Brain Stimulation 9 (2016) 911–918

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Closed-Loop Interruption of Hippocampal Ripples through Fornix Stimulation in the Non-Human Primate

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ARTICLE INFO

Article history:
Received 19 February 2016
Received in revised form 13 June 2016
Accepted 27 July 2016
Available online 2 August 2016

Keywords:
CA3
Sharp-wave ripple
Ripple interruption
Contingent deep-brain stimulation
Responsive DBS
SPW-R
Neuromodulation

ABSTRACT

Background: Hippocampal sharp-wave ripples (SWRs) arising from synchronous bursting in CA3 pyramidal cells and propagating to CA1 are thought to facilitate memory consolidation. Stimulation of the CA3 axon collaterals comprising the hippocampal commissure in rats interrupts sharp-wave ripples and leads to memory impairment. In primates, however, these commissural collaterals are limited. Other hippocampal fiber pathways, like the fornix, may be potential targets for modulating ongoing hippocampal activity, with the short latencies necessary to interrupt ripples.
Objective: The aim of this study is to determine the efficacy of closed-loop stimulation adjacent to the fornix for interrupting hippocampal ripples.
Method: Stimulating electrodes were implanted bilaterally alongside the fornix in the macaque, together with microelectrodes targeting the hippocampus for recording SWRs. We first verified that fornix stimulation reliably and selectively evoked a response in the hippocampus. We then implemented online detection and stimulation as hippocampal ripples occurred.
Results: The closed-loop interruption method was effective in interrupting ripples as well as the associated hippocampal multi-unit activity, demonstrating the feasibility of ripple interruption using fornix stimulation in primates.
Conclusion: Analogous to murine research, such an approach will likely be useful in understanding the role of SWRs in memory formation in macaques and other primates sharing these pathways, such as humans. More generally, closed-loop stimulation of the fornix may prove effective in interrogating hippocampal-dependent memory processes. Finally, this rapid, contingent-DBS approach may be a means for modifying pathological high-frequency events within the hippocampus, and potentially throughout the extended hippocampal circuit.

Introduction

Sharp wave ripples (SWRs) are hippocampal oscillations that are associated with widespread activation of neocortex, and as a consequence of this co-activation, SWRs are believed to underlie memory consolidation [1]. SWRs are produced by synchronous activity of CA3 pyramidal cells, which in turn excite CA1 pyramidal cells [2–4]. The ventral hippocampal commissure in rodents contains CA3 pyramidal cell collaterals, making it possible to interrupt ripples through online detection and stimulation of this pathway. Interruption using this method suppresses the synchronous spiking typical of SWRs and impairs performance on memory tasks, supporting a role for SWRs in memory consolidation and/or retrieval [5–8]. Sharp wave ripples are also seen in humans [9–11] and macaques [12,13]; but because ripples have not been experimentally manipulated in primates, their role in memory less clear. Unlike rodents, primates have a weak, sparsely connected ventral hippocampal commissure [14–16], making the murine approach to ripple interruption

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http://dx.doi.org/10.1016/j.brs.2016.07.010

untenable in primate brains. The fimbria-fornix fiber tract, however, is robust and well-conserved [17–19] and its integrity is important for memory formation in primates [20–29]. Furthermore, preliminary and case studies using fornix stimulation in humans has been linked to memory improvements and changes in hippocampal structure and function [30–34]. The fornix contains projections from within the hippocampus proper and connected subicular complex, and from extra-hippocampal structures known to modulate ripples in rodents [35–39], suggesting the potential to interrupt ripples. The effect of fornix stimulation on hippocampal ripples, however, is unknown.

In this study, we sought to 1) detect ripples in real time in the primate brain and 2) measure hippocampal ripple-band and unit responses to fornix stimulation. We show that fornix stimulation evoked responses in hippocampus, that ripples were detected in real time, and that the closed-loop fornix stimulation interrupted ripples and suppressed ripple-associated hippocampal multi-unit activity.

