Neurobiology of Disease

Evidence for Consolidation of Neuronal Assemblies after Seizures in Humans

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The establishment of memories involves reactivation of waking neuronal activity patterns and strengthening of associated neural circuits during slow-wave sleep (SWS), a process known as "cellular consolidation" (Dudai and Morris, 2013). Reactivation of neural activity patterns during waking behaviors that occurs on a timescale of seconds to minutes is thought to constitute memory recall (O'Keefe and Nadel, 1978), whereas consolidation of memory traces may be revealed and served by correlated firing (reactivation) that appears during sleep under conditions suitable for synaptic modification (Buhry et al., 2011). Although reactivation has been observed in human neuronal recordings (Gelbard-Sagiv et al., 2008; Miller et al., 2013), reactivation during sleep has not, likely because data are difficult to obtain and the effect is subtle. Seizures, however, provide intense and synchronous, yet sparse activation (Bower et al., 2012) that could produce a stronger consolidation effect if seizures activate learning-related mechanisms similar to those activated by learned tasks. Continuous wide-bandwidth recordings from patients undergoing intracranial monitoring for drug-resistant epilepsy revealed reactivation of seizure-related neuronal activity during subsequent SWS, but not wakefulness. Those neuronal assemblies that were most strongly activated during seizures showed the largest correlation changes, suggesting that consolidation selectively strengthened neuronal circuits activated by seizures. These results suggest that seizures "hijack" physiological learning mechanisms and also suggest a novel epilepsy therapy targeting neuronal dynamics during post-seizure sleep.

Key words: **consolidation; epilepsy; learning; memory; neural assemblies; seizures**

Introduction

An elegant chain of events at the behavioral, circuit, and cellular level has been described for how experiences are translated into memories, providing compelling evidence for the involvement of Hebbian learning through long-term potentiation (LTP) (McGaugh, 2000). LTP strengthens connections between coactivated neuronal pairs, prompting the phrase "neurons that fire together, wire together" and provides a mechanism by which activity present during waking behaviors could be translated to persistent memories through the modification of synaptic connectivity (Hebb, 1949; Bliss and Lømo, 1973; Malenka and Nicoll, 1999). Correlated neuronal activity patterns exhibited offline during wake (after a behavior) repeated on a timescale of seconds to minutes is a reactivation, which is thought to constitute the recall of recent events (O'Keefe and Nadel, 1978). During subsequent sleep, correlated neuronal firing patterns similar to those observed during wakfulness re-emerge during slow-wave sleep (SWS), which is a reactivation thought to be part of the memory formation process called "consolidation" (McGaugh, 2000). During seizures, a subpopulation of neurons is activated repetitively and synchronously for an extended time period while most neurons remain silent (Babb et al., 1973; Bower and Buckmaster, 2008; Truccolo et al., 2011; Bower et al., 2012), mimicking the activation of neuronal assemblies undergoing consolidation of physiological behaviors.

As proposed by Hebb (1949), modification of neuronal assemblies provides a means by which new information can be connected to existing memories (i.e., pattern completion) while still maintaining the fine differences between existing memories (i.e., pattern separation) by partially overlapping membership of neurons in multiple different assemblies (McNaughton and Morris, 1987). Encoding information through neuronal assemblies also allows different brain structures to interact with and shape one another even if their own internal data representations

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Table 1. Clinical patient information including age of epilepsy onset and epilepsy risk factors

Patient characteristics	Intracranial electrodes	Interictal EEG location	Seizures (anatomic location of IOZ)	MRI	Surgery, pathology, and outcome
Patient no. 1 Age of onset: 13 y Age: 37 y RFs: none Sex: F	Left temporal; strips: 3 neocortical, 8 contact strips (superior, middle and inferior temporal gyrus); depths: AD and PD hybrids	Left temporal: AD 1, 2, 3, 4; PD 1, 2, 3	#1 left temporal: AD 1, 2; PD 1, 2	Normal	Resective surgery: left ATL; path: gliosis; outcome: ILAE-1; follow-up 18 mo
Patient no. 2 Age of onset: 3 y Age: 27 y RFs: bacterial Meningitis 3 y Sex: F	Right and left temporal; depths: RTD and LTD 8-contact hybrid	Bitemporal: LTD 1, 2, 3; RTD 1	Right temporal seizures: RTD 1, 2 (AMD); left temporal seizures: LTD 1, 2 (HC)	Bilateral HC a trophy (L > R)	Resective surgery: no; path: N/A; outcome: N/A
Patient no. 3 Age of onset: 38 y Age: 47 y RFs: none Sex: F	Right and left temporal; depths: RTD and LTD 8-contact hybrid	Bitemporal: LTD 1, 2; RTD 1, 2	Left temporal seizures: LTD 1, 2 (AMD and AHC); right temporal seizures: RTD 1, 2, 3, 4 (AMD and AHC)	Normal	Resective surgery: no; path: N/A; outcome: N/A
Patient no. 4 Age of onset: 15 y Age: 22 y RFs: febrile convulsion 9 mo Sex: M	Right and left temporal; depths: RTD and LTD 8-contact hybrid	Bitemporal: LTD 1, 2, 3, 4; RTD 1, 2	Left temporal seizures: LTD 1, 2 (AHC)	Bilateral HC atrophy and T2 signal L > R	Resective surgery: left ATL; path: MTS; outcome: ILAE-1; follow-up 18 mo
Patient no. 5 Age of onset: 22 y Age: 58 y RFs: closed head injury with convulsion at age 13 y Sex: M	Left temporal; strips: 3 1 × 8 strips (superior (LSS), middle (LMS), and inferior (LIS) temporal gyrii); depths: AD and PD 4-contact hybrids	Left temporal: LMS 2; AD 1, 2, 3, 4; PD 1, 2, 3	Left temporal: AD 1, 2; PD 1, 2; LMS 2, 3	Normal	Resective surgery: left ATL; path: subpial gliosis; outcome: ILAE-1; follow-up 24 mo
Patient no. 6 Age of onset: 12 y Age: 21 y RFs: none Sex: F	Left temporal; grid: 24 contact (4 × 6); strip: 1 × 8 anterior temporal (ATS); depths: AD, MD, and PD 4-contact hybrids	Left temporal: ATS 1, 2, 3, 4; AD 1, 2; MD 1, 2	Left temporal seizures: AD 1, 2 (AMD); MD 1, 2 (AHC)	Normal	Resective surgery: left temporal corticectomy; path: subpial gliosis; outcome: ILAE-1; follow-up 28 mo

AD, Anterior depth electrode; PD, posterior depth electrode; RTD, right temporal depth electrode; LTD, left temporal depth electrode; LMS, left mesial strip electrode; ATS, anterior temporal strip electrode; ATL, anterior temporal lobectomy; RF, risk factor; HC, hippocampal.

Portions of this table were previously published in Bower et al. (2012).

differ, as has been proposed for hippocampus and neocortex (Marr, 1970, 1971) in the "two-stage" model of learning (Buzsáki, 1989). Seizures are known to activate sparse assemblies (Bower and Buckmaster, 2008; Truccolo et al., 2011; Bower et al., 2012) and the mechanisms underlying cellular consolidation remain intact (Titiz et al., 2014), implying that seizure-related consolidation (SRC) could strengthen specific networks after seizures. A rich literature linking LTP and epilepsy (Schwartzkroin and Prince, 1978; Malenka and Nicoll, 1999; Zhou et al., 2007) raises the possibility that seizures might "hijack" these physiological learning processes (Beenhakker and Huguenard, 2009). Seizures are known to disrupt the formation of new memories both in animals (Lenck-Santini and Holmes, 2008) and in patients (Hermann et al., 1997; Bohbot et al., 2000) and poor cognitive outcome is generally associated with poor seizure control (Elger et al., 2004). We hypothesized that the activation of neuronal assemblies during seizures should be observable as persistent changes in pairwise correlation during non-REM sleep from preseizure baseline lasting hours after the seizure.

