The human hippocampus is essential for the processing of sensory information into retained memories. The transformation of sensory stimuli into memory in mammals occurs through a highly specialized, hierarchical network of interconnected neuronal ensembles of the CA1 and CA3 hippocampal subfields. Any attempt to repair dysfunctional hippocampal circuitry in patients with memory impairment due to neurological disorders such as Alzheimer’s disease requires network intervention to restore proper memory encoding.

Keywords: magnetic resonance; depth electrode recording; cross-correlation; functional connectivity; single neuron; memory; cognition

Abbreviations: DMS = Delayed-Match-to-Sample; NHP = nonhuman primate.

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the performance of memory encoding can be predicted based on preceding encoding events that resulted in successful recall. Successful firing patterns can then be mimicked during working memory performance via delivery of electrical stimulation in a pattern that emulates an ensemble code for memory. Stimulated encoding has been shown to improve performance when hippocampal function is limited, or to replace memory encoding when hippocampal ensembles cannot generate a successful code to perform a task. Recording and stimulation of hippocampal neural ensembles has been demonstrated in preclinical rodent and primate models, although human subjects are currently being assessed. Successful implementation of such a hippocampal prosthesis in humans requires the following: 1) successful localization of electrodes within the specific hippocampal sublayers CA1 and CA3, 2) accurate recording of firing patterns from CA3 and CA1 subfields (Fig. 1A), and 3) evidence of successful stimulation of CA1 with the predicted neuronal firing patterns from prior successful encoded events. Examination of patients with medically refractory epilepsy provides a unique opportunity to assess hippocampal neuronal firing during memory tasks. Intracranial monitoring for seizure localization requires stereotactic neurosurgical placement of depth electrodes into suspected regions of seizure origination, often involving the hippocampus and amygdala. Via intracranial electrodes, direct assessment of hippocampal ensemble activity can be performed without additional risks to patients. Moreover, successful hippocampal electrode placement requires accurate identification of the hippocampal CA3 and CA1 sublayers and the exact location of the electrode, something not easily accomplished by imaging alone. Ulbert et al. provided one of the first descriptions of layer-specific electrophysiology within the human hippocampus through intraoperative recordings performed during resection of the medial temporal lobe and confirmed with immediate postoperative histology. Electrophysiological recordings were limited due to anesthesia, and this approach required additional time and risk associated with placing depth electrodes during planned temporal lobe resection.

In this study we demonstrate a combined imaging and electrophysiological recording methodology that successfully confirms electrode placement within the CA1 and CA3 subfields of the human hippocampus without requiring postoperative histological confirmation. By demonstrating that firing patterns of CA3-to-CA1 neuronal ensembles directly influence CA1 task responses, we are able to establish the necessary groundwork to initiate successful hippocampal stimulation for brain-computer interfacing and/or neural prosthetic research.

**Methods**

A multidisciplinary team examined 23 patients with medically refractory focal epilepsy requiring invasive monitoring prior to the planning of a potential resection. All patients underwent prior comprehensive preoperative testing including long-term noninvasive video-EEG analysis, preoperative MRI, and neuropsychological evaluation. Depth electrode placement was determined on the basis of presurgical data and clinical necessity for further evaluation. All patients had at least one hippocampal (anterior) electrode (Table 1).

Surgical procedures were performed at the Wake Forest Baptist Medical Center and approved by the IRB of Wake Forest School of Medicine. Postoperative monitoring and neurocognitive testing were performed at the Comprehensive Epilepsy Center at Wake Forest Baptist Medical Center. Twenty-three patients provided written informed consent prior to participation in this study, separate from consent for surgical procedures, standard seizure monitoring, and clinical management.

**Electrode Implantation**

FDA-approved intracranial depth probes capable of single-neuron and field-potential recording (Macro-Micro electrode, MM16C-SP05X-000, Ad-Tech Medical Instrument Corp.; Fig. 1D) were surgically placed using either a stereotactic head frame (CRW Precision Arc, Integra LifeSciences) or frameless stereotactic system (VarioGuide, Brainlab AG) at the discretion of the operating surgeon. Electrodes were placed through the head of the hippocampus perpendicular to its long axis in order to localize within CA3 and CA1 subfields (Fig. 1A). Calvarial entry points were created using either cranial burr holes or bone flaps as dictated by the clinical needs of each individual patient. A small puncture incision of the dura mater was performed and the electrode was placed at the preplanned location, with at least one hippocampal electrode implanted in each patient. Intraoperative neuronal monitoring was performed in each patient to confirm adequate neural recording prior to securing each electrode to the scalp and closing the craniotomy and scalp incision.
Postoperative localization of electrode placement was verified by MRI (Fig. 1B and C). Confirmation of electrode placement within the CA1 and CA3 subfields was determined by comparison with a morphometric survey of 3-Tesla MRI scans from 46 normal (i.e., nonepileptic) patients and 26 patients with a history of epilepsy but no prior depth electrode implantation, providing average dimensions of the hippocampus along typical implantation tracks. The typical duration of implantation was 10–20 days, as established by each patient’s care team to allow sufficient time to assess seizure localization.