Materials and methods

Subject and surgical implantation

All procedures were approved by the local ethics and animal care authorities. The 10 kg adult female macaque (*Macaca mulatta*) underwent electrode implantation surgeries conducted under sterile conditions and with the animal maintained under approximately 2% isoflurane anesthesia. The animal was implanted bilaterally with a 4-lead NuMed mini-DBS electrode alongside and anterior to the post-commissural fornix of each hemisphere, just caudal to the anterior commissure (Fig. 1A). The leads had contacts of 0.5 mm separated by 1.5 mm (model FTML4E, NuMed, Inc., Hopkinton, New York). Implantation of the stimulating electrodes was guided by preoperative MR images, aligned to fiducial markers, using the Brainsight system (Rogue Research Inc., Montreal, Quebec, Canada). Over the right hippocampus, we implanted an indwelling array of two electrode bundles, each containing 4 independently depth-adjustable platinum/tungsten multicore tetrodes (96 micron outer diameter; Thomas Recordings, Giessen, Germany; Neuralynx, Bozeman, Montana). Post-operatively, tetrodes were lowered into the CA1/2 (bundle 1) and CA3/DG region (bundle 2) of the right hippocampus (Fig. 1B), verified through MR/CT coregistration and functional characterization of brain structures during lowering, including the appearance of SWRs. SWRs were observed in limited ranges of depths across tetrodes, and were associated with unit activity. Once the electrodes had been lowered into the layer, ripple-band activity was stable across sessions. One electrode was placed outside of the hippocampal formation, to measure non-ripple activity such as muscle activity, and to determine the selectivity of responses evoked by the stimulating electrodes ('control' electrode). All sessions took place while the animal was sitting quietly in a darkened booth. SWRs from this animal prior to stimulating electrode implantation were reported previously [13].

Electrophysiological recordings

Local field potentials were referenced to the titanium tetrode-array recording chamber and sampled at 32 kHz using a unity-gain HS36 head stage (Neuralynx, Inc., Bozeman, Montana, USA). The headstage was connected directly to the electrode interface board on the animal head, and powered by the acquisition system. As seen in Fig. 2A, digitized channels were processed in two ways – first, through the Cheetah 32 system (Neuralynx, Inc., Bozeman, Montana, USA). Second, the signal was split and sent to the High Performance Processing unit ('HPP', Neuralynx, Inc., Bozeman, Montana, USA). This processing unit is equipped with a Field-Programmable Gate Array (FPGA – ARM Cortex-A9 processor, Xilinx Inc., Cambridge, UK) capable of carrying all digital processing required for ripple detection and triggering the stimulator in real time. Ripples are neural events with band-limited, high-frequency (80–150 Hz) power compared to background levels of power in that band, therefore ripples can be detected when the band power or envelope exceeds a threshold [9,12,13,41]. Selecting the electrode channel with the highest-amplitude ripple activity, the threshold level should be optimized to maximize the number of true positives by user inspection, while minimizing false detection rate on this channel. That is, low thresholds will produce more false positives while high threshold values may have lower detection rate. The optimal threshold value is well above the baseline activity because band-limited activity of the ripples is considerably higher than the instantaneous activity [13]. In this study, we set the threshold to 6-sd of the band activity, a value similar to rodent interruption studies [5–8]. The 6-sd threshold was estimated based on the average and variance of the ripple band from earlier recordings which were consistent over days in these experiments (9.5 ± 0.1 μV mean±SEM).

The ripple detection algorithm was implemented on the high performance processing unit in three steps. First, the signals were bandpass filtered using a custom-designed finite impulse response (FIR) filter with 512 taps (16 ms delay, which is about one cycle of ripple activity). Activities slower than 80 Hz or faster than 150 Hz are suppressed more than 20 dB (Fig. 2B). Next, amplitudes were compared to the threshold across the target channel and 'control' electrodes that were not observed to record true ripples. These control electrodes were used to reject artifacts such as electromyography (EMG) or other transients that might have otherwise crossed threshold on the target channel, thereby preventing the target's threshold-crossing from generating an output pulse to the stimulator described below.

Artifact rejection and false detection reduction

EMG artifacts and other transients can show broadband signals with considerable power at the ripple band. As such, they can be mislabeled as ripples if a single electrode channel is used for ripple detection. Thus, a simple method to identify the muscle and other common artifacts in real-time was to measure excessive ripple-band activity at other locations, such as the control electrode that had been placed outside the hippocampus. When activity of this control electrode exceeded threshold, crossings on the ripple-detecting electrodes were ignored as a false positive, and the stimulator was not triggered.

Electrical stimulation

Stimulating electrodes were connected to an STG4002 stimulator (Multichannel Systems, Reutlingen, DE). Bipolar stimulation was applied across pairs of contacts using a 100 μs biphasic pulse width of 2 mA. The proximal 2 contacts in both of the stimulating electrodes yielded the strongest responses (i.e. the dorsal most pair of leads, Fig. 1A), and were therefore used to measure hippocampal evoked responses. To measure the hippocampal response to fornix stimulation, the fornix was stimulated for 3 minutes at 1.75 Hz intervals varying by current and number of pulses. The parameter space was single, 4, or 8 pulses and 1, 2, or 3 mA stimulation current. Each stimulation session was epoched using the stimulation triggers such that the last pulses were aligned at $t = 0$. Then the hippocampal response to each stimulation protocol was measured by averaging the epochs obtained during the stimulation session.