Materials and Methods

Patients. Informed consent was obtained from six patients (four female; Table 1) undergoing intracranial 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) containing Pt-Ir clinical macroelectrodes (4 or 8 contact, 2.3 mm diameter, 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, 500–1000 kΩ) were placed stereotactically into the mesial temporal lobe using an occipital or lateral approach (Stead et al., 2010).

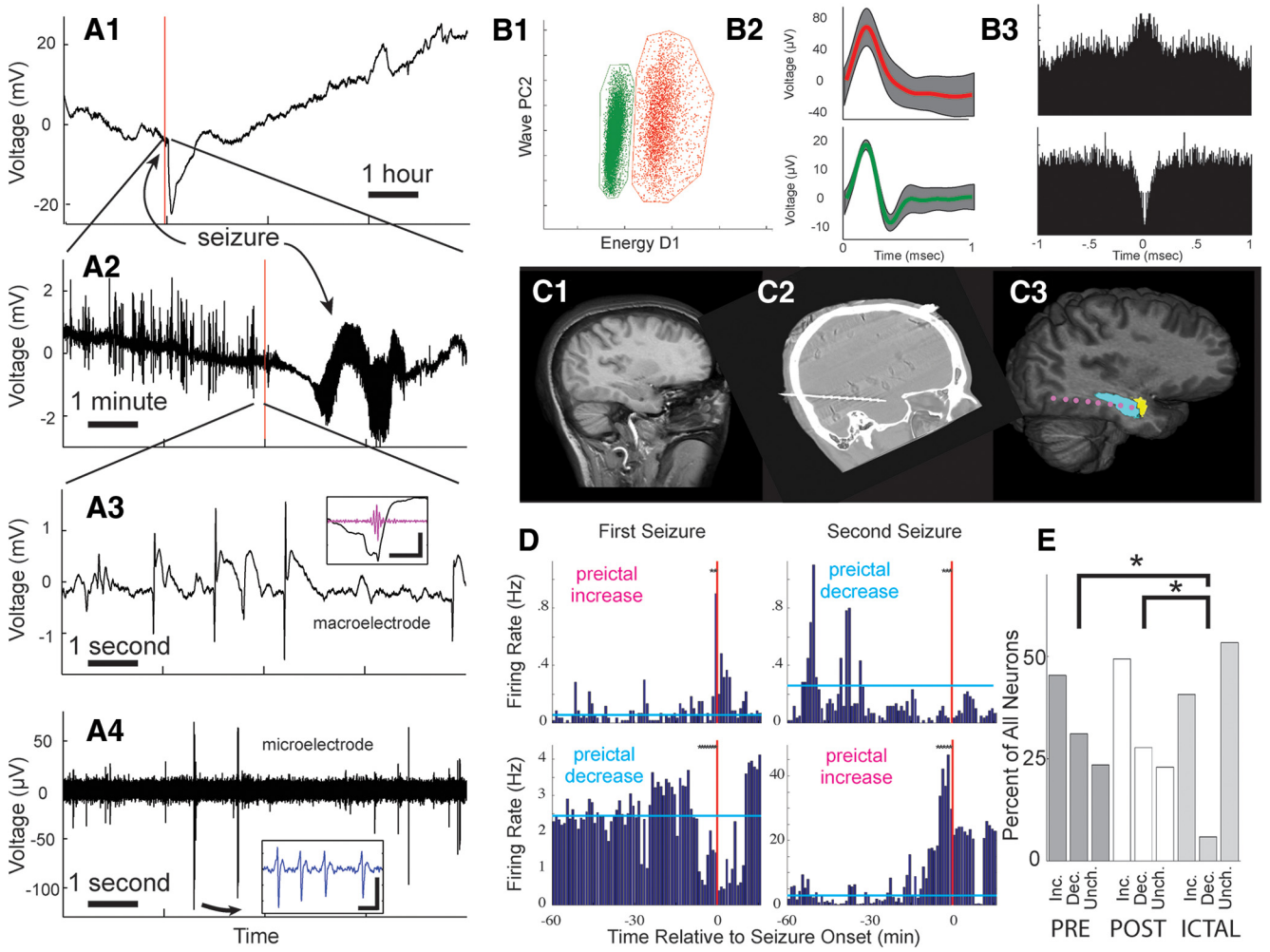

Figure 1. Continuous EEG, single neuron, and imaging data recorded from patients. ***A***, Continuous hippocampal EEG recorded with a clinical macroelectrode before, during, and after a seizure (vertical red line) showing 8 h (−2 to +6 h) (***A1***) and 8 min around seizure onset (***A2***); 8 s recorded from a clinical macroelectrode showing IISs and an HFO. Inset, HFO scaled 4× (***A3***), and from a filtered microelectrode (600–6000 Hz) showing multiple, single-neuron action potentials (APs; ***A4***). Inset, Burst of APs from one neuron; scale bar 50 μV and 10 ms. ***B***, All APs detected were at least three SDs above the RMS noise level. ***B1***, Cluster-cutting APs. Isolation of two, individual neurons from the same microelectrode (L_{ratio} = 1.27 and 2.56; ID = 1.9 and 1.1; Schmitzer-Torbert et al., 2005). ***B2***, Single neuron AP waveforms. ***B3***, Auto-correlograms for the same neurons in ***B2***. ***C***, Coregistered MRI and CT images were compared with the Montreal Neurological Institute atlas to localize electrodes (magenta dots) to specific brain structures [e.g., hippocampus (cyan), amygdala (yellow)]. ***D***, Single neuron firing rates for two neurons (top and bottom) during two sequential seizures centered on seizure onset (red, vertical line) and binned (1 min) showed heterogeneous firing rates within and across seizures. The cyan bar shows the mean baseline firing rate and the classification of preseizure activity ("preictal increase" and "preictal decrease"), showing that the same neuron can display two different behaviors before sequential seizures. ***E***, Percentage of neurons with increased, decreased or unchanged firing before the start of the seizure ("PRE"), after the start of the seizure ("POST"), and after the start of the seizure for those neurons that were classified as "unchanged" before the start of the seizure ("ICTAL"). The sparse neuronal networks underlying seizure generation are highlighted by the variability in neuron firing rate changes in relation to seizures and by the fact that the majority of neuronal firing rates are unchanged at seizure onset. $*\chi^2$, $p < 0.05$.

Electrophysiology. Only seizures with at least 1 h of continuous, seizure-free recording before and after the seizure were included in the analysis. Data were recorded continuously over days at a sampling frequency of 32 kHz. The action potentials of individual neurons were identified as described previously (Bower et al., 2012). Briefly, microelectrode data sampled at 32 kHz were recorded from patients in the neurological intensive care unit over multiple days and stored in a compressed, lossless format (Brinkmann et al., 2009). Offline, data were filtered (5-pole Butterworth) between 600 and 10,000 Hz and a series of voltage and time thresholds applied to each sample (Fig. 1*A*). Candidate waveforms were 3 SDs above RMS noise levels and were subsequently filtered by removing events with amplitude >1 mV and those that occurred simultaneously on >20% of all channels. Remaining action potentials were stored in the Neuralynx .nse format, for use in MClust (http://redishlab.neuroscience.umn.edu/MClust/MClust.html). Because many of these files were too large to be clustered first with an automated clustering algorithm (e.g., KlustaKwik), all files were clustered manually in MClust (MRB; Fig. 1*B*). All clusters were isolated from individual microelectrodes and had <1% of action potentials with interspike intervals <1 ms (i.e., less than the refractory period). Action potential detection times were written to cluster-specific files as "t files" for subsequent analysis. Although several neurons showed waveforms and firing distributions similar to principal cells and interneurons in hippocampus, clusters were not separated into specific cell types for analysis because microelectrodes were located in several different brain structures with neuronal classes that likely have different activity patterns. Extracellular action potential activity of a given neuron during a single seizure was labeled a "raster." Single-neuron action potentials from each raster were binned (bin size = 60 s), centered on seizure onset, and compared with preseizure SWS, which was used as a behavior-specific "baseline" (Staba et al., 2002). Simultaneous recordings from scalp electrodes provided additional EEG information to allow differentiation of wakefulness and SWS for 30 s time windows (see "Sleep scoring").

