity patterns observed during physiologic behaviors.[24] Patterned neural activity observed during behavior is reactivated during SWS, which is required for both permanent modification of neural activity patterns and behavioral learning,[24,51–56] a process known as cellular consolidation.[57] Whether epilepsy "hijacks" cellular machinery related to physiologic learning to promote epileptogenesis is unclear,[32] but seizures do activate learning-related immediate early genes,[58] and many genes linked to epilepsy are also linked to pathways involving neuronal synchrony.[59] The activation of sparse neuronal circuits during seizures shows that the reactivation of seizure-related activity can occur hours after the seizure and occurs selectively during SWS, similar to the environment-specific activation of sparse, neural assemblies[24] and immediate-early genes[60] following spatial learning tasks. Spatially, just as neuronal activation during the Pre-Onset epoch reveals a "fractured" geometry in the SOZ containing spatial gaps in seizure-related activity,[22,61] alterations in IIS were observed on macroelectrodes outside the SOZ and on macroelectrodes that were adjacent to macroelectrodes where no changes were observed (see Fig. 2B,C). These similarities between changes to neuronal and field potential activity suggest that seizure-related modifications to brain function span multiple spatiotemporal scales.[61]

The importance of postseizure sleep

The central role of sleep in epilepsy has a rich history,[62,63] but the study of continuing pathology during sleep (when plasticity mechanisms are known to be activated) following seizures has received less attention. Because animal studies have shown that interference with consolidation disrupts previously learned tasks, a similar therapeutic benefit may be derived from interfering with postseizure sleep.[64] Current epilepsy drug and stimulation therapies target the prevention of seizure initiation, but do not address effects following a seizure that may make future seizures more likely; that is, there are currently no epilepsy therapies that are antiepileptogenic. It is not clear whether the reactivation of seizure-related neuronal activity during postseizure sleep makes future seizures more likely to emulate past seizures, but it is reasonable to hypothesize that strengthening connections across the SOZ border could play a role in expanding the SOZ. If seizure-related, sleep-dependent, patterned reactivation (i.e., cellular consolidation) does play a role in expanding the SOZ, then it is also reasonable to hypothesize that interference with reactivation of seizure-related activity during SWS following seizures could produce a new class of therapies that would be "antiepileptogenic."

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The authors have no conflicts 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.

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