

## CALL FOR PAPERS | *Neurobiology of Deep Brain Stimulation*

# Sensing-enabled hippocampal deep brain stimulation in idiopathic nonhuman primate epilepsy

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<sup>1</sup>Brain Modulation Lab, Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania; <sup>2</sup>Medtronic Neuromodulation, Minneapolis, Minnesota; <sup>3</sup>Department of Neurology, University of Pittsburgh, Pittsburgh, Pennsylvania; <sup>4</sup>Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania; and <sup>5</sup>Center for the Neural Basis of Cognition and McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

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**Lipski WJ, DeStefino VJ, Stanslaski SR, Antony AR, Crammond DJ, Cameron JL, Richardson RM.** Sensing-enabled hippocampal deep brain stimulation in idiopathic nonhuman primate epilepsy. *J Neurophysiol* 113: 1051–1062, 2015. First published November 26, 2014; doi:10.1152/jn.00619.2014.—Epilepsy is a debilitating condition affecting 1% of the population worldwide. Medications fail to control seizures in at least 30% of patients, and deep brain stimulation (DBS) is a promising alternative treatment. A modified clinical DBS hardware platform was recently described (PC+S) allowing long-term recording of electrical brain activity such that effects of DBS on neural networks can be examined. This study reports the first use of this device to characterize idiopathic epilepsy and assess the effects of stimulation in a nonhuman primate (NHP). Clinical DBS electrodes were implanted in the hippocampus of an epileptic NHP bilaterally, and baseline local field potential (LFP) recordings were collected for seizure characterization with the PC+S. Real-time automatic detection of ictal events was demonstrated and validated by concurrent visual observation of seizure behavior. Seizures consisted of large-amplitude 8- to 25-Hz oscillations originating from the right hemisphere and quickly generalizing, with an average occurrence of  $0.71 \pm 0.15$  seizures/day. Various stimulation parameters resulted in suppression of LFP activity or in seizure induction during stimulation under ketamine anesthesia. Chronic stimulation in the awake animal was studied to evaluate how seizure activity was affected by stimulation configurations that suppressed broadband LFPs in acute experiments. This is the first electrophysiological characterization of epilepsy using a next-generation clinical DBS system that offers the ability to record and analyze neural signals from a chronically implanted stimulating electrode. These results will direct further development of this technology and ultimately provide insight into therapeutic mechanisms of DBS for epilepsy.

deep brain stimulation; hippocampus; temporal lobe epilepsy; local field potential

EPILEPSY IS A COLLECTION of diverse disorders, varying in pathogenesis, site of seizure onset, and response to treatment. Temporal lobe epilepsy (TLE) is a common form of the disorder, characterized by seizures originating in the temporal lobe, most frequently in the hippocampus and amygdala. In cases where

pharmacological therapy either fails to adequately control seizures or is not well tolerated, resective surgery is an effective treatment, suppressing disabling seizures in 50–80% of patients undergoing mesial TLE (MTLE) resections (Engel et al. 2003). Seizure freedom occurs in fewer than 50% of patients undergoing extratemporal resections (de Tisi et al. 2011), however, and resective surgery is not an option for cases where the seizure focus is not well localized or when resection would cause unacceptable functional deficits. These problems, coupled with the nonreversible nature of resective surgery, underscore the need for new and more effective alternative treatments for medically refractory epilepsy.

Deep brain stimulation (DBS) is a promising emerging therapy for focal epilepsy. Most efforts to date have focused on modulating nodes within the limbic circuit of Papez, a network often implicated in seizure generation and propagation. Two types of brain neuromodulation, anterior thalamic DBS and responsive neurostimulation at seizure foci, are supported by Class I evidence of effectiveness: The SANTE (Stimulation of the Anterior Nucleus of Thalamus for Epilepsy) trial (Fisher et al. 2010) reported a 29% greater reduction in seizures in patients who received stimulation in the anterior nucleus of thalamus compared with the control group. In contrast to this traditional open-loop stimulation paradigm, the RNS (Responsive Neurostimulation) trial (Spencer et al. 2011) evaluated closed-loop or responsive stimulation of specific seizure foci, including the hippocampus, in patients with medically refractory partial epilepsy. A similar response was reported, with a modest 21% greater reduction in seizure frequency in stimulated subjects compared with control subjects at the conclusion of the blinded period (4 mo). The median percent reduction in seizures in the open-label period was 44% at 1 yr and 53% at 2 yr. In addition, smaller, open-labeled trials have suggested that direct stimulation of the hippocampus and amygdala may be effective in seizure suppression (Velasco et al. 2000, 2007a, 2007b; Vonck et al. 2002). Despite these recent advances in applying DBS to the treatment of epilepsy, poor understanding of the mechanisms underlying the effects of electrical stimulation on seizure networks remains a significant barrier to improving therapeutic efficacy.

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To elucidate the effect of electrical stimulation on the activity of neural substrates of TLE, we performed DBS concurrently with local field potential (LFP) recordings in the hippocampus of a nonhuman primate (NHP) with idiopathic epilepsy, using a novel platform for simultaneous stimulation and long-term recording of electrical brain activity (PC+S, Medtronic) (Afshar et al. 2012; Freestone et al. 2013; Ryapolova-Webb et al. 2014; Stypulkowski et al. 2013, 2014). Using this modified version of a standard clinical DBS device, Stypulkowski et al. recently examined the acute effects of DBS on limbic neural networks in the normal ovine brain. They found that the same stimulation pattern that induced seizures at higher stimulation intensities in the hippocampus caused a transient suppression of LFP activity at lower stimulus intensities. This finding led us to hypothesize that seizure suppression may be achieved through chronic stimulation using patterns that acutely inhibit LFP activity. To test this hypothesis, we first characterized a case of idiopathic epilepsy in a NHP, using the PC+S system to record interictal LFPs bilaterally from the hippocampus and to detect seizures in real time. Furthermore, we examined the effect of acute and chronic hippocampal stimulation paradigms on spontaneous LFPs and on epileptiform activity. This study aimed to improve our understanding of the neural dynamics underlying TLE, and to elucidate the way in which they are altered by specific hippocampal stimulation patterns.

## MATERIALS AND METHODS

**Animal subject.** One male 6-yr-old NHP (*Macaca mulatta*; 10 kg) was used for this study. All aspects of animal care were in accord with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 1996), and all procedures were approved by the University of Pittsburgh Institutional Animal Care and Use Committee. The NHP was observed to have spontaneous recurrent seizures for at least 2 yr prior to study initiation. A high-resolution, 3-T magnetic resonance imaging (MRI) scan demonstrated no abnormal findings. The animal originally had been treated with levetiracetam but had received no treatment during the year prior to beginning the study. This animal had not undergone any invasive procedures prior to this

study, having only begun to be used in behavioral experiments by another investigator when the seizure disorder was discovered.

**Interventional MRI-guided DBS implantation.** The animal underwent interventional MRI (iMRI)-guided implantation of DBS electrodes into the hippocampus bilaterally, in a Siemens MAGNETOM Allegra 3-T MRI scanner, using the ClearPoint (MRI Interventions, Irvine, CA) platform (Larson et al. 2012; Richardson et al. 2011). The surgical approach involved a transfrontal trajectory under general anesthesia and standard aseptic conditions. Lead extenders were tunneled subcutaneously in the posterior neck and subsequently were connected to the Activa PC+S pulse generator, which was implanted in the subcutaneous space between the scapulae.

**Recording.** Intracranial LFP recording was carried out bilaterally in the hippocampus with standard clinical DBS electrodes (model 3389, Medtronic, Minneapolis, MN). The LFP signals were amplified, filtered from 0.5 Hz to 100 Hz, digitized at a sampling frequency of either 200 or 422 Hz, and recorded with the chronically implanted Activa PC+S device (investigational device, Medtronic). Recording parameters were set, and data were saved to memory and subsequently uploaded for analysis periodically via a wireless Medtronic model 8180 sensing programmer, a modified tablet computer, and the Medtronic model 37642 patient programmer designed to noninvasively interface with the Activa PC+S neurostimulator via radiotelemetry, as previously described (Ryapolova-Webb et al. 2014; Stypulkowski et al. 2013). During telemetry the monkey was anesthetized with ketamine (Ketaset, 5 mg/kg), as data download required ~30 min per session.