Anatomical localization. CT data were coregistered and resliced to the patient's MRI space using normalized mutual information function in

SPM8 (Fig. 1*C*). Mutual information was used to coregister images from multiple modalities and previous studies have shown that mutual information performs well for the coregistration of CT and MR images. Normalization to SPM MNI template space was done using a 12 parameter affine transformation followed by nonlinear normalization based on default 7 × 8 × 7 smooth spatial basis function. Locations of desired electrodes were identified manually on the normalized CT by selecting center of high-intensity clusters. Electrode coordinates were then automatically labeled by SPM Anatomy toolbox. The coregistration of CT and MRI yields clinical macroelectrode accuracy of ± 5 mm. Due to their small size, microelectrodes cannot be clearly identified in the imagery, so they are localized based on their known relation to the clinical macroelectrodes.

Sleep scoring. Visual, manual sleep scoring was performed by a neurologist (E.K.S.) board certified in sleep medicine (ABSM and ABMS/ABPN) and electroencephalography (ABCN and ABMS/ABPN CNP) in accordance with standard methods (Iber et al., 2007; Berry et al., 2012), with modification for omission of electrooculogram (EOG) recording in some patients. Stage W (Wake) was determined by the presence of eye blinks and rapid eye movements visualized in EOG or FP1 and FP2, accompanied by posteriorly dominant α (8–13 Hz) frequency rhythms comprising >50% of the epoch (i.e., 16 or more seconds within a 30 s epoch). N3 (slow-wave) sleep was scored when high-voltage (>75 uV) delta (0.5–2.0 hertz) 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 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.

Statistical software. All statistical tests were computed in MATLAB (The MathWorks) or R (http://www.r-project.org/).

Explained variance. Explained variance (EV), or partial correlation, quantifies the correlation during the latter two time epochs (seizure and postseizure SWS) after controlling for the linear effects of any preexisting correlations of the preseizure time epoch (Kudrimoti et al., 1999). Correlation coefficients were computed for three pairs of time epochs (preseizure, seizure, and post-seizure) and then input as variables to the following equation:

$$EV = \left(\frac{r_{seizure,\,post} - r_{pre,\,seizuer} r_{pre,\,post}}{\sqrt{1 - r_{pre,\,seizuer}}\sqrt{1 - r_{pre,\,post}}} \right)^2$$

Assembly computation. Assembly membership weights were computed using independent components analysis (ICA) (Lopes-dos-Santos et al., 2013). We used the recommended parameters: opts.Patterns.method: 'ICA'; opts.threshold.method: 'MarcenkoPastur'; opts.Patterns.number_of_iterations: 500. Membership weights were computed for each seizure from data collected during a total of seven epochs: Control-SWS, Control-Wake, SWS-before, Wake-before, Seizure, SWS-after and Wake-after. For each seizure, assemblies were ranked according to their normalized, summed activation during the "seizure" epoch, a 1 minute window centered on seizure onset beginning 30 s before seizure onset. The assembly with the largest percentage of total activation during the seizure was designated as the first or "dominant" assembly ("a1"), the assembly with the next highest percentage was designated as the second assembly ("a2"), and so on.

Inter-ictal spike detection. Data from macroelectrodes sampled at 32 kHz were low-pass filtered with a cutoff at 1 kHz and then down-sampled to 5 kHz. Inter-ictal spikes (IISs) were detected using a previously published algorithm (Barkmeier et al., 2012). Default parameters were used (data were analyzed in 1 min blocks; detections were identified as 4 SDs away from the mean). Data were then loaded across all macroelectrode channels in 1 minute blocks and IIS detections written. Only data from electrodes identified as being within the seizure onset zone (SOZ) or in the early propagation zone by visual inspection of EEG at seizure onsets (by G.A.W.) for at least one seizure were used in the analysis.

High-frequency oscillation detection. High-frequency oscillations (HFOs) were detected using a modification of a previously described algorithm (Worrell et al., 2008). Data were filtered between 100 and 600 Hz and signal line lengths computed for 50 ms windows. Events exceeding 5 SDs from the mean (computed from a 10 s sliding statistical "window") were detected and surrounding data extracted. Oscillations containing three or more peaks were identified as HFOs. An additional cascade of feature filters, including amplitude, was used to remove "physiological" HFOs (e.g., "ripples"; Matsumoto et al., 2013).

Results

Intracranial recordings were obtained from six patients undergoing treatment for mesial temporal lobe epilepsy in accordance with a Mayo Clinic Institutional Review Board-approved protocol (Table 1). A total of 9 seizures (n = 1, 3, 1, 1, 1, 2) with seizure-free recording before (mean = 4.8 h; range 1.0–11.3 h) and after (mean = 7.6 h; range = 1.0–20.3 h) each seizure were analyzed. Data were recorded from a total of 211 40-μm-diameter microcontacts (n = 62, 34, 28, 24, 32, 31), of which 127 were located on the shaft of the electrode and 84 were within wire bundles extending from the electrode tip, allowing the isolation of 252 unique, single neurons (n = 22, 64, 50, 25, 34, 57; McNaughton et al., 1983; Bower et al., 2012). Fifty-eight microcontacts (27.5%) had zero clusters, 78 (36.9%) had a single cluster, 52 (24.6%) had two clusters, 22 (10.4%) had 3 clusters, and 1 microelectrode (0.6%) had 4 clusters. Neuron cluster separation measures (Schmitzer-Torbert et al., 2005) were used to identify poorly isolated neurons. Although these measures were developed for quantifying separation of clusters from multicluster tetrode recordings (Schmitzer-Torbert et al., 2005) and 78 of the 153 contacts that recorded neurons had only one cluster (51%), we identified 19 neurons with an L_{ratio} >1.0 and Isolation Distance (ID) <1.0 that were dropped (n = 1, 7, 3, 0, 5, 3), leaving 233 neurons for analysis with a median L_{ratio} = 0.21 and a median ID = 5.5. This produced a total of 401 rasters (n = 21, 171, 47, 25, 29, 108). Although, on average, no difference was observed in the number of clusters isolated from bundle microelectrodes (1.11 cluster/microelectrode) compared with shaft microelectrodes (1.25), there was a cluster separation difference in terms of L_{ratio} (median for bundle = 0.21, shaft = 0.27, p = 0.047, Wilcoxon two-sample rank-sum), but not for ID (median for bundle = 5.2, shaft = 4.3, p = 0.099, Wilcoxon two-sample rank-sum). As has been observed previously in rodent (Bower and Buckmaster, 2008) and human studies (Babb and Crandall, 1976; Truccolo et al., 2011; Bower et al., 2012), a heterogeneous set of seizure-related changes in activity was observed before and after seizure onset (Fig. 1*D*): persistent increases and decreases, along with no change in the firing rate of individual neurons. The average percentage of seizure-related responses in each group was similar to what has been observed previously in patients (Truccolo et al., 2011; Bower et al., 2012; Fig. 1*E*).