For the ripple interruption experiments, we used bipolar stimulation across the adjacent, proximal 2 leads of each electrode, delivered bilaterally at 2 mA, in short bursts of 4 or 8 pulses at 2 ms

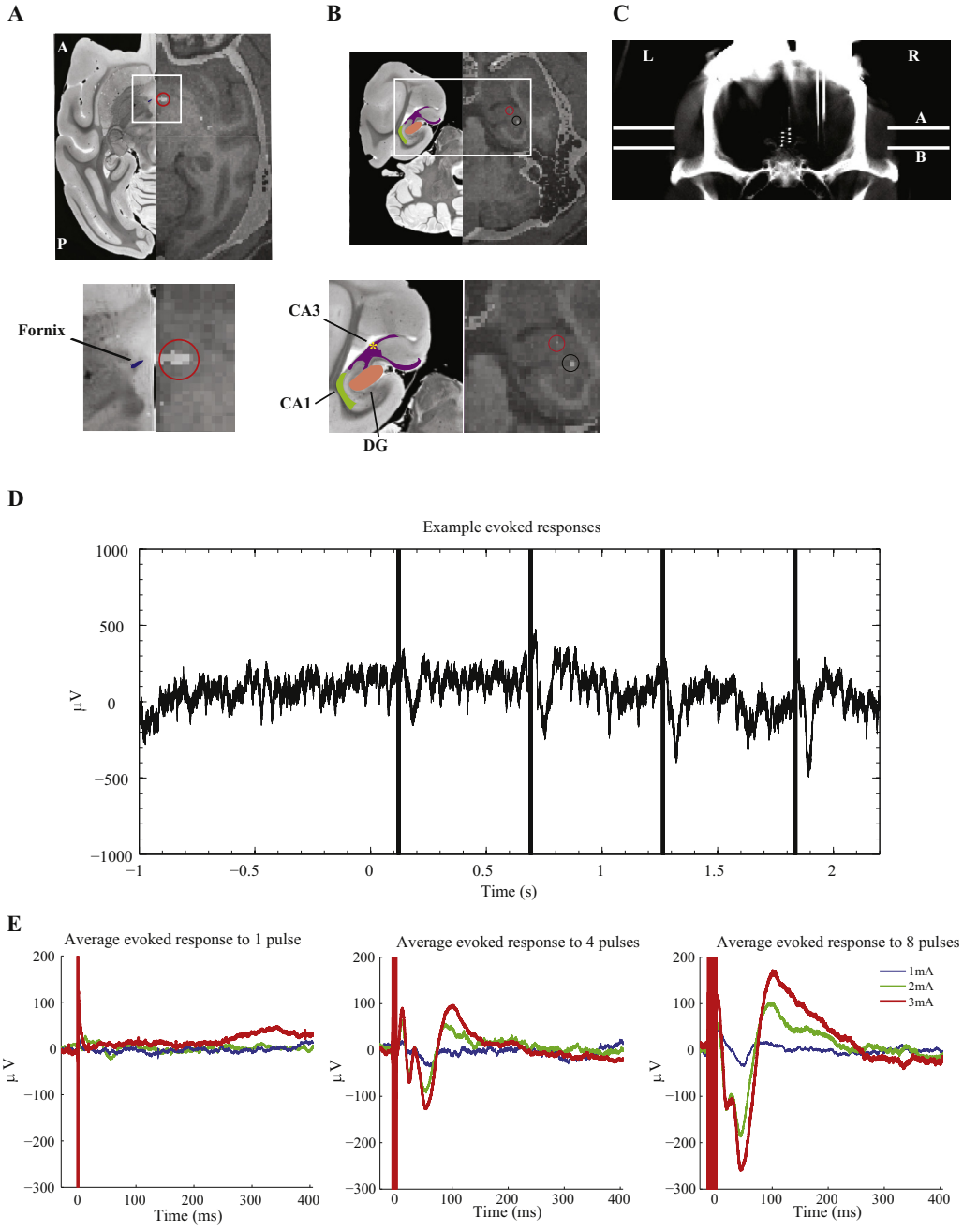

Figure 1. Verification of electrode placement and hippocampal activation. A) Coregistered and overlaid MRI and CT images in the axial plane of the right hemisphere. The location of the stimulating electrode in the CT scan is marked with a red circle. The left hemisphere is from the Saleem and Logothetis atlas [40], with the cross-section of the fornix tract colored in navy. Rostral/anterior is at the top of the image. The lower panel shows a magnified section containing the electrode location seen just anterior to the location of the fornix. B) As in A, but from a ventral slice that reveals the hippocampal recording electrode sites. Two electrode bundles are seen in the figure; the electrode used for ripple detection is circled in red, corresponding to CA3/DG subfields. CA3, CA1, and DG are colored in purple, green and orange, respectively. C) Averaged coronal CT images showing the location of stimulating and recording microelectrodes. Stimulating electrodes are seen close to the midline, whereas hippocampal recording electrode bundles are seen together in the right hemisphere. The horizontal crosshairs (A and B) indicate the axial sections shown in panels A and B of this figure. D) Example broadband hippocampal recording during 4 example stimulation trains (vertical lines). Evoked responses can be seen following each pulse train. E) Average evoked response in hippocampus following 300 stimulation trains. The responses increased from 4 to 8 pulses and 2 to 3 mA, with minimal response at the low, 1 mA level, at all conditions. Effective fornix stimulation evoked hippocampal responses with three peaks 20 ms, 42 ms, and ~100 ms, and two troughs at 33 ms and 53 ms after stimulation onset.