LFPs were recorded between specific contacts on each electrode, such that the contacts used for stimulation were positioned between the recording contacts. An automatic seizure detector utilizing the support vector machine (SVM) detection capability of the Activa PC+S was trained based on seizure events recorded during a training period using timed recordings as described previously (Afshar et al. 2012; Shoeb et al. 2009). Briefly, seizures observed under ketamine anesthesia provided an initial training data set to derive the frequency band, detector threshold, and duration constraints that could be used for SVM seizure detection. The PC+S detection algorithm was then refined based on training data collected over several weeks of chronic recording. After the chronic training period the SVM detector was retrained and finalized for optimal seizure detection performance based on visual validation of seizure events. Based on this training, the SVM detector used an onset duration of 25 s and a termination duration of 2 s to record time domain signals for detected seizure

Table 1. *Studies of hippocampal deep brain stimulation for epilepsy*

Reference	Patient Type	<i>n</i>	Stimulation Site	Current/Voltage	Frequency	PW, $\mu$ s	Mode	Effects
Velasco et al. (2007b)	MTLE	9	Bilateral HPC	300 $\mu$ A	130 Hz	450	1 min ON; 4 min OFF	Seizure reduction
Vonck et al. (2002)	TLE	3	Bilateral AMY and HPC	<3 V	130–200 Hz	60–450	Continuous	Seizure reduction
Boon et al. (2007)	MTLE	12	Bilateral AMY and HPC	2–3 V	130 Hz	450	Continuous	Seizure reduction: 1 seizure free; 10 seizure reduction; 1 nonresponder
Tellez-Zenteno et al. (2006)	MTLE		Left HPC	1.8–4.5 V	190 Hz	90	Continuous	No significant improvement
Boëx et al. (2011)	MTLE	8	Bilateral AMY and HPC	0.5–2 V	130 Hz	450	Continuous	Seizure reduction
McLachlan et al. (2010)	MTLE	2	Bilateral HPC	Variable	185 Hz	90	Continuous	33% Seizure reduction
Cukiert et al. (2014)	TLE	9	Unilateral or bilateral HPC	4 V	130 Hz	300	Continuous	>66% Seizure reduction
Tyrand et al. (2012)	TLE	12	Bilateral AMY and HPC	1 V	130 Hz	210/450	Acute stimulation only	No seizure data reported

TLE, temporal lobe epilepsy; MTLE, mesial TLE; HPC, hippocampus; AMY, amygdala; PW, pulse width.

events. Hippocampal activity was also recorded across all electrode pairs with a feature within the Activa PC+S device called montage search. This feature records activity in the hippocampus serially for 30 s on each electrode pair (6 30-s recordings for each 4-contact electrode).

**Stimulation.** DBS was delivered unilaterally through standard clinical DBS electrodes (Medtronic) with the Activa PC+S device (investigational device, Medtronic). The device is capable of delivering charge-balanced square voltage pulses at frequencies of 5–250 Hz with a pulse width (PW) of 30–450  $\mu$ s. Stimulation parameters were programmed with the 8840 Clinician Programmer (Medtronic). For monopolar stimulation, an electrode contact was used as the cathode and the implanted PC+S device case was used as the anode. For bipolar stimulation, current was passed between specific electrode contact pairs.

**Acute stimulation.** To assess the acute effects of DBS on LFP suppression, stimulation was delivered with the monkey under ketamine anesthesia (Ketaset, 10 mg/kg). To measure the acute effects of stimulation on spontaneous LFP power, 10-s stimulation epochs were delivered between selected contacts with at least 50 s between epochs. Any trials during which stimulation precipitated a seizure were not included in the analysis of power. Stimulation was delivered at various combinations of frequency (50 Hz, 130 Hz) and PW (60  $\mu$ s, 300  $\mu$ s) in an exploratory manner in order to maximize LFP suppression in the 4–40 Hz bandwidth. These parameters were chosen on the basis of previous studies that demonstrated suppression of local neural activity (Fisher et al. 2010; Stypulkowski et al. 2013) (Table 1).

**Chronic stimulation.** For chronic awake testing, stimulation was programmed via the clinician programmer while the monkey was briefly immobilized with a squeeze cage. Chronic stimulation was applied in

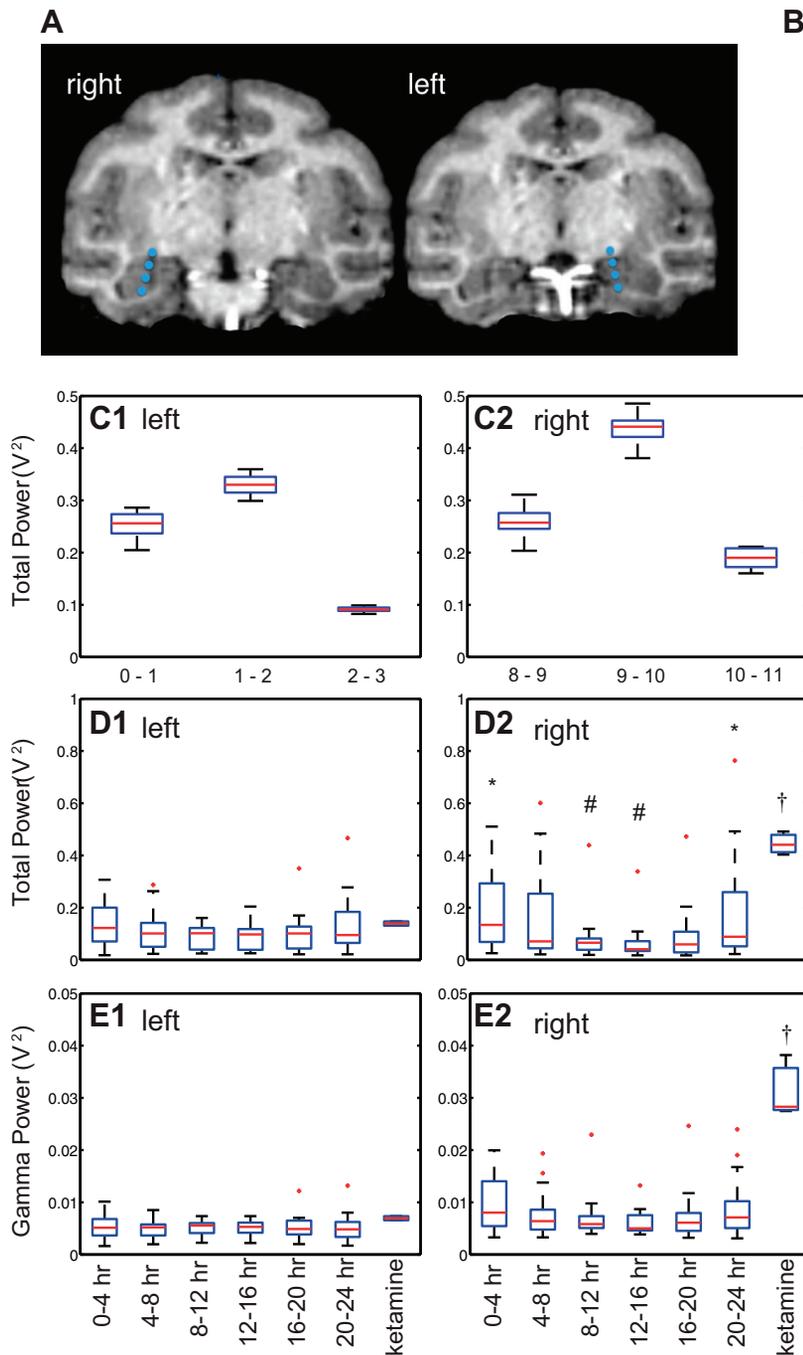


Fig. 1. *A*: deep brain stimulation (DBS) electrodes were implanted bilaterally in the hippocampus. *B*: contact configuration. L, left; R, right. *C1* (L) and *C2* (R): total power (0–60 Hz, 60 s) recorded between different pairs of contacts in montage mode. Power was lower in the dorsal location compared with ventral contacts. *D*: box plots of group spectral power data (0–60 Hz, 30 s) from local field potential (LFP) recordings carried out every 4 h over a period of 42 days plotted as a function of time of day for L (*D1*) and R (*D2*) hippocampus. Hippocampal LFP power followed a circadian rhythm. Ketamine increased spontaneous power only on R side. *E*: gamma band power (25–60 Hz, 30 s) showed a marked selective increase in R hippocampus following ketamine. \*Significantly different from #; † (ketamine) different from all other groups (ANOVA,  $P < 0.05$ ). Box plot labels in *E* also apply to *D*.

cycling mode, with a 15-s ON period and a 30-s OFF period. Cycling stimulation was used for chronic trials, based on the SANTE trial stimulation parameters (Fisher et al. 2010).