**Neurocognitive Testing and Recording**

Depending on individual patient clinical needs, neurocognitive testing was typically performed on postimplantation days 3–7. Patients with electrode implantation in this study (n = 23) performed a custom-designed visual Delayed-Match-to-Sample (DMS) memory task modeled after the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition Ltd.), adapted from prior implementation in nonhuman primate (NHP) studies. Patients were tested at bedside and were seated or reclining facing a touch-sensitive screen displaying the DMS trials. Each session consisted of 100 trials involving a “sample” phase in which a single image was presented, a randomized variable delay (1–75 seconds) with no images displayed, and a “match” phase in which the same sample image was displayed along with a randomized number of 1–6 distractor images. A correct response consisted of touching the same image in both the sample and match phases. Trials were separated by a 5-second intertrial interval.

Neurons were recorded on the microelectrode sites of the implanted electrodes using a Blackrock Cervello neural recording system. Extracellular action potential waveforms from neurons were isolated and identified for online and offline sorting of single-unit discharges. Continuous electrical digitized monitoring...
Neural recordings were obtained from 23 patients with electrodes implanted into the hippocampus. Figure 1B shows a coronal T1-weighted MR image captured at the region of the anterior hippocampus, demonstrating electrode placement bilaterally across the CA1 and CA3 cell fields. Figure 1B and C show optimal electrode placement, in which the electrode trajectory (linear shadow with beadlike swellings) is perpendicular to the long axis of the hippocampus, and the macroelectrode sites (Fig. 1D; see also “beads” on the electrode shadow in Fig. 1B and C) within the average dimensions of human hippocampal CA1 and CA3 cell fields (Fig. 1C). Placement of Ad-Tech MM16C-SP05X-000 macro- and micro-depth electrodes were compared (where possible) to presurgical MR images to confirm the presence of morphologically distinct CA1 and CA3 cell fields at the electrode recording sites.

**Results**

**Neural Recordings**

Neural recordings were obtained from 23 patients with electrodes implanted into the hippocampus. Figure 1B shows a coronal T1-weighted MR image captured at the region of the anterior hippocampus, demonstrating electrode placement bilaterally across the CA1 and CA3 cell fields. Figure 1B and C show optimal electrode placement, in which the electrode trajectory (linear shadow with beadlike swellings) is perpendicular to the long axis of the hippocampus, and the macroelectrode sites (Fig. 1D; see also “beads” on the electrode shadow in Fig. 1B and C) within the average dimensions of human hippocampal CA1 and CA3 cell fields (Fig. 1C). Placement of Ad-Tech MM16C-SP05X-000 macro- and micro-depth electrodes were compared (where possible) to presurgical MR images to confirm the presence of morphologically distinct CA1 and CA3 cell fields at the electrode recording sites.

**Hippocampal Morphometry**

Electrode placement for all patients was compared to a table of the skull on the left hemisphere, and 34.84 ± 2.78 mm on the right. There was no significant difference between the left and right CA1 depths (pairwise t-test, t(25) = 0.59, nonsignificant). The CA1 and CA3 cell fields were separated by a minimum distance of 1.68 ± 0.35 mm on the left and 1.83 ± 0.4 mm on the right, with a maximum outer span from edge to edge of 4.92 ± 1.86 mm on the left and 5.08 ± 1.52 mm on the right. There was no significant difference between right and left hippocampal CA1 depths (pairwise t-test, t(45) = 1.86, nonsignificant). In epilepsy patients without electrode implantation, the CA1 region was encountered at an average depth of 35.26 ± 2.43 mm from the outer table of the skull on the left hemisphere, and 34.98 ± 3.00 mm on the right hemisphere. There was no significant difference between left and right CA1 depths (t(20) = 1.75, nonsignificant). The CA1 and CA3 cell fields were separated by a minimum distance of 1.36 mm on the left and 1.34 mm on the right, with a maximum outer span from edge to edge of 4.53 mm on the left and 4.48 mm on the right. There was also no significant difference between the depths of the left CA1 between normal and epilepsy patient populations (t(23) = 0.62, nonsignificant), nor were there any significant differences between the implanted and nonimplanted epilepsy patient populations (Table 2). Thus, these distances were consistent with probe implantations with the most distal macro (EEG) recording site approximately 45 mm from the outer table of the skull and micro (single-unit) recording sites between 33 and 42 mm from the outer table of the skull.

