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Facilitation of memory encoding in primate hippocampus by a neuroprosthesis that promotes task-specific neural firing

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Abstract

Objective. Memory accuracy is a major problem in human disease and is the primary factor that defines Alzheimer’s, ageing and dementia resulting from impaired hippocampal function in the medial temporal lobe. Development of a hippocampal memory neuroprosthesis that facilitates normal memory encoding in nonhuman primates (NHPs) could provide the basis for improving memory in human disease states. Approach. NHPs trained to perform a short-term delayed match-to-sample (DMS) memory task were examined with multi-neuron recordings from synaptically connected hippocampal cell fields, CA1 and CA3. Recordings were analyzed utilizing a previously developed nonlinear multi-input multi-output (MIMO) neuroprosthetic model, capable of extracting CA3-to-CA1 spatiotemporal firing patterns during DMS performance. Main results. The MIMO model verified that specific CA3-to-CA1 firing patterns were critical for the successful encoding of sample phase information on more difficult DMS trials. This was validated by the delivery of successful MIMO-derived encoding patterns via electrical stimulation to the same CA1 recording locations during the sample phase which facilitated task performance in the subsequent, delayed match phase, on difficult trials that required more precise encoding of sample information. Significance. These findings provide the first successful application of a neuroprosthesis designed to enhance and/or repair memory encoding in primate brain.

Introduction

Memory deficits in humans are constantly related to an inability to recall items previously exposed in different contexts or to utilize the same items for different purposes (Jenkins and Ranganath 2010, Tubridy and Davachi 2011). It has been known from the initial characterization of factors which affect proper recall of information that after an intervening period of lack of exposure to the item, correct retention or retrieval of the item is dependent on the strength of
encoding of the information at the time of the initial exposure (Downes et al 2002, Moscovitch et al 2006). Understanding the neural basis of memory processes has progressed to the level of knowing that certain brain systems must be operative in order for effective encoding and subsequent retention to occur, and that many types of memory are different and utilize different structures related to functional behavioral endpoints (Naya and Suzuki 2011).

In the mammalian brain, the hippocampus has been shown to be the most important structure involved in the encoding and retention of new information in cognitive processes (Eichenbaum and Fortin 2003, Tulving 2002). It is well documented that impairment of the functional status of the hippocampus in human disease states leads to memory deficits that are detrimental to normal function, and in addition, such impairment has become the hallmark of brain ageing and deterioration as exhibited by Alzheimer’s patients (Carmichael et al 2012, Gemmell et al 2012). Unlike other approaches with neural prosthetics to rectify altered brain function, the recovery or replacement of memory is an objective that cannot be accomplished until we understand how the hippocampus performs the encoding of information to be retained at a later time (Manns et al 2007, Pastalkova et al 2008). Initial results from this laboratory have shown that a critical feature necessary for the retention of item-specific cognitive information is the pattern of firing across distinct cell groupings within the hippocampus (layers CA3 and CA1) that are synaptically connected and communicate during the encoding process. The ability to monitor activity in these areas in rodents while processing information in a memory task using an online nonlinear multi-input multi-output (MIMO) model (Berger et al 2011), provided the means to extract ‘strong’ and ‘weak’ codes or patterns of firing associated with correct or error trials in the same testing sessions (Hampson et al 2012d). The relevance of the MIMO-derived firing patterns was demonstrated by the injection of those same model-predicted patterns in the form of electrical stimulation into the hippocampal output layer, CA1, which facilitated the retention of task-specific information in the same manner as when the patterns were generated spontaneously in CA1 via synaptic input from CA3 (Berger et al 2011, Hampson et al 2012c).

The current study extends the same approach to assessing hippocampal involvement in the encoding of relevant information by nonhuman primates (NHPs) engaged in a more complex cognitive memory task requiring the retention of several stimulus features as well as trial-specific information to perform correctly as demonstrated in several prior reports (Deadwyler et al 2007, Hampson et al 2004, 2009, Porrino et al 2005). In order to implement the previously successful MIMO model prosthesis (Hampson et al 2012a) for the recovery of memory loss in the primate brain, it is necessary to demonstrate how this model enhances normal memory under conditions where the retrieval of information is less effective in more difficult task-related contexts (Berger et al 2011, 2012, Hampson et al 2012c, 2012d). Successful application in prior studies in rodents served as the basis for testing the MIMO model in the primate hippocampus, utilizing interposed delivery of extracted patterns of successful CA3–CA1 cell firing as electrical stimulation to the same regions.