Consolidation of seizure-related neuronal activity during SWS

Periods of continuous SWS and wakefulness (Wake) were identified before and after a seizure (SWS: 8.3 ± 2.6 min; Wake: 9.2 ± 5.1 min) and for a "shifted" period at least 4 h before seizure onset (SWS: 6.3 ± 3.0 min; Wake: 7.1 ± 3.2 min) that served as the control (Fig. 2*A*). For each pair of neurons, EV was used to compute the significance of correlation changes given the preexisting correlation between those neurons before the seizure (Wilson and McNaughton, 1994; Kudrimoti et al., 1999) for 1 min time windows and 100 ms time bins. EVs were computed for each 1 min block across the −2 to 0 h preceding the seizure and the 0 to

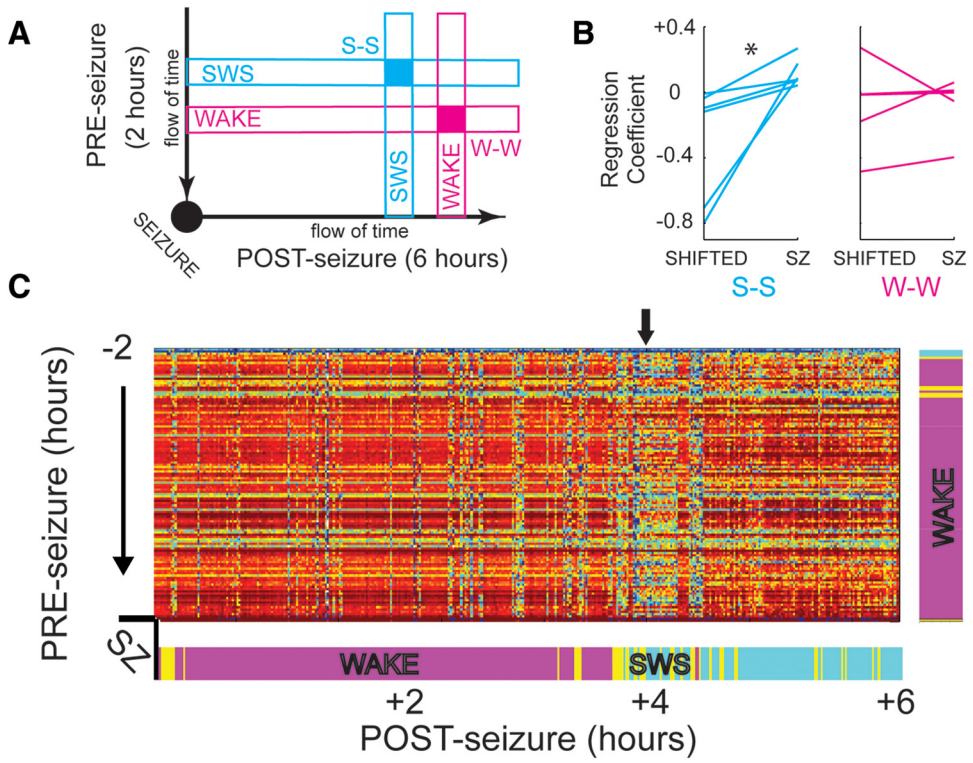

Figure 2. Consolidation of human neuronal firing patterns shown by increased cross-correlation between neuronal pairs only during SWS. ***A***, Schematic of "shifted" control and seizure PRE and POST time periods relative to seizure onset. ***B***, Compared with the same behavior (SWS or Wake) in the "shifted", control period, increased EV was significant during SWS after the seizure compared with SWS before the seizure (cyan "S-S"), but not during Wake after compared with before (magenta "W-W"). ***C***, Example plot of *p*-values (blue is significant) from −2 to + 6 h. Behavioral scoring alongside shows periods of SWS (cyan) and Wake (magenta). Arrow highlights a burst of significant cross-correlations occurring early in the first bout of SWS after the seizure.

+6 h after the seizure. Pairs of neurons displaying correlated activity during 1 min of data centered on seizure onset showed increased correlations during SWS after the seizure compared with the "shifted," control SWS period (Fig. 2*B*, paired *t* test, df = 5, $p = 0.0424$), but not during wakefulness (df = 4, $p = 0.9430$). Overlaying the behavioral state revealed a linkage between pre-post behavior and EV through periods of behavior-related changes in EV identifiable as horizontal and vertical "bands" associated with pre-seizure and post-seizure SWS, respectively (Fig. 2*C*).

If seizures initiate memory-formation processes, then the correlation changes observed by partial correlation should be relatively unaffected by the amount of time that passes between the seizure and the first episode of SWS. Neuronal firing rates were unchanged for SWS and Wake after seizures (SWS: before 1.05 ± 0.72 Hz, after 0.96 ± 0.72 Hz, $p = 0.72$; Wake: before 0.76 ± 0.53 Hz, after 1.01 ± 0.76 Hz, $p = 0.35$; paired *t* test). To determine whether the seizure-related changes in cross-correlation were persistent, we correlated the changes in EV during SWS and Wake with the latency from seizure onset. Latencies to both SWS and Wake regarding seizure onset varied widely due to their dependence on patient behavior (Pre: SWS −53.4 ± 44.7 min relative to seizure onset, range: 0 to −117 min, Wake: −63.6 ± 35.5 min, range: −20 to −110 min; Post: SWS +123.0 ± 80.5 min, range: 82–301 min, Wake +163.4 ± 81.4 min, range: 127–335 min), but EV showed little dependence on time from seizure, persisting for hours after the seizure (Fig. 3*A*). Correlation during SWS between pairs of neurons that were correlated during the seizure increased relative to periods of wakefulness (paired *t* test, df = 8, $p = 0.0089$; Fig. 3*B*).

In the context of cellular consolidation, these results can be compared to those from a learned behavior (Wilson and McNaughton, 1994), in which pairwise correlations during maze running were more similar to those observed during SWS after maze running than those preceding the behavioral experience. Likewise, pairwise correlations during seizures were more similar to those observed during SWS after the seizure than those preceding it. This suggests that correlated activity during SWS before seizures does not bias activity during subsequent seizures, but rather that post-seizure correlations during SWS are strongly influenced by correlated firing during the previous seizure (Fig. 4).

Inter-ictal epileptiform discharges

One alternative explanation for these results is that inter-ictal epileptiform discharges (IEDs) that are known to alter neuronal firing rate and synchrony occurred more frequently during SWS after seizures, perhaps unrelated to consolidation. Two such pathological IEDs known to occur in patients with epilepsy are IISs and HFOs (Fig. 1*A3*). One possibility is that IIS and HFO rates were significantly altered during the analysis time windows and that changes in neuronal firing correlations reflected these alterations, rather than the effects of consolidation. IIS rates increase after seizures (Gotman and Koffler, 1989) and neuronal synchrony increases during IIS (Keller et al., 2010; Alvarado-Rojas et al., 2013), so the increased correlation observed during SWS could be due to increased, synchronous firing observed in some neurons during IIS, specifically during SWS. To test this, IISs were identified (see Materials and Methods: "Inter-ictal spike detection") and aligned to seizure onset times and the number of