Recordings of electrical signals from the macroelectrode recording sites were used to isolate single-neuron activity from the human hippocampus. Each signal was recorded with a 60-Hz hardware notch filter to remove line noise, and then digitally bandpass filtered (500–5000 Hz) to isolate single-neuron action potential waveforms. Figure 2 illustrates the digitization and filtering of neural activity to yield isolated single-neuron recordings from the 17-μm microelectrode sites on the macro-micro electrodes. Microelectrode neuron recordings were digitized at 30,000 samples/sec (Fig. 2A). Signals were alternating current coupled and bandpass filtered at 500–5000 Hz to isolate single-neuron action potentials (Fig. 2A, part b, ex-
panded in Fig. 2B) or direct current coupled and notch filtered at 60 Hz to preclude inclusion of artifactual “spikes” due to amplifier overdriving (Fig. 2A, part c, expanded in Fig. 2C). Individual neurons (i.e., “single units;” see 1, 2, and 3 in Fig. 2) were identified by consistent waveform shape and amplitude from filtered recordings (Fig. 2B). Figure 2D shows mean action potential waveforms and autocorrelograms for neurons 1–3 identified in Fig. 2B, thus positively identifying single neuronal recordings. A 2-msec “gap” at 0 seconds is visualized, consistent with the time span of single-neuron refractory periods.

Validation of Hippocampal Neural Recordings

Table 1 summarizes the data gathered from 744 neurons recorded from the 23 patients examined in this study. Neurons were recorded from a total of 46 implanted electrodes as follows: 7 patients had a single electrode implanted (unilateral anterior hippocampus); 5 patients had 2 unilateral electrodes (anterior and posterior); 7 patients had 2 bilateral electrodes (anterior); 1 patient had 3 electrodes placed (bilateral anterior and 1 posterior); and 3 patients had 4 electrodes (bilateral, anterior, and posterior). Neurons were sorted by recording electrode location within the putative boundaries of CA1 and CA3 cell fields (Fig. 1, Table 2), and then by firing rate (Table 3). Neurons with steady-state resting firing rates > 20 Hz (i.e., clearly interneurons) were not recorded. An additional 27 CA1 and 41 CA3 neurons were putatively identified as interneurons due to steady-state firing rates between 10 and 20 Hz and were recorded, but not subjected to further analy-
sis. The remaining neurons were further sorted into categories with firing rates between 0.5 and 5.0 Hz consistent with hippocampal pyramidal cells in lower vertebrates\textsuperscript{2,8,17} and rates between 5.0 and 10 Hz that have been shown to occasionally include hippocampal neurons with behavioral correlates in NHPs.\textsuperscript{17} Table 3 shows that approximately 5 times as many neurons exhibited firing rates below 5.0 Hz than above 5.0 Hz, although both categories of neurons

| Variable                              | Total | Mean ± SEM (per patient) | Min (per patient) | Max (per patient) |
|---------------------------------------|-------|--------------------------|-------------------|-------------------|
| No. of putative CA1 neurons           | 381   | 16.5 ± 2.4               | 7                 | 47                |
| 0.5–5.0 Hz                            | 291   | 12.6 ± 2                 | 2                 | 43                |
| 5.0–10.0 Hz                           | 63    | 2.7 ± 0.4                | 0                 | 9                 |
| 10.0–20.0 Hz                          | 27    | 1.1 ± 0.2                | 0                 | 6                 |
| No. of putative CA3 neurons           | 432   | 18.7 ± 2.8               | 7                 | 53                |
| 0.5–5.0 Hz                            | 325   | 14.1 ± 2.2               | 4                 | 47                |
| 5.0–10.0 Hz                           | 66    | 2.8 ± 0.813              | 0                 | 8                 |
| 10.0–20.0 Hz                          | 41    | 1.7 ± 0.3                | 0                 | 6                 |
| No. of CA1–CA3 pairs                  | 4070  | 101.7 ± 8                | 30                | 252               |
| No. of synchronous correlations (0-msec lag) | 2044 (50%) | 51.1 ± 5.6              | 4                 | 181               |
| No. of feed-forward correlations (2- to 5-msec lag) | 814 (20%) | 20.3 ± 1.4              | 6                 | 45                |
| No. of feed-forward correlations (>5-msec lag) | 257 (6%) | 6.4 ± 0.7               | 0                 | 19                |
| No. of feedback/negative correlations (negative lag) | 107 (2%) | 2.6 ± 0.5               | 0                 | 22                |
| No. of no connections (no correlation) | 849 (21%) | 21.2 ± 2.4              | 1                 | 58                |