The results presented here show that the application of the same MIMO model-derived stimulation, when applied to the hippocampal CA3 and CA1 subregions in NHPs, provides a high degree of facilitation of performance across different types of memory challenges, and therefore satisfies the same criteria to serve as a neural prosthesis in the primate brain as previously demonstrated in the prefrontal cortex of NHPs (Hampson et al 2012a). These results provide the first instance of application of a neuroprosthesis designed specifically for enhancing memory in the primate brain, and as such indicate the potential efficacy for recovering hippocampal dysfunction related to disease states and ageing in humans (Riddle and Lichtenwalner 2007).

**Methods**

All animal procedures were reviewed and approved by the Institutional Animal Care and Use Committee of Wake Forest University, in accordance with the US Department of Agriculture, International Association for the Assessment and Accreditation of Laboratory Animal Care and National Institutes of Health guidelines.

**Cognitive memory task.** Four NHP subjects (rhesus, Macaca mulatta) were trained for at least two years to perform the visuospatial delayed match-to-sample (DMS) task (Hampson et al 2012a, Opris et al 2012a, 2012b) for juice rewards (figure 1(A)), and all met criterion performance levels stable for at least one year. Animals were seated in a primate chair with a shelf-counter in front of them facing a large display screen during task performance. The right hand position on the counter top was tracked via a UV-fluorescent reflector affixed to the wrist and illuminated with a 15 W UV lamp. Hand position and movement was detected by a small LCD camera positioned 30 cm above the hand, digitized using a Plexon Cineplex scanner connected to a behavioral control computer, and displayed as a bright yellow cursor on the projection screen. Trials were initiated by the animal placing the cursor inside a centrally placed yellow circle or red square, either of which constituted the ‘start signal’ for a given trial. Following trial initiation by response to the start signal, a single image was presented randomly on the screen as the sample stimulus constituting the sample presentation (SP) phase of the task. The different visual features of the start signal presented in a trial conveyed the type of response contingency with respect to the sample stimulus (SP) after response to the start signal. If the start signal was (1) a yellow circle, it indicated object-type trials in which the sample stimulus clip-art image itself was to be responded to in the match phase irrespective of screen position or, (2) a red square, it indicated spatial-type trials in which the correct response was the screen position in which the sample stimulus was presented irrespective of which clip-art image occupied that same position in the match phase. Completion of the sample phase of the task required placement of the cursor into the displayed clip-art image, and was designated the sample response (SR). The SR initiated the delay interval phase of the
Figure 1. Illustration of DMS behavioral task and localization of hippocampal recording electrodes. (A) Behavioral paradigm showing the sequence of events in the DMS task presented on screen with correct cursor movement (orange dot) indicated for each phase of the task commencing with (1) ‘start signal’ presentation consisting of either a yellow circle (upper) or a red square (lower) signaling an object or spatial trial, respectively. Placement of the cursor into the start signal initiated the trial commencing with (2) the presentation of the ‘sample clip-art image’ in one of eight different locations on the screen. (3) SR consisted of movement of the cursor onto the sample image. (4) Variable ‘delay’ period of 1–40 s followed the SR, during which the screen was blank. (5) Match phase followed delay timeout, in which the ‘match clip-art image’ (same as the sample image) was presented randomly in one of eight locations on the screen accompanied by one–six other distracter (non-match) images in other locations on the same screen. Cursor movements onto trial-appropriate response targets in the match phase, either (a) the same sample image (object trial, red arrow) or (b) the same location on the screen where the SR was made irrespective of image identity (spatial trial, blue arrow), were rewarded by delivery of a squirt of juice reward. Placement of the cursor onto a non-match (distracter) image (object trial) or onto a different screen location from the SR (spatial trial) caused the screen to go blank without reward delivery. Inter-trial interval: 10.0 s. (B) Diagram of NHP brain in cross-section showing hippocampal tetrode tracks through temporal lobe and placement in the CA3 and CA1 cell layers. (C) Overall performance averages showing the interaction of interposed delays on task performance as a function of the number of distracter images in object trials. The dotted line at 60% is a marker below which performance is near chance levels. (D) Differential mean per cent correct performance in object and spatial trials (blue and red arrows in (A)) as a function of the number of (distracter) images presented in the match phase of the task.

trial, in which the screen was blanked for 1–90 s, randomly determined in a trial-to-trial basis. Timeout of the delay interval was signaled by the automatic onset of the match phase of the task, consisting of the simultaneous display of two to seven trial-unique images, including the sample image, all at separate randomly selected spatial locations on the screen with at least one screen position always left blank. Placement of the cursor into one of the images constituted a ‘match response’ (MR); however, as stated above, the selection of the correct image was dictated by the type of trial indicated by the start signal as noted above for cursor placement in the match phase (1) into the same image as the sample stimulus in object trials, or (2) into the same screen location where the sample stimulus appeared irrespective of image characteristics in spatial trials. Correct responses produced a juice reward delivered via a sipper tube located near the animal’s mouth, and blanked the screen. Placement of the cursor into one of the non-match (distracter) images or a different screen location constituted a non-match-error response and caused the screen to blank without reward delivery. Trials during the session were separated by a minimum of 10 s in which the start signal was presented following the termination of the match phase of the prior trial. All clip-art images presented (sample and distracters) were unique for each trial in the session (100–150 trials) and were selected randomly from an image reservoir (n = 5000) updated every month (Hampson et al 2004). All subjects were trained to overall performance levels of 70–75% correct in the least difficult trials with graded decreased performance in trials with increased delays and number of images in the above-described version of the DMS task.