**Data analysis.** Spectral analysis of LFP recordings was performed in MATLAB (MathWorks, Natick, MA) with fast Fourier transform (FFT) methods. To determine total power within a given bandwidth, an  $N$ -point discrete Fourier transform was computed on the recorded voltage time series, which was zero-padded to the next power of 2 ( $N$ ). Power was then summed within the bandwidth of interest. For spontaneous recordings and acute stimulation experiments, 30- or 60-s time segments were used at either 200- or 422-Hz sampling rate. Comparisons of LFP power recorded at different times of day and under ketamine anesthesia were analyzed by ANOVA with Bonferroni correction for multiple comparisons. Time-frequency spectrogram and coherogram plots were calculated with multitaper methods adapted from the Chronux (<http://chronux.org/>) analysis package (Mitra and Bokil 2008). A moving window of 5 s was used with a 1-s step size, and a 1-s moving window was used with a 0.1-s step size. To assess the effects of acute stimulation at different DBS parameters, LFP power in the 4–40 Hz bandwidth, during pre- and poststimulation 10-s epochs (stimulation), was analyzed at different stimulation intensities (voltage), frequencies, and PWs with a two-factor repeated-measure ANOVA (with stimulation and voltage as factors) with Bonferroni correction for multiple comparisons. To further investigate the potential selective effect of acute stimulation on LFP power within individual bandwidths, a two-factor ANOVA (with bandwidth and voltage as factors) with Holm-Sidak method for multiple comparisons was applied. Cross-correlograms between simultaneous recordings for the left and right hippocampus were calculated in MATLAB based on a 3-s time window centered on the area of interest, which was determined by examining the coherogram of time domain data. Statistics are reported as means  $\pm$  SE.

## RESULTS

**Electrode placement.** Medtronic 3389 leads were successfully placed in the bilateral hippocampi via a transfrontal approach using iMRI with real-time visualization of electrode placement. The center of the artifact of each contact on the final intraoperative scan was marked with BrainLab iPlan software and merged onto a preoperative, high-resolution 3-T MRI for optimum visualization of anatomical placement (Fig. 1A). Contacts 0–2 and 8–10 were located in the left and right hippocampus, respectively, with contacts 3 and 11 situated just dorsal to the hippocampus (Fig. 1B). As expected, LFP montage recordings carried out consecutively between different electrode contact pairs showed increased LFP power recorded between middle electrode contacts on each side compared with both the dorsal and ventral contact pairs that straddled the edges of the hippocampus (Fig. 1, C1 and C2).

**Spontaneous recording.** To characterize baseline physiology, the PC+S was initially programmed to acquire 30- or 60-s bilateral LFP recordings, in bipolar mode using the middle contact pairs, every 4 h over a period of 42 days. These data revealed variable LFP spectra that featured prominent theta and beta peaks. Overall oscillatory power followed a circadian pattern, particularly on the right side, where power was more variable than on the left (Fig. 1, D1 and D2). This circadian pattern was present across physiological frequency bands examined (Fig. 1, D and E). Ketamine anesthesia (10 mg/kg) significantly increased LFP power across frequency bands, particularly in the gamma range, in the right but not the left hippocampus (Fig. 1, D and E), consistent with a right hip-

pocampal hyperexcitable zone having the lowest threshold for seizure generation.

**Seizure characterization.** On the basis of clinical observation of seizure events before and after initiation of this study, the NHP was characterized as likely having a focal, complex partial and secondarily generalizing epilepsy. Likewise, electrographic ictal events captured while observing the animal under anesthesia were always accompanied by stereotypic jaw opening followed by varying durations of generalized tonicity and low-amplitude clonic movement of the extremities.

Electrographic seizure activity was monitored intermittently for a total of 56 days over a period of 144 days. Automatic detection yielded an average of  $0.71 \pm 0.15$  seizures/day, with ictal activity detected in the right hippocampus prior to the left in each case. The average seizure duration was  $56.7 \pm 3.0$  s. Seizure frequency and duration were relatively stable over the course of the experiment (Fig. 2, A and B). Seizures were more likely to occur early in the day compared with late in the day (Fig. 2C). Of 16 seizures for which a predetection period was recorded, 10 exhibited a stereotyped initiation pattern in the right hippocampal electrode. This initiation pattern was characterized by a pronounced slow wave followed by a low-amplitude ripple (wave-ripple) that quickly evolved into high-amplitude oscillations (Fig. 3A). In these instances, ictal onset in the left hippocampal electrode lagged behind the right side by  $7.7 \pm 0.2$  s. Seizures in which a clear wave-ripple was not

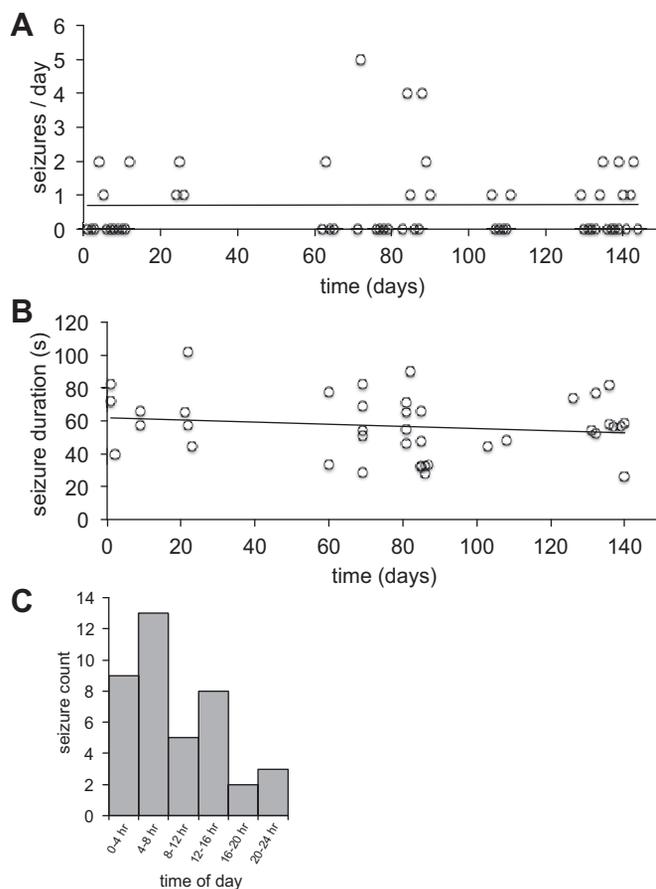


Fig. 2. A and B: frequency of seizure occurrence (A) and seizure duration (B) remained stable over the time course of the study. C: distribution of seizure times throughout the day. Seizures occurred more frequently early in the day compared with late in the day.

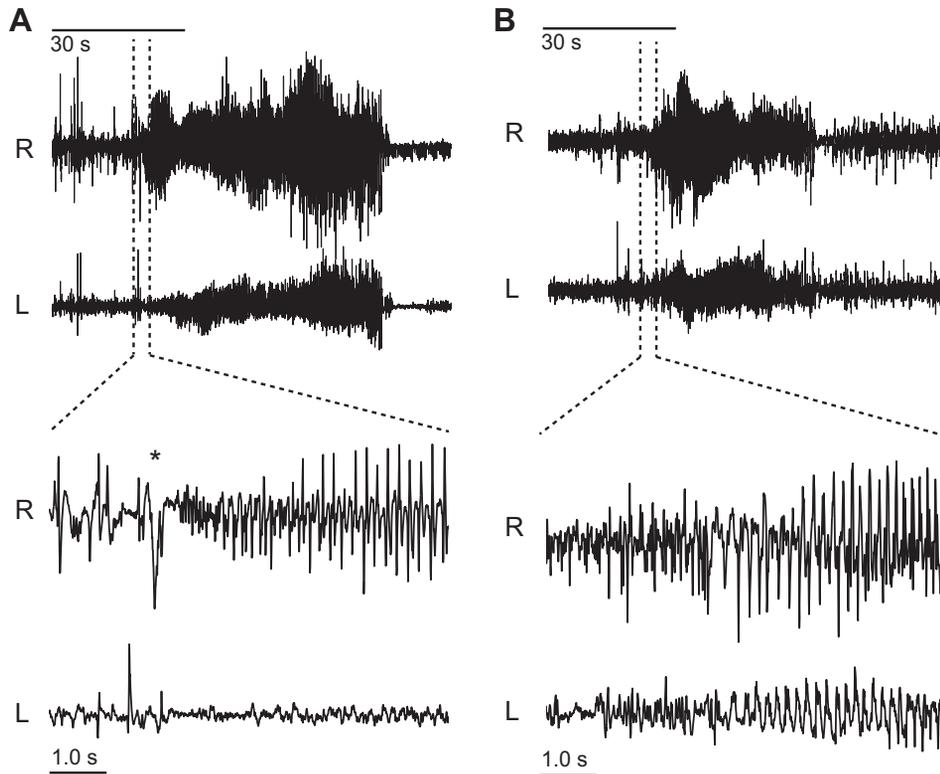


Fig. 3. Seizures were characterized electrophysiologically based on bilateral LFP recordings from the hippocampus: representative traces of R and L hippocampal LFP (*top*) and detail showing seizure onset (*bottom*) during 2 types of seizures. *A*: seizure onset was consistently characterized by a pronounced slow wave (\*) in the R LFP, followed by a low-amplitude ripple quickly evolving into high-amplitude oscillations. *B*: occasionally, seizure onset was observed simultaneously in L and R hippocampus as large-amplitude oscillations.

observed on the right side were characterized by a shorter left onset delay of  $1.3 \pm 0.9$  s (Fig. 3*B*).