**FIG. 3.** Mean peri-event firing across CA3 (n = 135) and CA1 (n = 131) neurons correlated to DMS sample and match responses. Solid arrows (horizontal) denote latency shift in pre-response peak firing. Open arrows (vertical) indicate suppression of peak firing on error trials. Mean firing was computed across neurons for 1555 correct and 355 error trials performed by 23 patients with intracranial electrodes targeting CA3 and CA1 cell fields.
were retained for analysis. Neurons recorded from depth electrodes targeted at the human hippocampus were thus subjected to 1) firing rate, 2) behavioral correlation, and 3) functional connectivity validation and quantification to verify localization of CA1 and CA3 principal cells.

**Behavioral Correlates**

Peri-event histograms of putative hippocampal neurons were examined for single-neuron firing correlation to behavioral events in the DMS task. Figure 3 shows the mean firing of neurons recorded from hippocampal recording sites targeting the CA3 and CA1 cell fields. Sample and match responses exhibit significant firing peaks (Z = [peak within sample or match phase − mean outside of sample and match phases]/standard deviation outside of sample and match phases; significant peak = Z > 3.09). Significant amplitude differences or latency shifts in peaks between conditions are indicated by arrows in Fig. 3.

A detailed indication of behavioral correlation of putative hippocampal neurons is shown in Fig. 4. Heat maps indicate the mean ensemble firing, averaged with respect to DMS sample (SR) and match (MR) responses. Task-relevant firing of CA1 and CA3 neurons was localized by electrode position, imaging, and cross-correlation as in Fig. 3, with the addition of anterior (Ant.) and posterior (Post.) hippocampal localization. Neurons were sorted as a function of intensity of firing ± 2 seconds around SR and MR responses in the DMS task.

**Functional Connectivity**

Proposed CA1 and CA3 neuron pairs were constructed between neurons recorded on the same electrodes, and then cross-correlograms were computed as spike-triggered histograms. As shown in Fig. 5 left, putative CA3 unit firing occurred at time = 0 msec, with mean CA1 unit firing plotted from −50 to +50 msec relative to the CA3 spike occurrence. Correlograms were analyzed via standard score: Z = (peak firing − baseline firing [−50 to −30 msec])/standard deviation of firing [−50 to −30 msec]. Five characteristic correlation patterns were identified by peaks (Z > 3.09, p < 0.001) in which 1) firing peaks occurred at 0 msec (i.e., 0-msec lag); 2) peak firing was shifted in the positive direction (2- to 5-msec lag); 3) peak was shifted more positively (> 5-msec lag); 4) no peak was detected (no correlation); and 5) peak firing was shifted negatively (inverse correlation). These correlation patterns were consistent with simultaneous driving of CA3 and CA1 (0 msec), feed-forward monosynaptic (2–5 msec) or multisynaptic (> 5 msec) connectivity, no correlation, or feedback connectivity (inverse correlation) incompatible with CA3-to-CA1 synaptic connectivity. Putative hippocampal principal cells with mean firing rates < 10 Hz as identified in Table 3 were examined for functional correlation as shown in the lower portion of the table.

Figure 5 right shows the distribution of correlation types
within the population of putative CA1 and CA3 neuron pairs recorded and analyzed from the human hippocampus. Only 2.6% of pairs exhibited a feedback (inverse) correlation. Misidentification of CA3 and CA1 neuron pairs would be expected to yield a higher percentage of inverse correlation. While only the 2- to 5-msec feed-forward correlations (20.3%) can be definitively identified as CA3-to-CA1 synaptic connectivity, the predominance of positive correlations (77.8%) and infrequent occurrence of inverse correlations suggest that the synchronous and multisynaptic correlate cell pairs are correctly identified with respect to CA3 and CA1 localization, and are further consistent with known common projections from entorhinal cortex to hippocampus, as well as indirect projections within the CA3 and CA1 cell layers.