intervals. Thus, when signal amplitude exceeded the threshold on the target channel, and threshold crossing was *not* identified on the control channel (as an artifact), the HPP triggered bipolar stimulation consisting of 4 biphasic pulses of 100 μs at 2 ms intervals on both of the stimulating electrodes, similar to the stimulation durations of 10 ms reported previously [6].

Data analysis

Online ripple detection and interruption were verified and quantified after each daily session, as follows. Four features were evaluated for each ripple event: total ripple duration, ripple duration after detection, ripple fundamental frequency, and multi-unit activity. Ripple

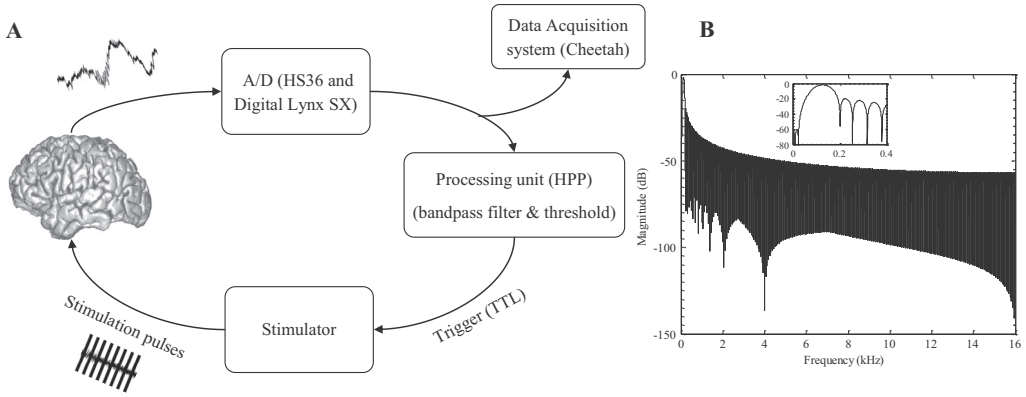

Figure 2. A) Schematic of the system used for ripple detection and fornix stimulation. First, neural recordings are digitized. Then, the HPP signal processing unit bandpass filters the signals from 80–150 Hz and compares their amplitude with threshold values. When the amplitude of signals crosses the threshold, a TTL trigger is sent to the stimulator to generate the pulses bilaterally. B) Frequency response of the filter used to filter the signals. The filter passed the activities between 80–150 Hz and attenuated slower or faster oscillations for over 20 dB. In addition, channels outside the hippocampus must not have crossed threshold, for the HPP to send a trigger.

duration after detection was the time interval between detection and the next minimum below 2-sd, which is approximately the average amplitude of the signal. Similarly, total ripple duration was quantified as the entire interval before and after the threshold detection until the ripple-band dropped below 2-sd. Ripple peak frequency (or fundamental frequency) was obtained from the maximum spectral density calculated between –100 ms and 100 ms of detection using FFT of the signal with 1 Hz resolution. Multi-unit activity was measured as the envelope of high frequency (750–1300 Hz) activity [42,43]. To assess the efficacy of our setup for interruption of hippocampal ripple activity, these four dependent variables were compared as a function of ripple status: fornix stimulation on ('Stimulated') or stimulation off ('Sham').