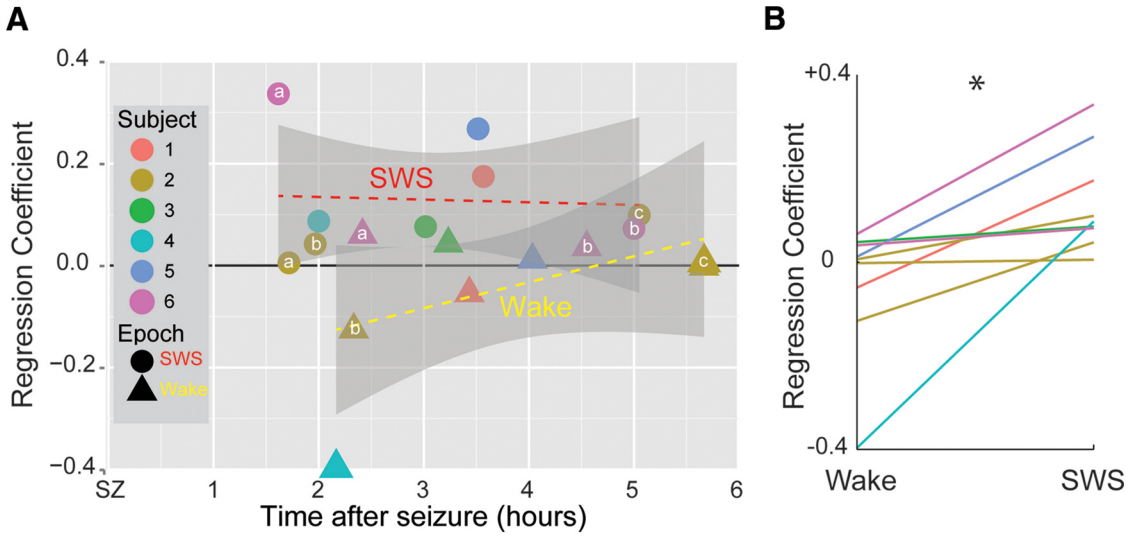

Figure 3. Consolidation is independent of the latency between seizure onset and first instance of SWS. ***A***, SWS and Wake regression coefficients for each seizure as a function of latency from seizure onset. For subjects with multiple seizures (Subjects 2 and 6), the letters "a," "b," and "c" show the order in which the seizures occurred. Dotted lines show regression computed for SWS (red) and Wake (yellow); gray contours show 95% confidence limits from a Loess curve fit. ***B***, Increased partial cross-correlation between neuronal pair firing during SWS relative to Wake by subject (paired *t* test, $p < 0.001$).

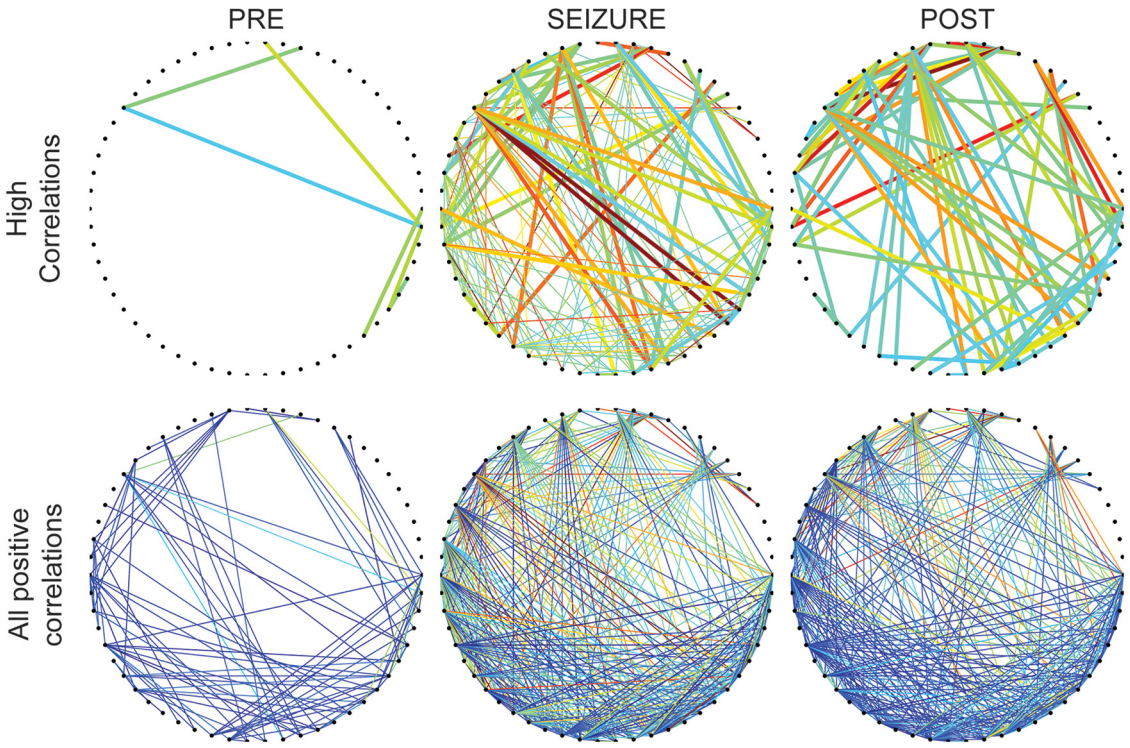

Figure 4. Effective connectivity of all neurons from patient 6 before, during, and after a seizure showing that post-seizure correlations during SWS are strongly influenced by correlated firing during the previous seizure. The format of this figure follows that of Figure 4 from Wilson and McNaughton (1994). Dots represent neurons ordered without regard to anatomy. Arcs represent pairwise correlations between neurons. Color of each arc shows the magnitude of the correlation (red = 0.3, blue = 0). PRE occurred 30 min before SEIZURE; POST occurred 1 h 40 min after SEIZURE. (TOP) Correlations >0.05 before ("PRE"), during ("SEIZURE") and after ("POST") the seizure. Wide arcs represent high correlations in the SEIZURE and either the PRE or POST panel; i.e., are highly correlated in at least two epochs. (BOTTOM) Arcs representing all positive correlations in the same epochs.

IISs occurring in the same Sleep-Wake analysis windows used for the EV analysis were counted. Although more IISs were observed during SWS than during Wake before seizures (*t* test, 2-tailed, df = 47, $\text{Wake}_{\text{before}} = 0.033 \pm 0.016$ Hz, $\text{SWS}_{\text{before}} = 0.078 \pm 0.055$ Hz, $p = 0.001$) and more IISs were observed during Wake after seizures (*t* test, two-tailed, $\text{Wake}_{\text{before}} = 0.033 \pm 0.016$ Hz, $\text{Wake}_{\text{after}} = 0.071 \pm 0.073$ Hz, $p = 0.023$), no change in IIS rate was observed during SWS after seizures (*t* test, 2-tailed, $\text{SWS}_{\text{before}} = 0.078 \pm 0.055$ Hz, $\text{SWS}_{\text{after}} = 0.071 \pm 0.046$ Hz, $p = 0.667$), suggesting that a change in IIS rate during SWS after seizures cannot account for the observed increase in partial correlation (Fig. 5*A*). In a similar manner, HFOs are more frequent during non-REM sleep (Staba et al., 2004) in seizure-generating brain regions (Worrell et al., 2008) and are thought to generate syn-