Group analysis of the detected oscillations showed an increase in spectral power above 3 Hz during seizures, compared with spontaneous, interictal activity, with a prominent peak at 5.6 Hz. The theta-band oscillation at ictal onset was most pronounced on the right side (Fig. 4*A*) and evolved to include higher-frequency bands—including a prominent gamma burst—as the seizure progressed (Fig. 4*B*). During the first 20–30 s of the seizure, the theta oscillation gradually decreased in frequency, producing a characteristic spectral chirp (Fig. 4*C*). During this initial phase, there was a brief period of high coherence between the right and left sides centered at  $5.5 \pm 0.1$  Hz with a consistent phase lag in the left side of  $23.6 \pm 2.7$  ms (Fig. 4, *D* and *E*). These results are consistent with a seizure onset zone in the right mesial temporal lobe. The time course and spectral content of ictal events were similar to seizures observed in human TLE with intracranial recording in the hippocampus (Fig. 5).

**Acute stimulation.** Acute stimulation under ketamine anesthesia had different effects on spontaneous activity depending on stimulation parameters and stimulation site. Stimulation parameters were explored during acute stimulation trials looking at various stimulation intensities (voltage), frequencies, and PWs. In these trials, stimulation at high voltages (2–3 V) through electrode contacts in the right hippocampus precipitated seizures that spread to the left hippocampus, while stimulation at lower voltages (<3.0 V) sometimes resulted in suppression of spontaneous LFP activity, which lasted several seconds after the end of stimulation (suppression carryover). The thresholds for suppression carryover and afterdischarge thresholds for various stimulation patterns are summarized in Table 2. Hippocampal LFP power suppression in the 4–40 Hz

bandwidth was achieved most frequently with 50-Hz, 300- $\mu$ s PW stimulation. An example of hippocampal responses to acute stimulation is shown in Fig. 6. This figure illustrates a stimulation-evoked seizure (Fig. 6*A*) as well as voltage-dependent suppression of hippocampal activity (Fig. 6*B*). The 50-Hz, 300- $\mu$ s PW stimulation, however, also resulted in voltage-dependent activation, depending on the contacts used. In particular, bipolar stimulation in the right hippocampus resulted in local suppression of LFP power when it was delivered in the dorsal hippocampus (Fig. 7*A*; 9-11+) compared with activation when it was delivered in the ventral hippocampus (Fig. 7*C*; 8-10+). Bipolar stimulation through the middle contacts (9-10+) in the right hippocampus resulted in a bimodal response, with suppression at lower voltages and activation at higher voltages (Fig. 7*B*). Monopolar stimulation at 1.6 V also was effective in suppressing spontaneous LFP activity (Fig. 7*D*); however, this mode of stimulation was observed to cause craniocervical muscle activation, presumably via direct electrical stimulation resulting from using the case as the positive node. Monopolar stimulation with a more narrow PW (60  $\mu$ s) and a higher frequency (130 Hz) did not significantly alter spontaneous power in acute experiments (Fig. 7, *E* and *F*). To further characterize the suppression and activation of hippocampal activity by different patterns of acute stimulation, these effects were analyzed with respect to power within individual bandwidths (theta, 4–8 Hz; alpha, 8–12 Hz; beta, 12–25 Hz; gamma, 25–40 Hz). While there was no effect of bandwidth examined on the suppression caused by bipolar stimulation in the dorsal (9-11+) and middle (9-10+) contacts (2-factor ANOVA; significant main effect of voltage,  $P \leq 0.002$ ; no effect of bandwidth,  $P = 0.23$  at 9-11+,  $P = 0.93$  at 9-10+), the activation following bipolar stimulation at the ventral (8-10+) contacts was dependent on bandwidth [main