**Discussion**

Continuous and randomized stimulation of the human hippocampus has been shown to be detrimental to recall in memory-associated tasks. In contrast, model-based patterned stimulation, previously assessed in rodents, NHPs, and humans, has been shown to significantly improve performance in a DMS memory task. To accurately assess the performance of a human neuroprosthetic that utilizes model-based stimulation for enhanced memory storage and recall, placement of stimulating electrodes within the CA3 and CA1 subfields of the hippocampus must be confirmed.

Hippocampal neurons have previously been identified with specific encoding of spatial, object, and task-related
features in rodents and NHPs through MRI verification in combination with assessment of neuronal firing patterns. Features identified in rodents and NHPs through MRI verification in combination with assessment of neuronal firing patterns in rodents and NHPs. These studies indicate that hippocampal stimulation can improve memory function.

In humans, prior efforts at stimulation of mesial temporal lobe structures have focused on assessing the potential of hippocampal stimulation for memory enhancement. However, these studies have limitations and require further investigation. More recently, there has been increased interest in the use of targeted hippocampal stimulation for memory enhancement.

In this study, we combined this MRI-based localization technique with detailed electrophysiological analysis of neural recordings. Using this technique, a total of 4070 pairs were analyzed from 23 patients who were to undergo preplanned depth electrode placement for seizure monitoring. The mean distances determined in this morphometric survey assisted in the targeting of depth electrode placement in epilepsy patients who were to undergo preplanned depth electrode placement for seizure monitoring. The distances obtained in this morphometric survey assisted in the targeting of depth electrode placement in epilepsy patients who were to undergo preplanned depth electrode placement for seizure monitoring.

To confirm localization and accuracy of electrode placement for this study, we combined this MRI-based localization technique with detailed electrophysiological analysis of neural recordings. Using this technique, a total of 1813 neurons were recorded and analyzed from 23 patients. A critical advantage of our approach is that correlation between CA3/CA1 pairs was established in 1071 of a total 4070 pairs, similar to the 20%–25% feed-forward correlation noted in animal studies. Misidentification of CA3 and/or CA1 neurons, as evidenced by feedback correlation, was noted in 2.6% of pairs, while multisynaptic correlations were noted in 6.4% of pairs (again, consistent with animal studies). This critical step allowed us to determine functional connectivity of the identified neurons, which will be necessary for the further design of specific, targeted stimulation interfaces to enhance neuronal encoding. Interestingly, characteristic differences were noted in the neural firing of the anterior and posterior hippocampus during the DMS trials; future studies will determine broadly if differential function occurs with respect to this or other memory tasks.

Conclusions

In this study we have presented data supporting placement and localization of depth electrodes within the CA3 and CA1 cell fields of the human hippocampus. Verification of placement was established through a combination of high-resolution MRI and validation of hippocampal neural recordings utilizing baseline firing rate analysis, behavioral correlation, and functional connectivity. This study provides confirmation of the ability to record neurons in vivo from identified structures and subfields of the human brain and represents an important step in validating and targeting coordinates for intracranial recordings in the human hippocampus. As brain-machine interface and neural prosthetic research continues to expand, it is essential to be able to record and stimulate critical sites within the neural circuits of interest.

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Conception and design: Hampson, Wicks, Witcher, Popli, Whitlow, Deadwyler. Acquisition of data: Hampson, Wicks, Witcher, Couture, Laxton, Popli, Fetterhoff, Dakos, Roeder. Analysis and interpretation of data: Hampson, Wicks, Witcher, Whitlow, Fetterhoff, Dakos, Roeder. Drafting the article: Hampson, Wicks, Witcher, Whitlow. Critically revising the article: Hampson, Wicks, Witcher, Dakos, Roeder. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hampson. Statistical analysis: Hampson, Wicks, Witcher. Administrative/technical/material support: Hampson, Couture, Laxton, Popli, Deadwyler. Study supervision: Hampson, Couture, Laxton, Whitlow, Deadwyler. Neurosurgeon for study patients: Couture, Laxton. Supervising physician for IRB: Couture. Clinical care oversight, oversight of Epilepsy Monitoring Unit, head neurologist for study patients: Popli.

Supplemental Information
Videos
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