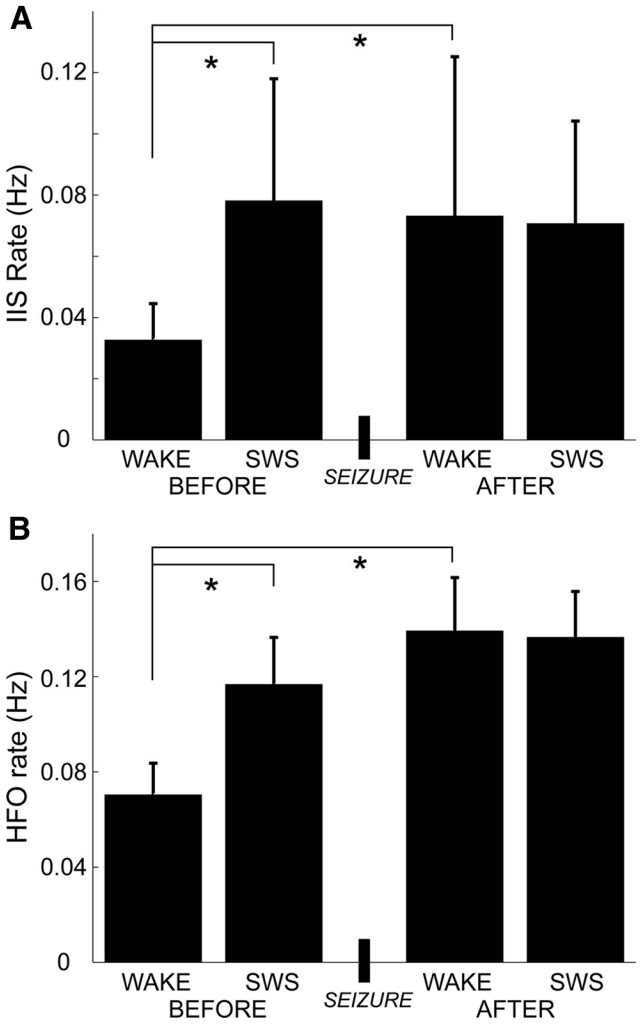

Figure 5. IEDs do not increase during SWS after seizures. ***A***, Before seizures (LEFT) IIS rates selectively favored SWS (Sammaritano et al., 1991), but increased during Wake after seizures. ***B***, HFO rate showed a similar preference for SWS before seizures (Staba et al., 2004) and, as for IIS, increased during Wake in the hour after seizures. These increased rates in pathological field potentials are unlikely to be due to a general increase in noise levels after seizures, because rates during SWS did not change. It is unlikely to have caused seizure-related consolidation (SRC), because IED rates were not altered during SWS and the increased rates during Wake after seizures would be expected to reduce observed SRC due to increased neuronal synchrony specifically during Wake.

chrony in local neuronal populations (Bragin et al., 2011; Burke et al., 2014; Kucewicz et al., 2014; Staba et al., 2014). If HFOs occur more frequently during sleep after seizures, this could account for changes observed in this study. To test this, HFOs were identified (see Materials and Methods: "High-frequency oscillation detection") and aligned to seizure onset times and the number of HFOs occurring in the same Sleep-Wake analysis windows used for the EV analysis were counted. Although more HFOs were observed during SWS than during Wake before seizures (paired t test, two-tailed, df = 8, $\text{Wake}_{\text{before}} = 0.070 \pm 0.013$ Hz, $\text{SWS}_{\text{before}} = 0.117 \pm 0.020$ Hz, $p = 0.028$) and more HFOs were observed after seizures during Wake (paired t test, two-tailed, $\text{Wake}_{\text{before}} = 0.070 \pm 0.013$ Hz, $\text{Wake}_{\text{after}} = 0.139 \pm 0.022$ Hz, $p = 0.003$), no change in HFO rate was observed during SWS after seizures (paired t test, two-tailed, $\text{SWS}_{\text{before}} = 0.117 \pm 0.020$ Hz, $\text{SWS}_{\text{after}} = 0.137 \pm 0.019$ Hz, $p = 0.096$), suggesting that a change in HFO rate alone cannot account for the observed increase in SWS-specific partial correlation (Fig. 5*B*).

Neuronal assemblies selectively activated by seizures

Increased coactivation of neuronal pairs is thought to underlie the formation of Hebbian assemblies (McGaugh, 2000), but little is known about assembly activity during seizures. To determine whether specific neuronal assemblies were selectively activated by seizures, neuronal assemblies were identified for SWS and Wake periods before and after the seizure, along with a 1 minute window centered on seizure onset that included the first 30 s of a seizure (Lopes-dos-Santos et al., 2013; see Materials and Methods: "Assembly computation"). Although most strong assembly groupings were observed for neurons recorded within the same brain structure and the same hemisphere, assembly membership often included pairs of neurons located in different brain structures and even opposite hemispheres (Fig. 6*A*). In addition, although the activity of most assemblies displayed a Gaussian distribution, the activity of a subset of assemblies diverged from this distribution and were labeled "dominant" assemblies (Fig. 6*B*).

To determine whether SRC was selective for dominant assemblies, assembly membership was determined using 1 min of activity beginning 30 s before seizure onset (including the first 30 s of the seizure) and changes in partial cross-correlation (ΔpCC) after-compared-with-before the seizure were computed. Compared with ΔpCC for the dominant assembly during SWS, ΔpCC decreased for the dominant assembly during Wake (SWS median = 0.0001, Wake = −0.0014, $p = 0.031$, Wilcoxon two-sample rank-sum) and for the second most active assembly during SWS ("dominant" median = 0.0001, second = −0.0035, $p = 0.007$, Wilcoxon two-sample rank-sum). Considering the total activation of all detected assemblies (Lopes-dos-Santos et al., 2013), most of the ΔpCC arose from a few "dominant" assemblies before, during, and after seizures [lighter (increased ΔpCC) and darker (decreased ΔpCC) cyan lines in Figure 7]. Although many changes occurred between pairs of hippocampal neurons, such changes were generally not limited to the hippocampus or to temporal cortex. Changes were observed that persisted both during SWS and Wake, which would be expected for persistent changes in synaptic connectivity and would also provide a mechanism by which seizures alter cognitive performance (McGaugh, 2000; Lenck-Santini and Holmes, 2008).

Largest correlation changes observed in the most active ("dominant") assembly

Combining results from the EV (Figs. 2, 3) and neuronal assembly analyses (Figs. 5, 6), EV changes were not limited to hippocampus or even to the hemisphere contralateral to seizure onset. Quantitatively, seizure-related changes in EV were signif-

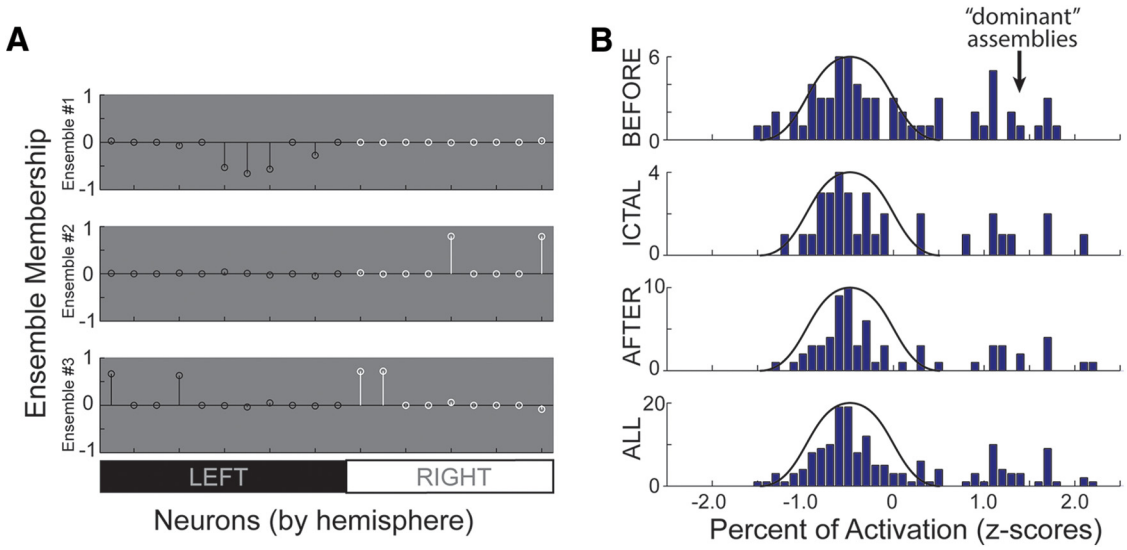

Figure 6. Neuronal assembly analysis showing activation of the "dominant" assembly before, during, and after the seizure. ***A***, Assembly membership "weights" for the three assemblies identified in one seizure showing one assembly in the left hemisphere, one in the right, and one containing neurons in both hemispheres. ***B***, For all seizures across all subjects, a subset of assemblies are activated more than all others and are identified as right "tails" extending beyond the normalized activation distributions (overlaid Gaussian curve) for all assemblies before, during, and after the seizure.

icant for main effects of sleep versus wake (ANOVA, df = 1, $F = 207.72$, $p < 0.001$), assembly (df = 3, $F = 2.74$, $p = 0.0418$) and brain structure (df = 5, $F = 15.43$, $p < 0.001$) and for the joint effect of epoch and assembly during SWS (df = 3, $F = 3.6$, $p = 0.0128$), but not for Wake (df = 3, $F = 2.03$, $p = 0.1076$). Separating pairs that involved mesial temporal structures (i.e., amygdala and hippocampus), the main effect on correlation of assembly was significant for mesial temporal structures (df = 3, $F = 7.00$, $p < 0.001$), but not for other brain structures (df = 3, $F = 2.06$, $p = 0.1034$). For neuron pairs involving the hippocampus and/or amygdala, the difference in changes in correlation during SWS was significant for the dominant assembly compared with the second-most active assembly (Wilcoxon rank-sum, $p = 0.0017$; Fig. 8*A1*) and for the dominant assembly in SWS compared with Wake ($p < 0.001$; Fig. 8*A2*), but not for the dominant assembly during SWS outside of the hippocampus-amygdala ($p = 0.1624$; Fig. 8*A3*).