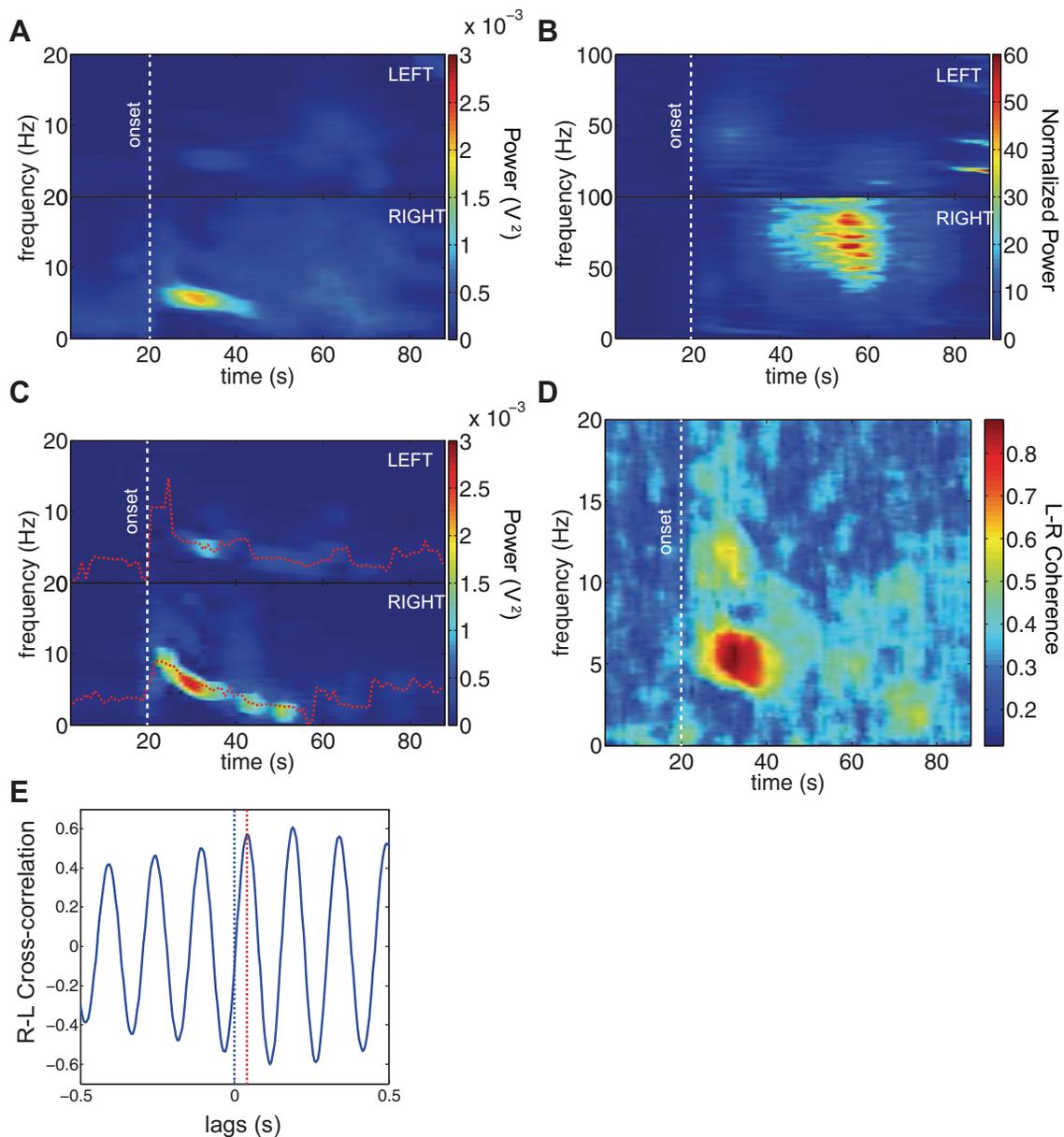


Fig. 4. *A*: mean spectrogram ( $n = 10$ ) showing the time course and frequency distribution of seizure activity in L (*top*) and R (*bottom*) hippocampal LFPs. Seizures are aligned at onset (dashed line). Prominent theta oscillation is apparent on R side at the onset of the seizures. *B*: mean spectrogram of data shown in *A* with power normalized to the preonset baseline within each frequency bin. Large gamma-band increase in power becomes apparent during the latter stages of seizure activity. *C*: example of a single seizure showing a spectral chirp at the ictal onset. Red dotted line represents the time evolution of the peak frequency in the spectrogram. *D*: mean time-frequency plot ( $n = 10$ ) showing time evolution of coherence between the L and R LFPs showing a prominent theta-band peak in coherence shortly after seizure onset. *E*: example of a R-L cross-correlogram based on a 10-s high-coherence epoch during a seizure in *D*, band-pass filtered at 4–8 Hz, showing a prominent oscillation with L side lagging behind R side (red dotted line).

effect of voltage ( $P < 0.001$ ) and bandwidth ( $P < 0.001$ ), significant interaction between voltage  $\times$  bandwidth ( $P < 0.001$ )). Specifically, after stimulation at the highest intensity (3.0 V, 8–10+), activation was greatest in the beta ( $677 \pm 98\%$  of baseline) and gamma ( $623 \pm 203\%$  of baseline) bands, intermediate in the alpha band ( $310 \pm 17\%$  of baseline), and lowest in the theta range ( $142 \pm 31\%$  of baseline). Analysis of monopolar stimulation yielded a significant effect of bandwidth only using a 50 Hz, 300  $\mu$ s pattern, with significant suppression in the alpha bandwidth compared with theta [alpha =  $88.6 \pm 3.9\%$  of baseline; beta =  $102 \pm 5.0\%$  of baseline; significant effect of voltage ( $P < 0.001$ ) and bandwidth ( $P =$

0.035)]. Effects of stimulation using a 60- $\mu$ s pulse width did not depend on the bandwidth examined.

*Chronic stimulation.* To assess the effects of a chronic stimulation pattern in the seizure onset zone on local LFPs and seizure frequency, right hippocampal stimulation was cycled (15 s ON/30 s OFF) continuously for 5 days with monopolar stimulation (*trial 1*; Fig. 8*A*; 9-C+, 1.6 V) and separately for 15 days with bipolar stimulation (*trial 2*; Fig. 8*B*; 9-10+, 2.0 V). Cycling stimulation ON/OFF durations were selected on the basis of results from the acute stimulation trials indicating that suppression could be achieved with 15 s of stimulation using these parameters but could recover  $\sim 30$  s later. The

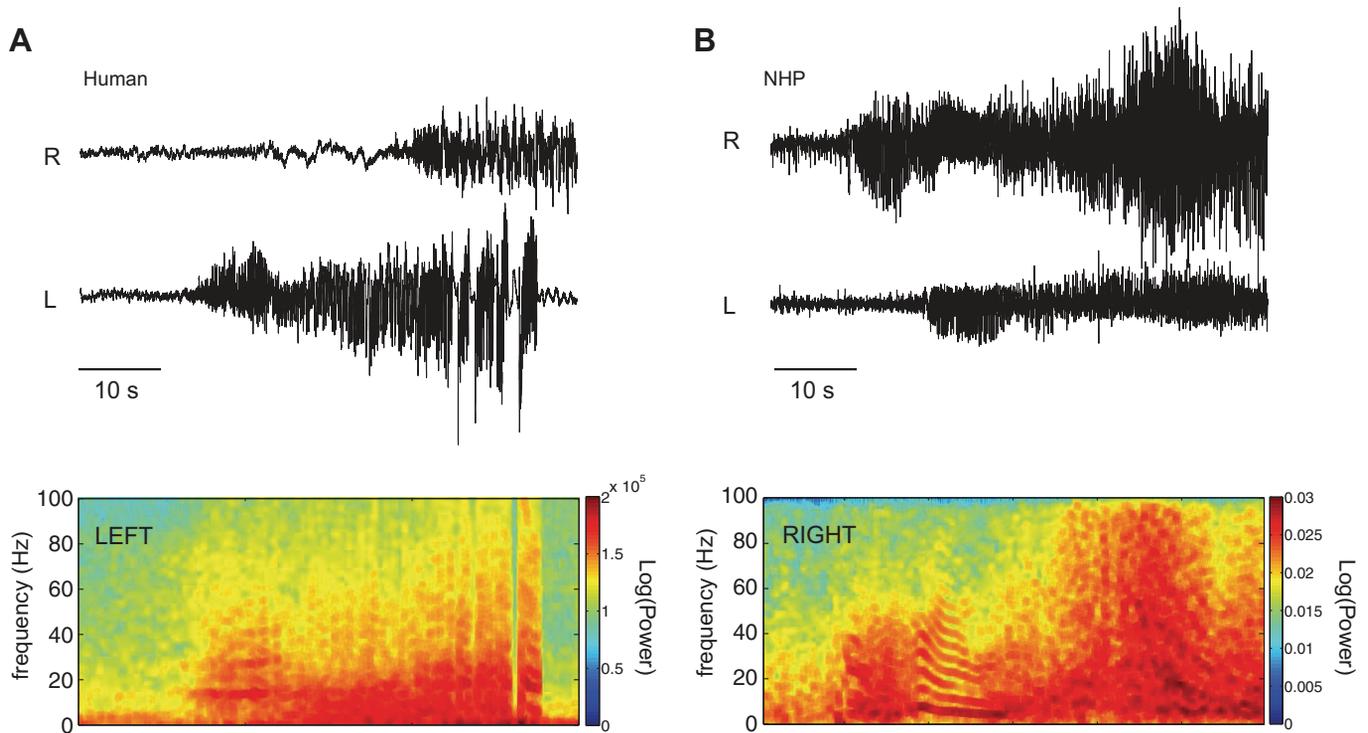


Fig. 5. Example of a human temporal lobe epilepsy (TLE) seizure (A) recorded from hippocampal depth electrodes shows remarkable similarity—with regard to interhemispheric timing and frequency bands involved—to nonhuman primate (NHP) seizures observed in this study (B).

monopolar stimulation parameters (9-C+, 50 Hz, 300  $\mu$ s, 1.6 V) were selected based on levels that produced hippocampal suppression during acute trials. Bipolar stimulation was selected for the second trial to avoid muscle contractions from electrical spread elicited by setting the pulse generator case as the positive node during monopolar stimulation. The bipolar voltage levels (2.0 V) were selected on the basis of acute trial suppression results.

Neither trial resulted in a significant suppression of seizures [ANOVA comparison of seizures per day before (PRE) during (STIM), and after (POST) stimulation; *trial 1*: PRE = 1.5, STIM = 0.73, POST = 0.33,  $P = 0.39$ ; *trial 2*: PRE = 0.50, STIM = 0.40, POST = 2.5,  $P = 0.25$ ]. Because of the limited capacity of the PC+S device (51 min total at 200 Hz sampling rate), it was not possible to record continuously during an entire chronic stimulation session; recordings were instead triggered by seizure detection. However, to determine whether the suppression of spontaneous LFP activity observed under ketamine anesthesia was present during cycling stimulation in the awake animal, a brief period of awake cycling stimulation (9-10+, 2.0 V) was recorded continuously in a separate session (data not shown). Comparison of pre- to poststimulation power for each cycle in this awake session revealed no suppression

following each ON period (prestimulation power =  $0.259 \mu\text{V}^2$ , poststimulation power =  $0.256 \mu\text{V}^2$ ;  $P = 0.50$ , *t*-test), contrasting results of acute stimulation using the same parameters under ketamine anesthesia.

To determine whether the seizure onset during chronic cycling stimulation was correlated with cycling stimulation, the onset of each seizure detected within *trial 2* was examined. The onset times of 11 seizures that occurred during the *trial 2* stimulation period were not correlated to the timing of stimulation cycle (Fig. 8C). It should be noted, however, that seizure onset could not be detected if it occurred during the ON phase because of stimulation artifact.