Surgery. Animals were surgically prepared with cylinders for daily attachment of a microelectrode manipulator over the specified brain regions of interest. During surgery, animals were anesthetized with ketamine (10 mg kg$^{-1}$), then intubated and maintained with isoflurane (1–2% in oxygen 6 L min$^{-1}$). Recording cylinders (Crist Instruments, Hagerstown, MD) were placed over 20 mm diameter craniotomies for electrode access (Hampson et al 2012a, Opris et al 2011, 2012a, 2012b) to stereotaxic coordinates of the hippocampus (12 mm anterior relative to the inter-aural line and 12 mm lateral to the midline/vertex) previously shown by PET imaging (Porro et al 2005) to become activated during task performance (figure 1(B)). Two titanium posts were secured to the skull for head restraint with titanium screws embedded in bone cement. Following surgery, animals were given 0.025 mg kg$^{-1}$ buprenorphine for analgesia and penicillin to prevent infection. Recording cylinders were disinfected thrice
weekly with Betadine during recovery and daily following task
recording.

Recording from hippocampus. Electrophysiological procedures and analyses utilized the 64 channel MAP Spike Sorter by Plexon, Inc. (Dallas, TX). Customized tetrode arrays (Santos et al 2012) were manufactured specifically for recording spatially distinct locations in the CA3 and CA1 cell fields in primate hippocampus (Hampson et al 2004) such that multi-cell (n > 12) recordings could be obtained from each anatomically distinct location. The Schaefer collateral projections from CA3 to CA1 are ubiquitous enough to ensure that the locations recorded from in CA3 were likely to be connected synaptically to the locations recorded from CA1 in each tetrode pair located in the same mediolateral plane or ‘chip’ of hippocampus in two distinct anterior–posterior locations as shown in figures 1 and 6. This tetrode arrangement ensured that only cells in CA3 and CA1 were isolated and recorded, since the appearance of activity on each vertically inserted probe occurred at depths of insertion for CA1 that required prior traversal through cell layer CA3 placed in the same cross-sectional plane of the hippocampus as shown in figure 1(B).

Identification of CA1 and CA3 hippocampal cell layers. Electrode locations in the appropriate cell layers with individual tetrodes were validated by placement using the same coordinates in different animals to ascertain localization in both CA1 and CA3 cell layers. These placements were verified on a daily basis and were utilized as markers for correct placement. Histological verification was confirmed in three animals euthanized after this study was completed. Statistical analyses also determined whether there were differences in firing rates for cells in different layers (i.e. CA1 versus CA3) during activation in the sample and match phases of the task.

Data analysis. Task performance was determined for each animal (n = 4) as per cent correct responses within trial groups sorted according to duration of delay and the number of images presented in the match phase (figures 1(C) and (D)). The number of correct and incorrect trials were summed, and the percentage of correct responses computed within sessions, with the average performance computed across a minimum of three sessions (Hampson et al 2012a). Recordings of multiple CA3 and CA1 neuron firings in individual trials (Hampson et al 2004) during the sample and match phases of the DMS task were summed within 100 ms bins, and accumulated across trials within a session for display as peri-event histograms (PEHs) of mean firing rate (i.e. spikes s⁻¹) relative to the sample or match events (figures 2 and 3). Cell types were identified as regular firing hippocampal cells in terms of baseline (non-event) firing rate (Hampson et al 2004, Opris et al 2009, 2011) and peaks in single trials in PEHs derived for intervals of ± 2.0 s relative to the onset of the screen image display (0.0 s) in the sample and match phases of the task (figures 2 and 3). Significant firing peaks were identified by the maximum firing rate ± 0.5 s relative to the DMS event by the standard score (Z = [peak–baseline firing rate] ÷ standard deviation of baseline, z > 3.09 values indicated significant (p < 0.001) peak increase in firing rate). Firing rates for simultaneously recorded CA1 and CA3 neurons were analyzed in 100 ms bins over ± 2.0 s relative to the time of initiation (0.0 s) of the sample and match phases of the task. Neurons were only included in the analysis if their firing rates were significantly elevated (Z-scores, ANOVA F test p < 0.01) relative to the pre-event screen presentation baseline period (−2.0 to 0.0 s). The correspondence of firing between cells in different layers was tested via the comparison of trial-based histograms (TBHs) spanning more than one task event within a phase to construct templates related to how the hippocampus encoded trial-specific information. PEHs demarcated firing differences for individual events and to provide the basis for nonlinear model analyses of firing during particular sample and match events within a given trial.