Discussion

These results combine and extend previous results from the fields of learning and memory and epilepsy by providing evidence that neuronal mechanisms involved in human memory formation could be used by pathological processes in seizures and epilepsy. Combined with the observations of reactivation of waking neuronal activity patterns in humans (Gelbard-Sagiv et al., 2008; Miller et al., 2013), the results presented here suggest that sleep-related mechanisms similar to those first observed in animal studies of learning and memory (Wilson and McNaughton, 1994) play a role in the formation of long-term memories in humans too. In 1881, Gowers famously asked, "Do seizures beget seizures?" (Gowers, 1881). These results provide at least a partial answer by suggesting that seizure-related changes in neuronal, pairwise correlations occur preferentially during SWS and could modify neural circuitry selectively such that future seizures could follow in their traces, consistent with consolidation of the seizure engram. Although these results do not address how consolidation of physiological, learned behaviors (e.g., spatial navigation) occurs in humans, the observation of structure-specific changes after seizures could also provide an explanation for why different epilepsies present and progress differently. Specifically, hippocampus and neocortex are modified by complimentary learning systems (Marr, 1970, 1971) favoring pattern stability in neocortex and thus the emergence of similar patterns or "motifs" (Truccolo et al., 2011) and pattern flexibility in hippocampus and thus more hippocampal interseizure variability (Babb and Crandall, 1976; Bower et al., 2012). Furthermore, these results show that effective connectivity changes preferentially favor both neuronal pairs belonging to the neuronal assembly that was most strongly activated during the seizure and neuronal pairs that are anatomically located within mesial temporal structures. It is unclear whether these preferences arose because the seizures analyzed in this study originated in the mesial temporal lobe or whether they were due to the inherent neuronal circuitry of the mesial temporal lobe, but these results do support the hypothesis that seizures use (or "hijack") the same neuronal modification mechanisms used to generate episodic and semantic memories.

Cross-correlation studies have several known limitations and confounds, particularly in regard to assigning action potentials to incorrect groups (i.e., errors in "clustering"), but it is unlikely that these have affected our results. Absolute cross-correlation values are affected by a number of factors, including detection thresholds (which affect observed firing rates), behavioral state, and the presence of multiunit activity (Cohen and Kohn, 2011). Our study, however, was concerned with relative changes before and after seizures for the same neurons and was confined to comparisons within behavioral state (SWS and Wake). Spurious cross-correlations may also be observed for neuronal pairs recorded on the same microelectrode (Cohen and Kohn, 2011), but such pairs were excluded from our analysis. Cross-correlation values are also known to depend on the underlying firing rate of neurons (de la Rocha et al., 2007), which can produce spurious increases in observed correlation coefficients during periods of increased firing, but no change in firing rate was observed during either SWS or Wake after seizures compared with before seizures. Finally, it is unclear how such confounds would affect only spe-

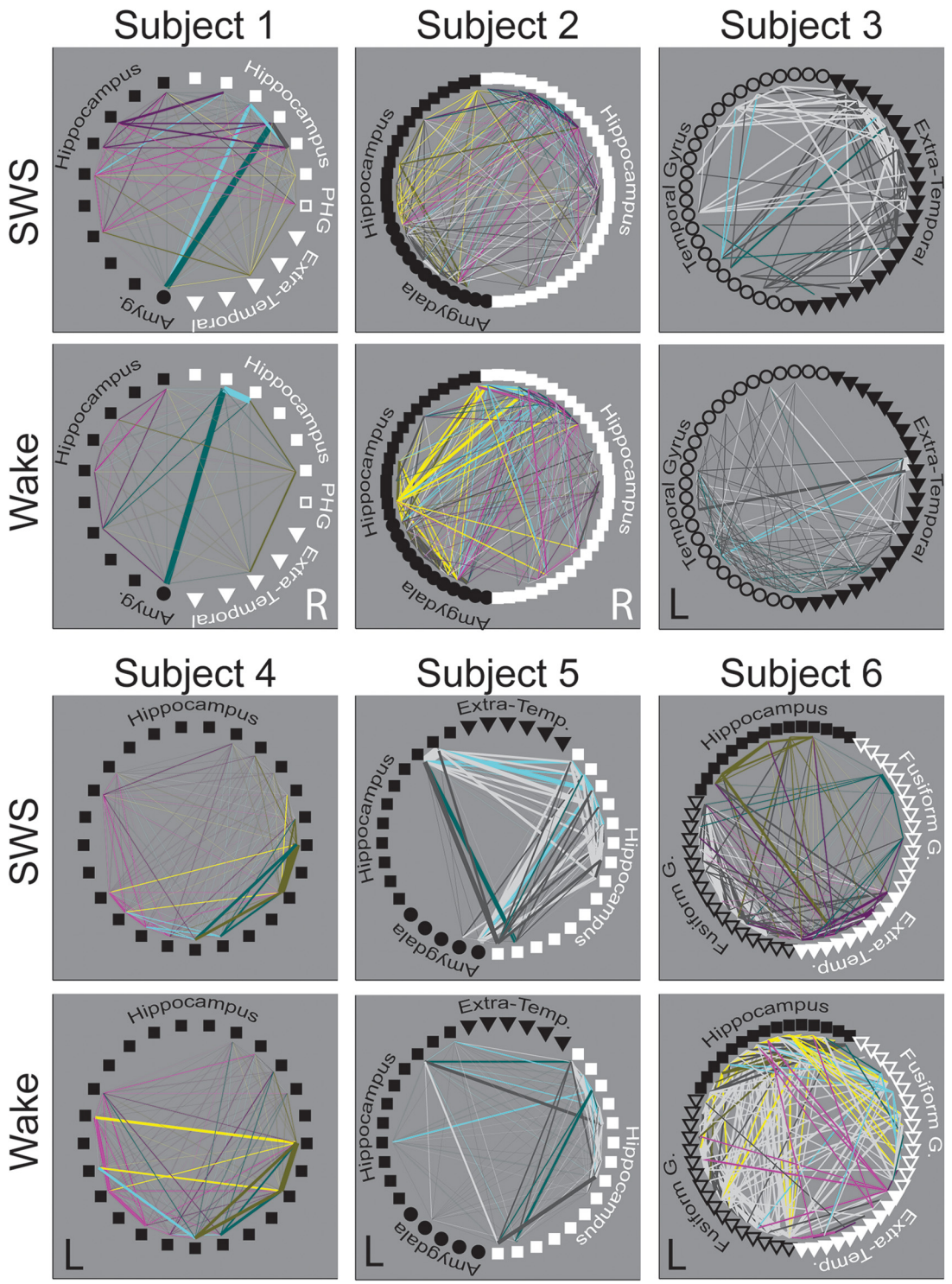

Figure 7. Pairwise neuronal cross-correlation (CC) changes within assemblies and across structures during SWS showing changes involving interhemispheric and extra-hippocampal structures. Arc width indicates the magnitude of the change in cross-correlation and color indicates both the sign of the change and the assembly to which that correlation belongs. Increased/decreased CC changes are displayed as brighter/darker shades for the dominant assembly (cyan), the second most active assembly (magenta), the third most active (yellow), and all others (gray). In some cases, fewer than three assemblies were identified (e.g., in Patient 5, only one assembly was identified; correlations belonging to that assembly are shown in cyan, whereas all others are shown in gray). CC changes by assembly and anatomy for SWS (TOP) and Wake (BOTTOM) organized anatomically and by hemispheres (left, black; right, white). Boldface letter at bottom indicates the hemisphere where the seizure originated. Anatomical location is given by shape: open circle, temporal gyrus; open square, parahippocampal gyrus; open triangle, fusiform gyrus; solid circle, amygdala; solid square, hippocampus; solid triangle, extratemporal.

cific neuronal assemblies and behavioral epochs to produce the main effect observed in this study.