Characteristic spectral coherence chirps within the theta band that occurred prior to chronic stimulation (Fig. 8D) were also observed during cycling stimulation (Fig. 8E). However, the peak in coherence between left and right hippocampus was delayed in seizures recorded during cycling stimulation compared with those recorded in the absence of stimulation [Fig. 8F; time to peak L-R coherence without ( $11.0 \pm 0.4$  s) and during ( $15.2 \pm 0.4$  s) cycling stimulation;  $P < 0.01$  *t*-test]. Cross-correlation analysis of coherence revealed no difference between the frequency of peak theta coherence during seizures (Fig. 8G; STIM =  $5.48 \pm 0.06$  Hz, NO STIM =  $5.43 \pm 0.09$  Hz;  $P = 0.67$ , *t*-test); however, phase lag in theta coherence was significantly delayed during stimulation (Fig. 8H; STIM =  $23.6 \pm 2.7$  ms, NO STIM =  $32.8 \pm 2.4$  ms;  $P = 0.023$ , *t*-test).

Table 2. Summary of acute stimulation effects

Stimulation Pattern	Suppression Carryover	AD Threshold
8-10+		1.8 V, 2 V
9-10+	2.6 V, 2.8 V	3 V
9-11+	2.6 V, 2.8 V	3 V
9-C+	1.6 V, 1.8 V	3 V
10-Cs+	2 V	>2.5 V

AD, afterdischarge.

## DISCUSSION

In this study, a next-generation sensing-enabled DBS system was utilized for the first time in idiopathic epilepsy. Implantation of this clinical device in a NHP with spontaneous recurring seizures enabled us to validate novel device features in a highly unique clinical model. Chronic recording, acute stimulation,

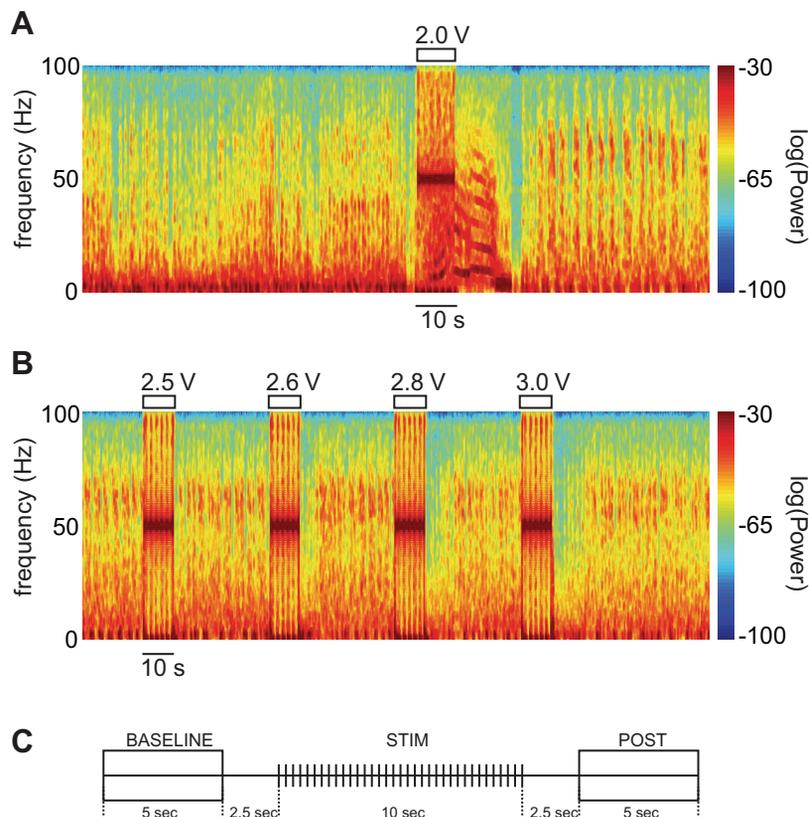


Fig. 6. Acute stimulation modulates local LFP activity. *A*: example of a bipolar (9-11+) stimulation trial at 50 Hz, 300  $\mu$ s that precipitated a seizure. *B*: example of bipolar (9-10+) stimulation trials at 50 Hz, 300  $\mu$ s where increasing voltage resulted in suppression carryover of spontaneous power. *C*: effects of acute (10 s) stimulation were assessed based on power in the 4–40 Hz bandwidth during a 5-s window during stimulation (STIM) and after stimulation (POST) relative to the power in the 5-s window before stimulation (BASELINE). Stimulation was delivered in bipolar mode between a pair of specific electrode contacts or between a specific contact and the PC+S device case.

and chronic stimulation experiments revealed electrophysiological characteristics of the animal's seizure onset zone and response to local stimulation. Acute stimulation was found to either activate or inhibit local activity in the hippocampus, depending on stimulation parameters. However, stimulation that caused acute inhibition did not cause seizure suppression when the same stimulation was applied chronically.

Despite the inherently higher value of NHP models over those in the rodent brain, relatively little NHP epilepsy work has been done in the past 50 years. A variety of approaches have been attempted for modeling human TLE in the NHP. Early electrical stimulation studies in NHPs have shown that seizures can be induced in NHPs through kindling (Delgado 1959; Eidelberg et al. 1959; Goddard et al. 1969). While results from these experiments have yielded a species dependency, commonly reported problems included lengthy kindling durations, unstable spontaneous seizure development, and inconsistent brain damage. Pharmacological models utilizing alumina gel (Ribak et al. 1998), pilocarpine (Perez-Mendes et al. 2011), bicuculline (Gunderson et al. 1999), and penicillin (Blauwblomme et al. 2011) successfully recreated complex partial seizures in NHPs; however, they failed to create some of the pathophysiological and clinical signs seen in human TLE. These models have face validity but limited construct validity, considering the differences in how seizures originate in the models compared with human TLE. The study of naturally occurring TLE in a NHP mitigates these limitations. However, because of the difficulties associated with identifying multiple NHPs with a seizure disorder, this study is limited to a single case. It is therefore important to use caution in drawing general conclusions from these findings, and to un-

derstand them in the context of other preclinical and clinical studies.

Timed bilateral recordings from the NHP hippocampi revealed a highly variable diurnal pattern of activity, characterized by elevated LFP power and higher variance during the night compared with daytime. The animal's sleep-wake cycle, as well as interictal discharges, may have contributed to this pattern of activity. Sleep-wake-related changes in LFP power are expected to be symmetric between hemispheres, while asymmetric changes may correspond to interictal pathological activity. The exaggerated pattern of increased LFP power in the right hippocampus suggests that frequent interictal discharges occurred on this side.

The predominant right hippocampal onset of the detected ictal events and the characteristic initiation pattern were also consistent with a right temporal lobe focus. Furthermore, right-left theta band coherence ( $>0.75$ ) typically peaked after the right-sided onset, suggesting that epileptic activity spread to the left hippocampus during this time, where it continued independently. The lag time of  $23.6 \pm 2.8$  ms observed in seizure theta synchronization between right and left hippocampal LFPs is consistent with interhemispheric delay of  $\sim 25$  ms (Queiroz and Mello 2007; Votaw and Lauer 1963). Administration of ketamine caused a marked increase in LFP power selectively in the right hippocampus and consistently gave rise to seizures. The actions of this NMDA receptor antagonist have been implicated in seizure generation; however, its role appears to be complex. While ketamine has been reported to have some anticonvulsant effects in a variety of animal models, other preclinical and clinical reports suggest the drug may precipitate epileptic discharges (Ghasemi and Schachter 2011). Dose, mode of