MIMO model for hippocampal neural activity during the DMS task. Prior studies (Berger et al 2011, Hampson et al 2012a) have shown that a MIMO nonlinear dynamic model applied to spatiotemporal patterns of multiple recordings from rodent hippocampal CA1 and CA3 neurons capable of extracting patterns of firing related to the successful performance of a non-match-to-sample memory task could be used to facilitate and recover performance when administered to the same locations as patterns of electrical pulses (Berger et al 2011, Hampson et al 2012a, 2012c, 2012d). The same structure MIMO model as in the earlier studies has been adapted (with coefficients unique to the current data) to the current data to assess the spatiotemporal nonlinear dynamics underlying spike train transformations between CA3 and CA1 cells to predict CA1 output firing patterns from input patterns of CA3 neural activity via the well-characterized Schaffer collateral synaptic connectivity between these areas in primate hippocampus (Deguchi et al 2011, Klausberger and Somogyi 2008). This type of general Volterra kernel-based nonlinear model has been applied in other formats which have also been shown to be effective in rodents (Marmarelis et al 2012, 2013). The MIMO version of the model was applied here to the data recorded by the multiple tetrode probes in NHPs performing the DMS task described in figure 1, and is structurally similar to the model previously shown to facilitate DMS performance when applied to NHP prefrontal cortical neurons in a prior study (Hampson et al 2012a).

Results

Adult male rhesus macaques (n = 4) were trained to perform the combined DMS task shown in figure 1 (Hampson et al 2011, Opris et al 2012b), by making hand tracking cursor movements on the screen in front of them to obtain a juice reward for selection of either the same sample image or sample location on the screen, in the match phase which varied randomly from one of eight different positions on the screen in each trial. The start signal for a given trial indicated whether the animal was required to remember either (1) which sample clip-art image (object trial) was presented or, (2) in which one of the eight positions on the screen the sample image was presented (spatial trial). Animals were rewarded for the appropriate selection in the subsequent match phase of the same trial. Key variables in the task that changed randomly on
Figure 2. Hippocampal neuron firing in the sample phase of the DMS task. (A). Upper (CA1 cells, \(n=431\)) and lower (CA3 cells, \(n=801\)) plots show TBHs of average firing of all cells in those cell layers, across all NHPs (\(n=4\)). Each trace indicates one of the four conditions listed on the left for comparison of object versus spatial and correct versus error trials. The three events within the sample phase are listed on the x-axis and shown as vertical dotted lines of each TBH as Strt = start signal, SP = sample image presentation, SR = sample response. Horizontal dotted lines provide a basis for comparing mean firing levels prior to the onset of the sample phase, in terms of each of the three mean peaks as significantly increased over the baseline by standard scores (\(Z > 3.09, p < 0.001\), see Methods). Trials were sorted by object/spatial/correct/error trials, with mean per cent correct performance calculated per session, and averaged across animals (\(n = 4\)) and sessions (\(n > 5\) per animal). (B) Plots of mean peak responses to the same three sample phase events across the same four trial conditions shown in (A) for CA1 (upper) and CA3 (lower) neurons summed over all four animals to indicate relations of overall firing tendencies and differential encoding under different task conditions including correct and error trials. \(* p < 0.01, \# p < 0.001 \) object versus spatial trial peaks, \(* * p < 0.001 \) correct versus error trial peaks.

a trial-by-trial basis were the number of images (two—seven) presented in the match phase, the duration of the sample-to-match phase delay interval (1–90 s) and the placement of the sample image randomly on the screen in one of eight different positions in the match phase (after the delay interval), all of which have been characterized in previous studies (cf Hampson et al 2012a). Several important cognitive features such as attention, short-term memory, cognitive workload, reward expectancy, as well as a ‘decision process’ in the match phase, associated with the performance of the task have previously been shown to be related to task-related neuron activation in different brain regions (Hampson et al 2010, 2012b, Opris et al 2011). In addition, the specificity of single neuron firing in the hippocampus in the same task including encoding of image features presented in the sample phase has been documented in prior studies (Hampson et al 2004). However, prior work in NHPs did not employ simultaneous multi-cell recording in the hippocampus with spatiotemporal specificity in relation to CA3–CA1 activation or synchronous firing under trial-specific conditions as described here.