Results

Hippocampal evoked response to fornix stimulation

Electrodes that recorded hippocampal SWRs [13] also recorded evoked responses during bilateral fornix stimulation. A single time series shows responses following each 8-pulse burst of fornix stimulation, repeated at 1.75 Hz intervals (Fig. 1D). The average of over 300 evoked responses to single/4/8 pulses and 1/2/3 mA fornix stimulation varied with respect to stimulation parameters (Fig. 1E). Whereas single pulse stimulation does not evoke any response in hippocampus with any stimulation intensity, the 4 and 8 pulse stimulation protocols showed a current-dependent response. Specifically, the responses increased from 4 to 8 pulses and 2 to 3 mA, with minimal response at the low, 1 mA level, at all conditions. Effective fornix stimulation evoked hippocampal responses with three peaks 20 ms, 42 ms, and ~100 ms, and two troughs at 33 ms and 53 ms after stimulation onset. Hippocampal responses to stimulation of the ipsilateral fornix were smaller, and fornix stimulation was less effective per stimulation parameter. We therefore selected the most conservative effective protocol of 4 pulse trains bilaterally delivered at 2 mA which is expected to influence hippocampal activity within 20 ms of stimulation onset.

Effect of ripple-triggered stimulation on local field potentials and multi-unit activity

Recordings were collected over a total of 95 daily sessions, with each session typically lasting 50 minutes. In non-human primates, the sharp-wave ripples can occur over various levels of vigilance, i.e. activity, quiescence, or sleep states [13]. In our study, the ripples occurred under all states and occupancy over the state was roughly proportionate, 4 out 5 ripples were during sleep periods. Peak (fundamental) frequencies of ripples were similar in the Stim and Sham conditions (Stim: 125 ± 14 Hz, mean ± SD, n = 1048 Sham: 125 ± 16 Hz, mean ± SD, n = 4286; p = 0.97, Ranksum test), suggesting that stimulation did not alter the underlying mechanisms for ripple generation. An example of an interrupted and a Sham-condition ripple along with their ripple-band envelopes reveals a truncation of the interrupted ripple following stimulation (Fig. 3A–D). It is noted that evoked response to stimulation may not be visible in presence of sharp waves, (see the example shown in Fig. 3C); however, hippocampal evoked responses are recognizable when interrupted ripples are averaged (Fig. 3E). These results are consistent with the population average amplitudes of ripple-band LFP (Fig. 4A). Whereas the amplitude of both stimulation groups was similar prior to detection/delivery of fornix stimulation, the ripple amplitude was effectively eliminated after stimulation. In contrast, stimulation had no effect on a simultaneously-recorded electrode from the same implant bundle as the hippocampal recording electrodes, but lowered to a position outside the hippocampus (Fig. 4, gray lines).

It is conceivable that in previous interruption studies and in the present study, only the tail of the ripple is interrupted, after much of the information-rich spiking sequences contained in ripples have passed. To estimate how much of a ripple's lifecycle has been truncated, we measured total ripple duration defined as 2-sd to 2-sd crossing (pre- to post-detection). Ripple durations were shorter following stimulation pulses, whether measured as total duration ($p = 2 \times 10^{-98}$, Ranksum test) or duration from stimulation offset ($p = 8 \times 10^{-70}$, Ranksum test) (Fig. 4C and 4D). Interruption was manifest as a sharp truncation of the ripple, with a median duration of 25 ms and where over 90% of ripples reached baseline activity by 40 ms after stimulation onset (Fig. 4C). Moreover, the earliest effects of interruption on the ripple-band envelope compared to Sham-condition ripples emerged at 20 ms following stimulation, at about the time of the first evoked potential dip (Fig. 4C, 4D, 1F).

As described in the literature [12,13,44], multi-unit activity during spontaneous ripples is enhanced several fold and returns to pre-ripple levels within 100 ms of detection (Fig. 4B). In contrast, MUA was completely disrupted by fornix stimulation (Fig. 4B, red trace). At control electrode sites, no change in MUA is seen, suggesting the stimulation-induced suppression of MUA is at least partly local to the hippocampal layer, consistent with ripple interruption, and thereby capable of interfering with the spiking contents of ripples.