The observation of both increased and decreased cross-correlation even within dominant assemblies (Figs. 7, 8) does not support simplistic models of seizure-related change that only strengthen seizure-related activity patterns indefinitely. Rather, seizure-related changes might also include weakening effective connectivity between neuronal pairs, even those that were coacti-

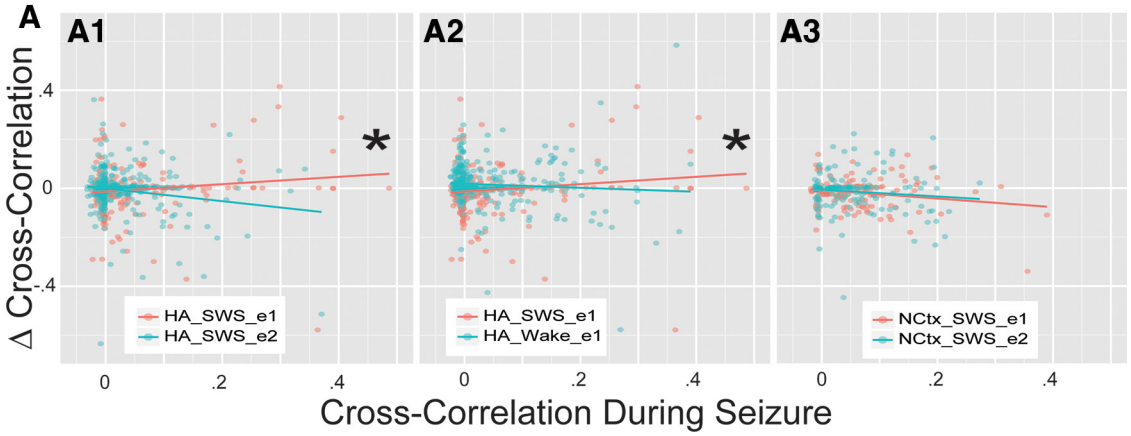

Figure 8. Changes in CC as a function of CC during the seizure grouped by behavior, assembly and brain structure. ***A1***, hippocampal-amygdala (HA) pairs during SWS for the dominant (***A1***, magenta) and next most-active (***A2***, cyan) assembly. ***A2***, Dominant HA pairs during SWS (magenta) and Wake (cyan). ***A3***, Neocortical (NCtx) pairs during SWS for the dominant (***A1***, magenta) and next most-active (***A2***, cyan) assemblies. *Significance of the Wilcoxon two-sample (i.e., between groups) rank-sum test ($p < 0.05$).

vated during seizures, perhaps by activating mechanisms such as LTD. At the synaptic level, different portions of seizures with different dominant frequencies (i.e., the stereotypic "spectral progression" through the seizure) may be involved in selectively strengthening and weakening various connections. Such a complex interplay between strengthening and weakening connections would help to explain why the powerful, synchronous activation of neuronal pairs does not lead immediately to hyperstrengthened, "saturated" synapses that cannot be strengthened further. Such a system would be inherently unstable; one seizure would almost certainly lead to a subsequent string of seizures. The observation that changes in pairwise correlation were strongest for assemblies within mesial temporal structures shows that cellular consolidation mechanisms remain intact in patients with MTLE, similar to what has been observed in rodent models of epilepsy (Titiz et al., 2014). The degree of synchronous activation provided by seizures can also be seen in the comparison of changes in effective connectivity shown in Figure 4 of this study and Figure 4 of Wilson and McNaughton (1994). Although such a comparison involves only a single example in each case, the similarity between correlated activity during seizure and post-seizure SWS was clearly greater than that observed for maze running.

These results also suggest several consequences for epileptogenesis, including a mechanism by which seizure onset zones could expand with repeated seizures. One possibility is that seizure-related consolidation (SRC) leads to the formation of pathological interconnected neuron clusters (PINs) (Bragin et al., 2000) starting from pairs or groups of neurons that are coactivated during a seizure and the interconnections of which are subsequently strengthened during sleep. Although repeated, stereotypic seizures do not necessarily activate the same neurons in the same manner during sequential seizures (Babb and Crandall, 1976; Bower and Buckmaster, 2008), effective connectivity between pairs of coactivated neurons could still use small changes after seizures to establish networks that are strengthened during specific local field oscillations (e.g., fast ripples). SRC provides a mechanism by which seizure onset zones could spread from one hippocampus to another and by which seizures originating in the hippocampus could spread to neocortex during consolidation, in the same manner that patterned hippocampal activation is transferred to neocortex after learned tasks (Hoffman and McNaughton, 2002). The complementary memory system of archicortex and neocortex described by Marr (Marr, 1970, 1971), however, suggests that because the two systems possess different learning mechanisms in terms of pattern completion and separation, SRC may not be as effective at expanding from one system to another (i.e., from hippocampus to neocortex and vice versa). Clearly, however, the replay of seizure-related activity from hippocampus into neocortex could provide disruptive information for memory formation of learned tasks after seizures via interference (Lenck-Santini and Holmes, 2008). The observation of increased IIS and HFO rates after seizures specifically during Wake could be related to the spread of pathological activation arising from seizures or it could reflect a temporary breakdown after seizures in the mechanisms that normally bias IED to occur during sleep, but it could also be due to tapering of patient medication for intracranial monitoring or increased patient movement after seizures. It is unlikely to arise from a general increase in recording noise levels because rates during SWS did not change after seizures. Regardless of the cause, if increased pathological field activity caused nonspecific increases in partial correlation, then increased IIS and HFO activity during Wake should reduce observed SRC and so is unlikely to have produced the main effect observed in this study.

At the systems level, although reactivation is thought to be integral to strengthening long-term memories, reactivation also makes existing memories more labile and susceptible to modification through the process of reconsolidation (Nadel and Moscovitch, 1997; Nader et al., 2000). Pharmacological (Squire et al., 1980; Nader et al., 2000; Milekic and Alberini, 2002) and behavioral (Walker et al., 2003) interference with reactivation during SWS is known to disrupt reconsolidation of existing memories of learned tasks (Alberini and LeDoux, 2013) and has been suggested as a means for treating established memories associated with PTSD (Taubenfeld et al., 2009). These observations raise the possibility of a new kind of epilepsy therapy that aims to interfere with consolidation after a seizure, which might not only disrupt the consolidation of a recent seizure, but might also destabilize the engram of long-established seizure pathways, limiting the likelihood or spread of future seizures. Given the observation presented in this study that seizures preferentially activate neuronal assemblies during consolidation, such an approach could be particularly well suited to the disruption of SRC, because the disruption of patterned activity might specifically target those

neuronal pairs that were part of the neuronal assembly that was most active during the previous seizure.

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