Hippocampal neural activity during task information encoding in the sample phase

Hippocampal neuron firing during the sample phase of the DMS task reflects the degree of stimulus encoding required for accurate recall and selection of the proper target in the match phase of the DMS task after an interposed variable delay period (see figure 1(A)). Figure 2(A) shows that neurons in CA1 and CA3 exhibited significantly increased peaks in the average firing rate computed across all animals during the three critical events in the sample phase: trial start signal—Strt (\(z = 5.21–27.58, p < 0.001\)), sample (image) presentation—SP (\(z = 4.13–22.40, p < 0.001\)) and the behavioral response to the sample image—SR (\(z = 3.42–12.68, p < 0.001\)). An important feature regarding the significance of this phase of the task in addition to the three distinct events for encoding sample information, was the significantly elevated overall firing above baseline levels (dotted lines in figure 2(A)) for neurons in both CA1 and CA3 (\(z = 4.81, p < 0.001\)) in a manner that was different with respect to (1) the type of trial and (2) the consequence on correct or error trials.
Figure 3. Hippocampal neuron firing in the match phase of the DMS task. (A) TBH plots as in figure 2(A) show TBHs of average firing of CA1 and CA3 neurons during the match phase of the DMS task. The two task events indicated by the vertical dotted lines were (1) match screen presentation (MP) occurring at the end of the prior variable delay period and then (2) the subsequent match phase response (MR) for correct versus incorrect selection of the sample feature executed in the presence of one–six other images. Each peak was significantly increased over the baseline by standard scores ($Z > 3.09$, $p < 0.001$, see Methods). The peaks with error bars after the MR occurred in correct trials when the juice reward valve sounded. Plots reflect sustained elevated mean firing rates throughout the entire match phase for both CA1 and CA3 hippocampal cells in each of the four indicated conditions with respect to screen presentation of images and performance of that type of trial. (B) Average peak firing rates of CA1 and CA3 hippocampal cells in the match phase shown for each of the events (MP, MR) in each trial type (object and spatial) sorted with respect to performance (correct and error) in the same trials. $^*$p < 0.01, $^{**}$p < 0.001 object versus spatial trial peaks, $^{*p}$ < 0.01, $^{##}$p < 0.001 correct versus error trial peaks.

Figure 2(B) shows this differentiation for all four possible outcomes with respect to trial type and performance. What is very important is the fact that mean firing rates in CA1 and CA3 were significantly different with respect to the Strt (trial type) and SP events on object versus spatial trials (TS: $F(1,7239) = 11.14$, $p < 0.001$, SP: $F(1,7239) = 8.22$, $p < 0.01$); however, mean firing rates during the SR were similar in both CA1 and CA3 with respect to subsequent correct versus error performance in the match phase (figure 2(B)) of the same trial (SR: $F(1,7239) = 5.20$, NS).

Hippocampal neural activity during target selection in the match phase

The basis for effective CA1 and CA3 encoding activity in the sample phase of the task culminated in the selection of either the same sample image (object trial) or the same sample screen location (spatial trial) in the match phase of the DMS task. Figures 3(A) and (B) show the average firing rates of the same CA3 and CA1 neurons described in figure 2 in the subsequent two primary events in the match phase of the same trials. This includes: (1) onset of the match screen image presentation (MP) and (2) movement of the cursor into a screen location selection as the MR. The MR determined a correct or error trial with respect to the previously presented sample information (figure 2(B)). Figure 3(A) shows the mean firing rate of CA1 and CA3 neurons at the onset of the match phase (MP, $z = 5.59–22.17$, $p < 0.001$) continuous through initiation and completion of the MR ($z = 4.11–40.79$, $p < 0.001$). The average firing rate of CA1 and CA3 neurons associated with performance differences for both types of trial (object and spatial) is shown for both MP and MR events in figure 3(A). A display of match phase average peak firing rates during the same events is shown in figure 3(B). Peak firing in CA1 and CA3 during the MR distinguished correct versus error performance with respect to both object and spatial trials with CA1 neurons exhibiting higher rates than CA3 neurons (CA1: $F(1,7239) = 7.50$, $p < 0.01$, CA3: $F(1,7239) = 11.16$, $p < 0.001$) under those conditions. There were also much lower firing rates during the MP compared to MR in both CA1
and CA3 and less difference with respect to firing on correct versus error trials (figure 3(B)).