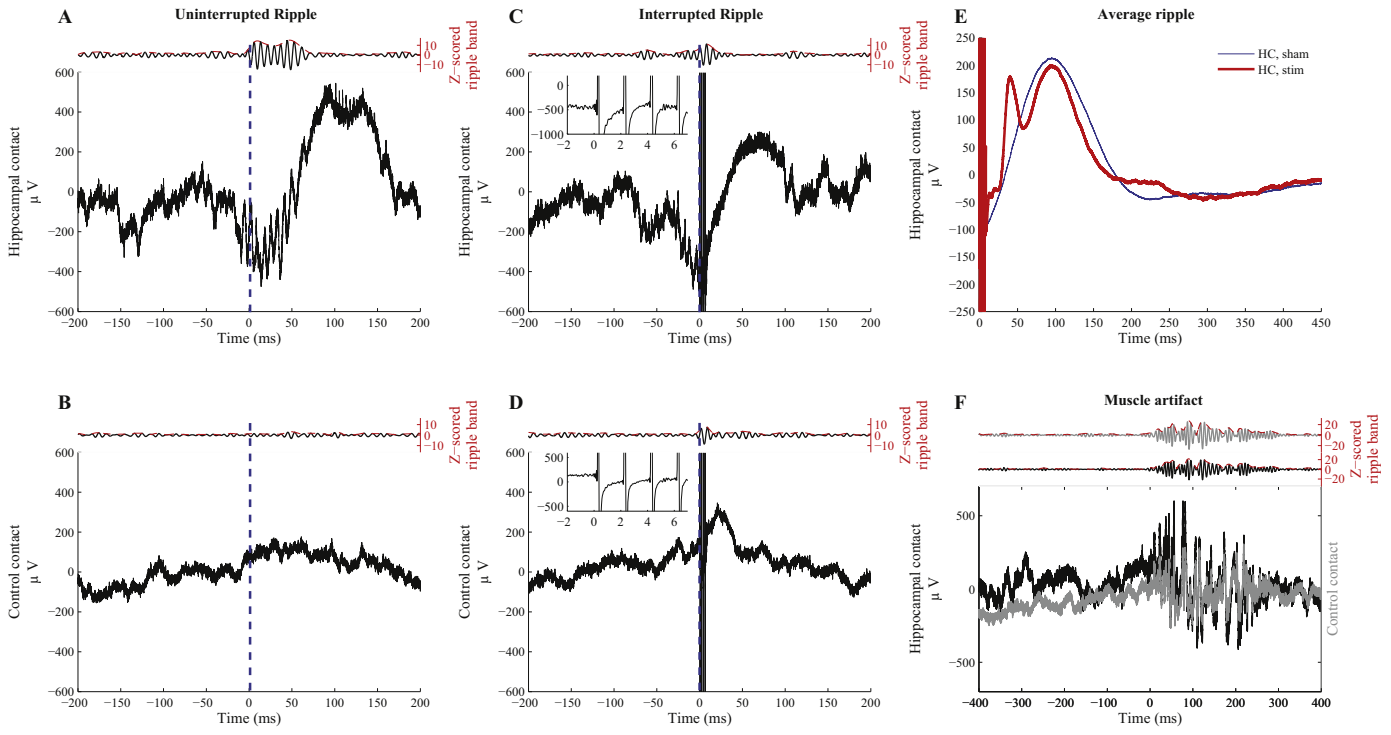

Figure 3. Examples of interrupted and uninterrupted ripples. The detection point is marked by blue vertical lines. A–C) Broadband traces during interrupted and uninterrupted ripple activity showing 200 ms pre- and post-detection. Stimulation pulses are seen after the detection point only for the interrupted ripple (C). Broadband traces were bandpass filtered between 80 Hz and 150 Hz (shown on top). The envelopes and corresponding z-values are shown in red. The ripple-band activity of the uninterrupted Sham ripple is present over 50 ms after the threshold crossing, whereas the ripple-band activity of the stimulation-interrupted ripple returns to the baseline within 20 ms after the detection. B–D) Broadband traces of control electrode during interrupted and uninterrupted ripples shown in A and C. Ripple activity (80–150 Hz) is not observed on this contact. Stimulation pulses are seen after the detection point only for the interrupted ripple (D). E) Average of traces, aligned to the detection point, are shown for Stimulated (red, N = 1048) and Sham (blue, N = 4286) ripples. Hippocampal response to stimulation is identified by a peak 40 ms after the first stimulation pulse. F) Example of muscle artifact is shown on hippocampal and control electrodes. The ripple band activity exceeds the threshold on both channels simultaneously.

Ripples false detection rate

Precise measures of false-positive rates are not possible over the Interruption sessions due to the effect of stimulation on hippocampal activity; however, we estimated the false-positive rate using the Sham sessions when the ripples were detected without simultaneous stimulation of the fornix. Ripples have been characterized as events with excessive band activity and durations longer than 32 ms (4 cycles at 125 Hz). With this definition, the false-detection rate is estimated to be 12% (Fig. 4D).

Discussion

We developed and tested a system to detect and interrupt hippocampal ripples in primates through stimulation of the fornix. Local field potentials and multi-unit activity from the CA3/DG layer of hippocampus illustrated the efficacy of this method to curtail ripples and suppress the ripple-related increase in spiking activity, respectively. This closed-loop system demonstrates the feasibility to selectively disrupt ripples in primates, a paradigm that had previously only been applied to rodent models.