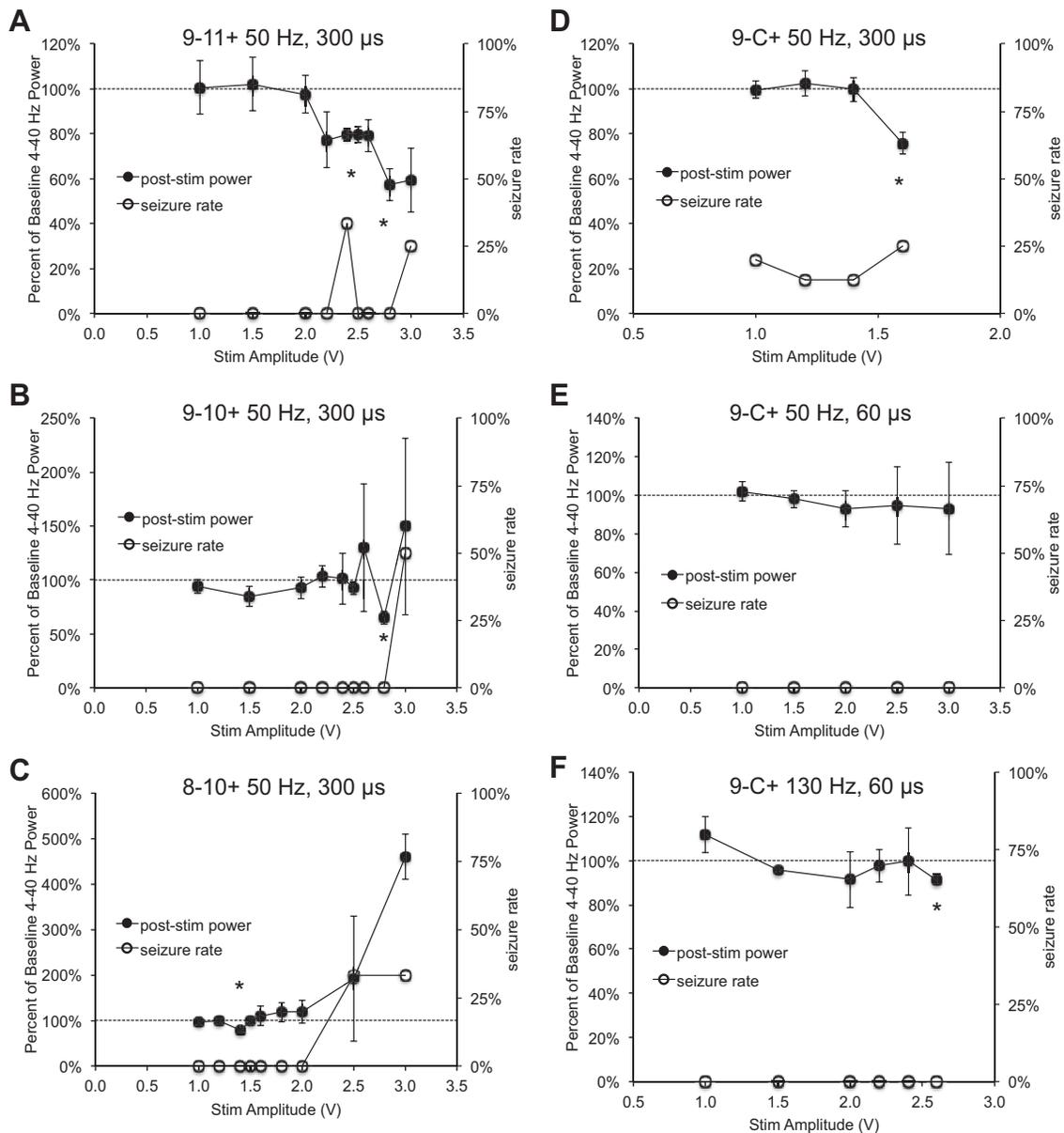


Fig. 7. Acute stimulation modulates local LFP activity: group data. A–F: effects of acute DBS on local power and seizure induction with different electrode contact configurations and stimulation amplitudes. Bipolar stimulation in R hippocampus resulted in local suppression of power when it was delivered across dorsal contacts (A; 9-11+) compared with activation when it was delivered across ventral contacts (C; 8-10+). \*Significant difference from prestimulation baseline ( $P < 0.05$ , repeated-measures ANOVA).

administration, and the resulting site of action may be critical determinants of ketamine's conflicting effects on seizure activity. Consistent with the present findings, however, ketamine has been reported to increase gamma oscillations in rat hippocampus (Caixeta et al. 2013).

The spectral content of ictal events was similar to seizures observed in human TLE (see Fig. 5). The occurrence of spectral chirps at ictal onset has also been reported and has implications for understanding epileptogenesis as well as for improving seizure detection algorithms (Molaei-Ardekani et al. 2010; Schiff et al. 2000). Thus these findings are consistent with focal, right MTLE. Comparison to human data indicates that the NHP seizures are consistent with seizures arising in hippocampus. This hypothesis cannot be proven definitively, as it is not feasible in this study to implant additional depth

electrodes to definitively map the seizure focus, as would occur in a patient undergoing intracranial monitoring in an epilepsy monitoring unit. Nonetheless, we have shown that this animal provides a valid model for idiopathic, nonlesional MTLE.

**Acute stimulation.** Consistent with the hypothesis that the seizure focus was located in the right temporal lobe, acute stimulation in the right—but not left—hippocampus was capable of precipitating seizures under ketamine anesthesia. Furthermore, stimulation through electrode contacts that recorded the highest spontaneous hippocampal energy (8-10+) resulted in the lowest afterdischarge thresholds, shown in Table 2. In accordance with recently reported results of stimulation in the normal ovine hippocampus, 50-Hz stimulation at a 300- $\mu$ s PW resulted in suppression of spontaneous activity but could also induce afterdischarges at