These features are rearranged in figure 4 to show the correspondence between SR and MR firing in each type of trial and its success or failure with respect to being a correct or error outcome. Figure 4 shows that match phase firing was portioned in the same manner as sample phase firing in correct versus error trials. This provides the confirmation that significantly increased firing in the sample phase at the time of the SR was the basis for subsequent correct MR selection in the match phase. It is clear that the ratios of mean firing in correct and error trials in CA1 and CA3 were similar for the critical events in each phase of the task (SR and MR). Object trials were encoded and responded to almost identically in CA1 and CA3. There was more differentiation between correct and error spatial trials in CA3 during the SR which was well above firing levels in CA1 neurons recorded in CA3 that were transferred to synchronize with the notion that both areas were encoding the same type of hippocampal neuron firing recorded during the sample phase of the DMS task. The MIMO model provided direct evidence that the hippocampal SR firing rate (figure 2) determined whether the information was available in the same trial for use later in the match phase. Clearly, if the duration of the delay was short (<11.0 s), or the number of match phase images few (two–three) as in ‘easy’ trials (figures 1(C) and (D)), the SR firing rates in CA1 and CA3 were lower than the SR rates required for correct choices on more ‘difficult’ trials with increased delays (20–40 s) or number of images (four–seven) (CA1: $F(3,7239) = 11.93$, $p < 0.001$, CA3: $F(3,7239) = 12.47$, $p < 0.001$). The fact that nearly the same relations to different trial parameters existed for both CA1 and CA3 firing is consistent with earlier demonstrations of these same relations (Hampson et al 2004) and supports the notion that both areas were encoding the same type of sample information via the synaptic connections between the two cell layers (Deguchi et al 2011, Klausberger and Somogyi 2008). Figure 5 shows that accurate retention of trial-specific information was dependent on increased CA1 and CA3 neuron firing during the SR which was well above firing levels in error trials with the same delays and number of match phase distracter images.

MIMO model extraction of successful hippocampal processing of sample information

The MIMO model was applied as shown in figure 6 to the same type of hippocampal neuron firing recorded during the sample phase of the DMS task. The MIMO model provided the identification of spatiotemporal patterns from neurons recorded in CA3 that were transferred to synchronize with neurons recorded in CA1 (Berger et al 2011, Marmarelis 2004, Marmarelis and Berger 2005, Song et al 2009). These were formulated as the estimation of the MIMO model decomposed into a series of multi-input single-output models with a physiologically identifiable structure expressed by the following equations:

$$w = u(k, x) + a(h, y) + \varepsilon(\sigma), \quad y = \begin{cases} 0 & \text{when } w < \theta \\ 1 & \text{when } w \geq \theta \end{cases}$$

The variable $x$ represents input (CA3) spike trains; $y$ represents output (CA1) spike trains. The hidden variable $w$ represents the pre-threshold membrane potential of the output neurons, and is equal to the summation of three components: (1) post-synaptic potential $u$ caused by input spike trains, (2) the output spike-triggered after-potential $a$ and (3) a Gaussian white noise $\varepsilon$ with standard deviation $\sigma$. The noise term models both intrinsic noise of the output neuron and the contribution of unobserved inputs. The threshold, $\theta$, determines when an output spike is generated. Two nonlinear kernels complete the equation, as shown below.
The feedforward kernel $k$ indicates transformation from $x$ (input) to $u$ (membrane potential), and can be expressed as a Volterra functional series of $x$, as follows:

$$u(t) = k_0 + \sum_{n=1}^{N} \sum_{\tau=0}^{M_n} k_{n}^{(n)}(\tau)x_n(t-\tau)$$

$$+ \sum_{n_1=1}^{N} \sum_{n_2=1}^{N} \sum_{\tau_1=0}^{M_{n_1}} \sum_{\tau_2=0}^{M_{n_2}} k_{n_1,n_2}^{(n_1,n_2)}(\tau_1, \tau_2)x_{n_1}(t-\tau_1)x_{n_2}(t-\tau_2)$$

$$+ \sum_{n_1=1}^{N} \sum_{n_2=1}^{N} \sum_{n_3=1}^{N} \sum_{\tau_1=0}^{M_{n_1}} \sum_{\tau_2=0}^{M_{n_2}} \sum_{\tau_3=0}^{M_{n_3}} k_{n_1,n_2,n_3}^{(n_1,n_2,n_3)}(\tau_1, \tau_2, \tau_3)x_{n_1}(t-\tau_1)x_{n_2}(t-\tau_2)x_{n_3}(t-\tau_3)$$