The interruption studies in rats targeted the ventral hippocampal commissural fibers that interconnect the hippocampi in rodents through the axon collaterals of CA3 pyramidal cells [5–8]. Excitatory input from these cells, together with a subset of connected CA3 interneurons, are necessary for ripple initiation in CA3, and the consequent excitatory volley from CA3 that leads to ripples in CA1 [2–4]. Unfortunately, the CA3 commissural projections that proved instrumental for ripple disruption in rats are substantially weaker in human and non-human primates [14–16]. Interruption of ripples in primates may therefore require stimulation of an alternate tract.

The fornix of the macaque carries an estimated 500,000 fibers [17] with notable reciprocal projections in the basal forebrain cholinergic nuclei and subicular complex, projections from CA3, supramammillary nucleus, and monoaminergic nuclei; and projections targeting anterior thalamic nuclei, mammillary bodies, and nucleus accumbens [19,45,46]. As described in several reviews [47–49], these connections are associated with recollection, object-in-place memory, and/or rapid conditional learning in rats [50–52], monkeys [22,24,53–56] and humans [23,57,58]. Furthermore, fornix stimulation has been used to modulate hippocampal activity [30,32,34,59–61].

In the present study, fornix stimulation could have disrupted ripple activity through direct or indirect pathways. Direct projections may have been recruited from posterior hypothalamic regions to CA fields, such as supramammillary fibers [62–65]. These projections can pace hippocampal oscillations [66–68] and are important for spatial learning and memory (for review, see [69]). Alternatively, antidromic activation could arise from CA3 or subicular-complex pyramidal cells [19], though projections from CA3 through this specific part of the fornix have not been isolated. The subicular complex may stand as a feasible relay, due to extensive reciprocal fornix connections [70], in addition to GABAergic projections to CA3 cells, that can inhibit and entrain CA3 neurons [71]. Given the multiple possible routes of action, additional research is required to determine the underlying mechanisms of interruption to fornix