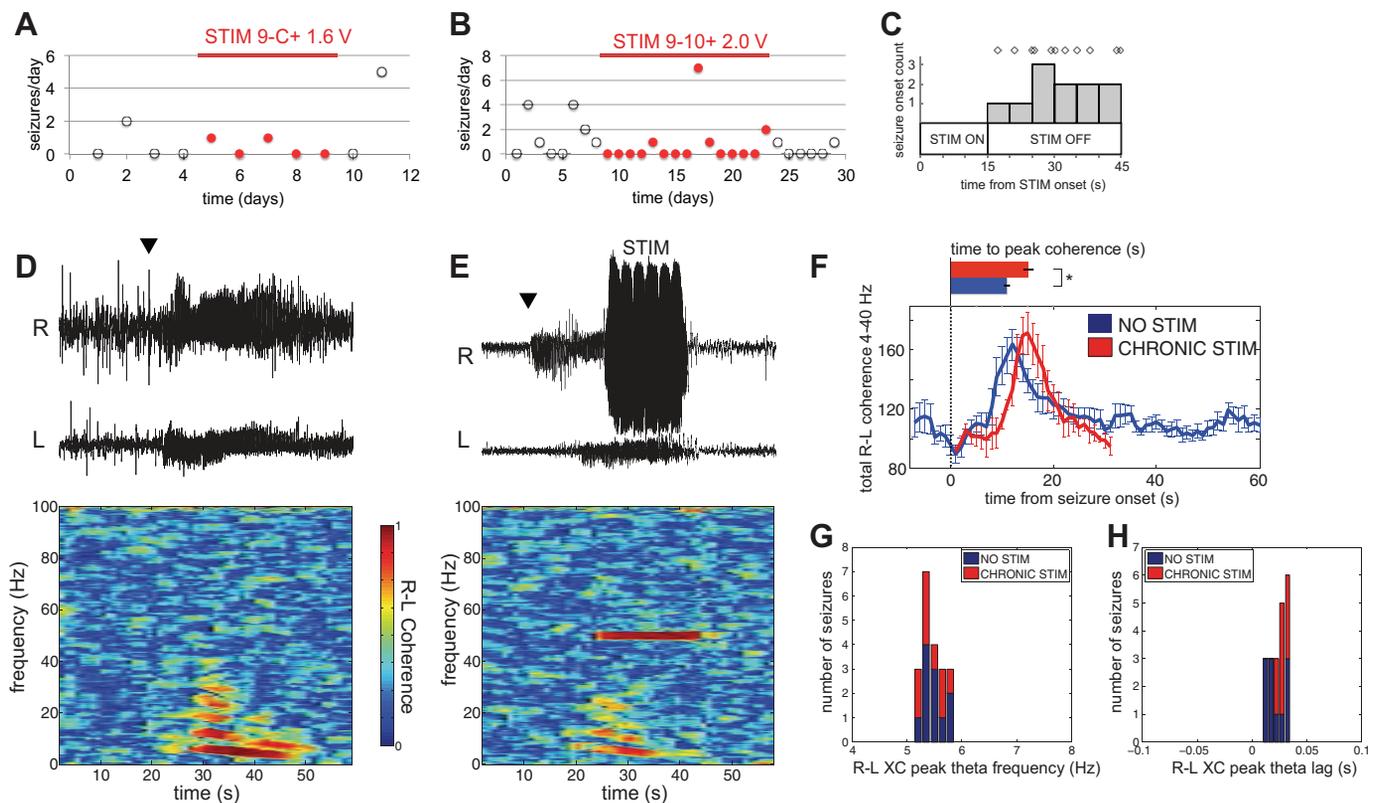


Fig. 8. Chronic cycling stimulation did not significantly alter seizure frequency. *A* and *B*: seizure frequency was monitored with the PC+S detection function and visually validated, before, during, and after chronic cycling stimulation of R hippocampus in monopolar mode [*A*; 9-C+, 50 Hz, 300- $\mu$ s pulse width (PW)] and bipolar mode [*B*; 9-10+, 50 Hz, 300- $\mu$ s PW]. Cycling DBS consisted of a 15-s ON phase and a 30-s OFF phase. *C*: onset times of 11 seizures that occurred during the 2nd chronic stimulation trial are plotted as diamonds and as a histogram, in relation to the STIM ON and OFF phases. There was no apparent relationship between the timing of seizure onset within the OFF phase. Note, however, that seizure onset could not be detected if it occurred during the ON phase because of stimulation artifact. After the onset of seizures (arrowhead in *D* and *E*), right and left hippocampal LFPs became coherent at characteristic frequencies within the theta-beta range. This phenomenon was observed in naturally occurring seizures during periods without stimulation (*D*) as well as during chronic cycling stimulation (*E*). *D* and *E*: representative examples of LFP traces (*top*) and corresponding R-L coherence time-frequency plots (*bottom*). A stimulation artifact (STIM; 9-10+ bipolar; 50 Hz, 300- $\mu$ s PW, 2.0 V) is visible in R LFP trace and as coherence line at 50 Hz in *E*. *F*: time course of R-L coherence in the theta-beta range (4–40 Hz) relative to seizure onset was not significantly different between seizures recorded without stimulation ( $n = 10$ ) and during chronic DBS ( $n = 5$ ). Peak frequencies (*G*) and lag times (*H*) in the R-L cross-correlation were consistent between seizures and were not altered by chronic stimulation.

higher stimulation voltages (Stypulkowski et al. 2013). Notably, acute bipolar stimulation-induced suppression occurred across the frequency bands examined, while activation was highest in the beta and gamma bands. This suggests that acute suppression may reflect a general inhibition of activity or a broadband desynchronization of local networks. By contrast, the observed activation appears to be a reflection of high-frequency afterdischarges.

Given the increased LFP power and apparently lowered seizure threshold induced by ketamine, caution must be exercised in interpreting the results of acute stimulation under ketamine anesthesia. However, several lines of evidence suggest that a common mechanism underlies both naturally occurring seizures and ketamine-induced epileptic discharges observed in these experiments. First, ketamine-induced ictal events bear the same electrographic signature as naturally occurring seizures and were confirmed to produce the same semiology in the anesthetized animal. Second, ketamine preferentially affects right hippocampal LFP activity, suggesting that ketamine lowers the seizure threshold of the right-sided seizure focus. Therefore, the results of acute stimulation were used to guide the selection of potentially therapeutic stimulation parameters in chronic stimulation experiments.

**Chronic stimulation.** Based on the successful suppression of spontaneous activity with right-sided acute stimulation under ketamine anesthesia, two chronic cycling stimulation trials were performed. However, no significant decrease in seizure frequency was observed. One possibility for why significant suppression was not achieved in these two chronic trials is that the 30-s OFF time may be too long. In some of the acute stimulation trials, hippocampal suppression of spontaneous activity recovered in <10 s. This stimulation OFF cycle time is one area that requires further exploration in future chronic trials. Furthermore, longer periods of chronic stimulation may be required to produce a therapeutic effect, in line with results reported in human clinical trials (Fisher et al. 2010; Spencer et al. 2011).

There are multiple challenges in developing an effective DBS-based therapy for epilepsy. First, there is an incomplete understanding of how DBS affects neural activity locally and how it affects afferent and efferent regions. Electrical stimulation of neural tissue has complex electrochemical effects and can generate both orthodromic and antidromic action potentials (David et al. 2010; McCracken and Grace 2007, 2009; McIntyre et al. 2004; Merrill et al. 2005). The therapeutic suppression of neural activity by DBS has been hypothesized to

involve synaptic inhibition, synaptic depression, and depolarization blockade (McIntyre et al. 2004). Another challenge is that the mechanism of seizure generation, and therefore response to potential therapeutic interventions, is still poorly understood and may vary between subjects. While suppression of local activity within a seizure focus might be intended to serve as a functional lesion, network regulation and long-term plasticity have also been hypothesized as potential seizure suppression mechanisms (Hellier et al. 2009).

In contrast to the ability to manipulate the clinical stimulation device in our epileptic NHP over multiple experiments, human studies of direct hippocampal stimulation have almost exclusively branched from an initial report of 10 patients undergoing intracranial monitoring. In the initial study, hippocampal depth electrodes were used to deliver continuous low-amplitude, high-frequency stimulation to the hippocampus (Velasco et al. 2000) as biphasic 450- $\mu$ s pulses at 200–400  $\mu$ A and 130 Hz. In this study, and subsequent open-label studies using similar parameters, significant reductions in the number of seizures have been reported (see Table 1). No large-scale trials, however, have been undertaken to rigorously assess hippocampal stimulation in MTLE.

Similarly, parameters for the multicenter, double-blind, randomized trial of bilateral stimulation of the anterior nucleus of the thalamus for localization-related epilepsy (SANTE) were derived from those used previously in the treatment of movement disorders, rather than evolving from preclinical work in adequate models. In this trial of continuous but intermittent stimulation, 60% of patients had seizure onset in the temporal lobe (Fisher et al. 2010). Although stimulation did reduce seizure rates in these patients, the results were less robust than hoped for, with a median seizure reduction compared with baseline of 44% in the stimulated group versus a 22% reduction in the control group. In an alternative approach to continuous stimulation, 90 patients with MTLE participated in the randomized multicenter double-blind controlled trial of responsive focal cortical stimulation (RNS System) (Heck et al. 2014). With this platform, each electrode contact can sense and stimulate, and the neurostimulator typically is programmed to detect and provide stimulation to interictal epileptiform abnormalities. The median percent reduction in seizures for this group after 2 yr of stimulation was 55%, although it is not clear how many of these patients received direct cortical versus direct hippocampal stimulation. In both of these studies, maximal benefit was obtained over the course of 2 yr, further highlighting the need to develop neuromodulation techniques that acutely and directly alter ictogenesis.

Our initial strategy has been to use the sensing ability of the PC+S system to monitor network effects of direct hippocampal stimulation, using parameters previously shown to achieve broadband suppression and to terminate stimulation-induced afterdischarges in the normal ovine brain. The lack of effect on seizure frequency in the reported data indicates the difficulties inherent to developing this technology. We have clearly demonstrated, however, the potential for sensing-enabled stimulation devices to provide a large amount of data that enables electrophysiological characterization of the seizure network before, during, and after stimulation. The complexity of this data, and the need to devise platforms for analyzing similar data in a patient-specific fashion, are also apparent. Future

work will include the testing of stimulation parameters in response to the detection of interictal biomarkers of epileptiform activity, such as high-frequency oscillations (Kondylis et al. 2014; Staba et al. 2004).

**Conclusions.** Chronic LFP recording in the primate epileptic brain, using a clinical device, is a highly valuable tool for developing neurosurgical techniques for real-time seizure detection and intervention. In this report, we have demonstrated that stimulation parameters previously shown to acutely suppress hippocampal activity may not be sufficient for the treatment of TLE. However, the NHP model presented here has the potential to fill an important gap in translational approaches to developing better therapeutic strategies to epilepsy (French et al. 2013). In particular, its similarity to human brain and its ability to accommodate a clinical sensing-enabled DBS system make the NHP model ideal to further our understanding of the etiology of the disease and refine DBS therapeutic paradigms. Furthermore, the ability to detect and record seizures chronically gives this system the potential to monitor the long-term therapeutic and potential adverse effects of different configurations of biomarker-sensing and triggered DBS therapy.

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#### DISCLOSURES

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#### AUTHOR CONTRIBUTIONS

Author contributions: W.J.L., S.R.S., J.L.C., and R.M.R. conception and design of research; W.J.L., V.J.D., S.R.S., and R.M.R. performed experiments; W.J.L., S.R.S., A.R.A., and R.M.R. analyzed data; W.J.L., S.R.S., D.J.C., and R.M.R. interpreted results of experiments; W.J.L. and S.R.S. prepared figures; W.J.L. and V.J.D. drafted manuscript; W.J.L., S.R.S., A.R.A., D.J.C., J.L.C., and R.M.R. edited and revised manuscript; W.J.L., V.J.D., S.R.S., A.R.A., D.J.C., J.L.C., and R.M.R. approved final version of manuscript.

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