$$\times (t-\tau_1)x_{n_1}(t-\tau_2)x_{n_2}(t-\tau_3) + \cdots$$

The zeroth-order kernel, $k_0$, is the value of $u$ with no input. First-order kernels, $k_{n}^{(n)}$, describe the linear relation between the $n$th input $x_n$ and $u$. Likewise, second- and third-order self-kernels, $k_{n_1,n_2}^{(n_1,n_2)}$ and $k_{n_1,n_2,n_3}^{(n_1,n_2,n_3)}$, describe the second- and third-order nonlinear relation between the $n$th input $x_n$ and $u$, respectively. Second-order cross-kernels, $k_{n_1,n_2}^{(n_1,n_2)}$, reflect the second-order nonlinear interactions between each unique pair of inputs $(x_{n_1}$ and $x_{n_2})$ as they affect $u$. $N$ is the number of inputs. $M_n$ denotes the memory length of the feedforward process, $t$ is a given (current) time point within the spike train, while $\tau$ identifies the time points of the most recent ($\tau$ or $\tau_1$), second most recent ($\tau_2$) and third most recent ($\tau_3$) preceding spikes.

The feedback kernel $h$ describes the transformation from $y$ (output) to $a$ (after hyperpolarization) and can be expressed as

$$a(t) = \sum_{\tau=1}^{M_h} h(\tau)y(t-\tau)$$

where $h$ is the linear feedback kernel and $M_h$ is the memory length (time in ms) of the feedback process. In summary, the model describes the temporal relationship of up to three prior neural CA3 spikes, within and across spike trains, which interact to determine the sequence of CA1 spike trains comprising outputs, taking into account differing noise levels and output spike-triggered feedback (the latter due to circuitry
Figure 6. Integration of the MIMO nonlinear model (A) to calculate SR encoding via spatiotemporal firing relations between hippocampal CA3 and CA1 recordings, (B) to predict CA1 firing (C) from CA3 recordings (D) and generate patterned stimulation (E) for feedback to layer CA1. The anatomical diagrams on the left show the placement of CA3 and CA1 multi-cell recording tetrodes into the associated transverse fields along the longitudinal axis of the hippocampus. The recordings in correct DMS trials from these spatially distinct and layer-specific tetrodes were fed into the MIMO model with CA3 as the input (blue arrow) and CA1 as the output pattern (red arrow). The MIMO model predicted correct CA1 output (i.e. ‘strong codes’) from CA3 input computed over the sample phase (shaded rectangles) based on fine temporal relationships between spike trains recorded on correct trials at different spatial locations within the hippocampus. On stimulation trials, trains of electrical pulses mimicking the predicted strong code output spike trains were delivered to the same CA1 hippocampal electrode locations the patterns were recorded from. MIMO model-controlled stimulation patterns applied to the respective CA1 recording locations consisted of multi-channel biphasic pulses of 10–50 μA, 1.0 ms duration with minimum 50 ms between stimulation pulses, with no more than 20 Hz stimulation pulses per channel.

Analyses included extraction of first-, second- and third-order temporal firing recorded by the dual tetrodes inserted into both layers across multiple recording sessions in order to extract relevant spatiotemporal patterns of CA3–CA1 activity related to successful image selection during the match phase of the task. The model defined inputs as firing from neurons in CA3 and outputs as firing in similar longitudinally located CA1 neurons which determined the nature of the output patterns extracted by the MIMO model. In this manner, model output predictions of CA1 firing related to successful performance were monitored online from tetrodes in CA3 during the task, as shown in figure 6, to detect when successful trials were about to be completed by appropriate target selection (MR).

MIMO model extraction of trial-specific CA1 neuron firing patterns related to CA3 neuron firing

Prior investigations applying MIMO model-derived patterns of electrical stimulation pulses to the rodent hippocampus provided the means to enhance performance in normal circumstances and overcome deficits induced by pharmacologic disruption in rodents trained to perform a short-term memory task (Berger et al 2011, Hampson et al 2012c). The approach employed here in NHPs was identical in that simultaneous spatiotemporal multi-neuron recordings from CA3 and CA1 were employed to construct a MIMO model capable of predicting CA1 output firing from online-monitored CA3 inputs to the MIMO model, as shown in figure 6. These patterns were derived specifically from simultaneous CA3 neuron firing and/or membrane biophysics, as well as neuron-specific differences in thresholds.
related to the trial start (TS), SP and SR task events. Figure 7(A) shows not only the trial-by-trial firing of a single CA3 neuron on both spatial and object trials (see figure 2), but also averaged PEHs across CA3 neurons which demonstrated mean firing responses to TS, SP and SR events even with individual trial and neuron variability. Representative object and spatial trial mean firing patterns for CA3 ensembles are paired with similar displays for CA1 neuron ensembles over the same time base via a graphic, ‘heat-map’ representation of the individual spike train firing of 16 neurons in a single trial. The MIMO model was used to predict specific CA1 firing patterns that coincided with CA3 firing in both object and spatial trials during the sample phase of the task (figure 7(B)). The upper two traces in figure 7(C) show similar representations of real-time recorded CA3 (‘input’) and CA1 (‘actual’) multi-neuron spike train firing patterns from single object and spatial trials. The MIMO-‘predicted’ CA1 output pattern shown at the bottom was produced by the developed MIMO model from the CA3 (input) spike trains shown above, and demonstrates the similarity to real-time (actual) recorded CA1 neuron firing over the same time period for both object and spatial-type trials.