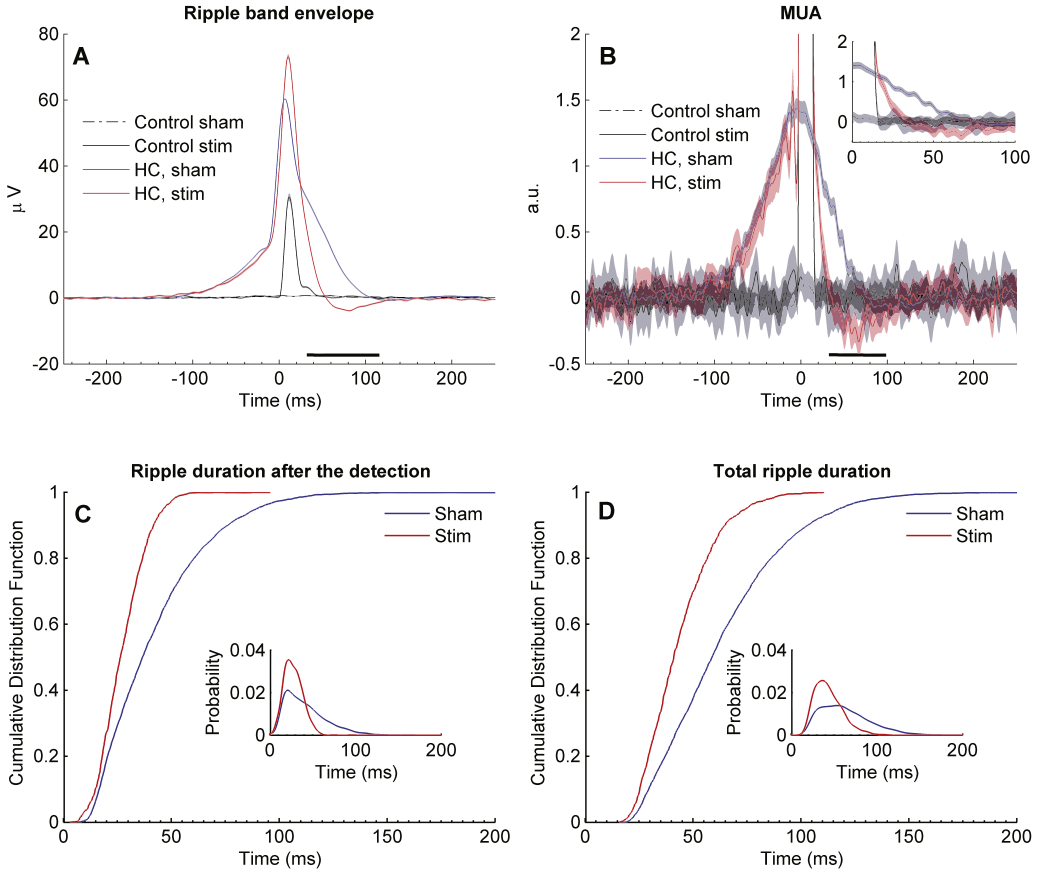

Figure 4. Population averages during ripples in hippocampal and control-site electrodes. Shaded areas represent SEMs. The hippocampal electrode was localized to CA3/DG and was used for ripple detection; the control electrode is located outside of the hippocampal formation. Traces of interrupted ripples are removed during the stimulation pulses to avoid stimulation artifacts. A) Average ripple-band envelope recorded during Stimulated (red, N = 1048) and Sham (blue, N = 4286) ripples on the hippocampal electrode, and on the control electrode (gray). Stimulated and Sham-stimulated ripples are similar prior to the detection (6-sd crossing) point, whereas stimulated ripples show suppressed ripple-band activity after stimulation. Black line at the bottom of the graph marks a period when envelops are significantly different (Ranksum test). Simultaneously recorded control electrode activity does not change during ripples (gray lines), elevated band activity seen over the stimulation sessions is caused by stimulation artifact. B) Changes in average multi-unit activity (MUA) for interrupted and normal ripples with respect to its baseline activity, taken from –250 to – 150 ms before ripple onset. MUA of interrupted ripples was reduced to below its baseline level following stimulation of the fornix, and slowly recovered to pre-ripple levels. MUA of normal ripples was elevated for 100 ms, consistent with the LFP response. Black line at the bottom of the graph marks a period when MUAs are significantly different (Ranksum test). Stimulation artifact is observed on both hippocampal and control electrodes between 0 and 10 ms. C) Cumulative distributions and probability densities (inset) of ripple durations after the detection point, for normal (Sham, N = 4286) and interrupted (Stim, N = 1048) ripples. D) Total duration of ripples (2-sd to 2-sd crossings). Conventions as in C.

stimulation. The utility of the method, however, is immediately relevant to studies of ripple function in behaving animals.

In rats, ripple occurrences after a task include activity patterns reflecting past events and that are thought to be important for communication between hippocampus and neocortex [1]. Ripples during learning and exploratory tasks have been shown to reflect trial outcome [13,72] and future success [73]. Ripple rate of occurrence increases after a new or unexpected experience ([74,75], but see [76]) and the goal-related place cell firing during SWRs is associated with later memory for goal locations [73]. Critical tests of ripple function, however, require causal manipulations. Disruption of ripples impairs memory performance, even after controlling for nonspecific effects from the ripple-disrupting stimulation, (i.e. when ripples and stimulation pulses are decoupled, allowing both to unfold [5,6,8]). It is noted that memory impairment was caused by truncating the ripples with electrical stimulation and not preventing the ripples, e.g. with pharmacological manipulations. Studies of the effects of ripple interruption on behavior have not been conducted in primates. This is of special interest, given the reduction in ripple rate in humans [77], and the observation of ripples during active exploration in macaques [13], not only in offline states or pauses in exploration.

Closed-loop detection of ongoing hippocampal activity to deliver responsive stimulation has implications beyond disrupting ripples. For example, some types of seizure activity bear similarities to ripples in the LFP under some circumstances, and may be good candidates for rapid detection using the methods described in the present study (see [78]). To date, no closed-loop hippocampal stimulation has been reported for this purpose, though the relevance is highlighted by a report of bilateral hippocampus stimulation in idiopathic epilepsy in a macaque [79]. There, direct stimulation to hippocampus altered LFP activity under anesthesia, but the stimulation was thus far ineffective at reducing seizures under the direct, local, and 'open-loop' stimulation protocols used.

In humans, open loop high frequency stimulation of the homologous regions of the fornix evoked memories of past events [30], occasional alleviation of memory decline in patients with Alzheimer's disease [31], and hippocampal activation [80]. Other targets for altering hippocampal-related memory function in the humans have been explored, again, in open-loop rather than responsive or

contingent approaches [61,81,82]. The effectiveness of closed-loop approaches for modulating other neural circuits and associated diseases, suggest that this may be an important improvement to open-loop designs [83–85]. Finally, as stimulation of human hippocampus continues to be explored, our results suggest that one possible effect of stimulation is the alteration of SWRs. Inasmuch as they facilitate memory formation and drive widespread cortical activation, the enhancement or suppression of SWRs by these emerging stimulation approaches in humans should be of particular interest moving forward.

Acknowledgments

We are grateful for funding received from The Krembil Foundation, Brain Canada, NSERC CREATE VSA, NSERC DG; and the CRANIA Project. We would also like to thank Steve Frey for assistance in adapting implants and learning the Brainsight system.

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