The same MIMO model was applied to specific performance conditions for both types of trials (object and spatial) in which sample phase CA3 and CA1 firing in the time frame from SP to SR (dashed red outline in figure 7(C)) was associated with correct or incorrect (error) consequences on trials with the same parameters. This is shown in figure 8 in which MIMO model-derived ‘strong code’ (correct) and ‘weak code’ (error) firing patterns in CA1 predicted performance on object- and spatial-type trials as a function of delay (upper) and number of images in the match phase (lower). Figure 8 validates the notion that normal performance over...
Figure 8. Influence of MIMO-predicted sample encoding strength on DMS performance. The upper heat-map rasters show the CA1 firing patterns (see figure 7, dashed red rectangle) extracted by the MIMO model in correct (strong code) and incorrect (weak code) trials for both object and spatial trials. Strong codes were obtained from the averaging of MIMO-derived CA1 spike trains in correctly performed trials of high difficulty (21–30 s delays, six–seven match phase images), while weak codes were obtained from averaging MIMO-derived CA1 spike trains in incorrectly performed less difficult trials (1–10 delays, two–three match phase images). Heat-map colors encode mean firing probability from MIMO model rate: <10% (blue) to >70% (red) as shown in inset. Plots below the heat-maps are graphs that show mean per cent correct behavioral performance in object and spatial trials. Normal: performance not sorted according to strength of sample encoding in the trial (non-defined encoding). Strong code: MIMO-derived SR firing constituted strong codes in each trial. Weak code: MIMO-derived SR firing constituted weak codes in each trial. Performance under these three conditions was sorted as a function of the length of the delay (upper) or the number of images in the match phase of the task (lower). ∗p < 0.01, ∗∗p < 0.001 versus normal.

Effects of MIMO-derived stimulation on the performance of the DMS memory task

The extraction of MIMO-derived strong and weak code CA1 firing patterns was translated to a means of injecting these patterns extraneously via multi-channel electrical stimulation of the same CA1 regions, delivered on trials in which the MIMO model did not detect the precursor CA3 firing for strong codes. This approach has been used previously in rodents (Berger et al 2011, Hampson et al 2012c, 2012d) and was also used successfully in prior studies with NHPs performing this same DMS task in which MIMO-formulated strong code stimulation patterns were delivered to the prefrontal cortex in the match phase (Hampson et al 2012d). If CA3 firing
Figure 9 demonstrates the effectiveness of the MIMO-derived CA1 stimulation patterns delivered to all four NHPs in which the facilitation of performance was directly related to trials with increased difficulty with respect to both delay and number of images, in the same manner that normal hippocampal cell firing and performance varied across the same parameters (figure 5). Delivery of the MIMO strong code stimulation pattern facilitated performance in all four NHPs and the degree of performance improvement was more pronounced on trials with increased delay duration (delay: $F(3,1682) = 7.04, p < 0.001$) and/or increased number of match distracter images (number of images: $F(5,1682) = 5.13, p < 0.001$). These changes produced by the delivery of strong codes during the sample phase resembled the same profile performance changes that occurred on trials where the MIMO model extracted natural strong code firing patterns, as shown in figure 8 (by delay: $F(3,3106) = 7.67, p < 0.001$, by images: $F(5,3106) = 9.04, p < 0.001$). In addition, even though performance on stimulation trials remained proportionately decreased as a function of increase in trial difficulty, the decrease was not of the same magnitude as in non-stimulated trials with the same parameters (figure 9).

Complementary to these findings was the demonstration of the specificity of MIMO SR stimulation which differentially enhanced mean performance across all animals as a function of the type of trial (object or spatial) presented, as shown in figure 10. It is clear that overall normal performance was more difficult on spatial versus object trials and that the delivery of trial-specific MIMO strong code stimulation significantly enhanced performance on longer delay spatial...
Figure 10. Effects of specificity of MIMO-derived stimulation as a function of the type of DMS trial. Performance levels averaged over all animals are shown for both object (left) and spatial (right) trials with respect to intervening delay (upper) and number of images (lower). Performance on MIMO scrambled stimulation trials was not above that on non-stimulated trials. In scrambled stimulation trials, patterns in which MIMO coefficients were randomized with respect to neuron and time had little or no effect and did not disrupt normal performance. Since only MIMO strong code patterns were used to generate the scrambled stimulation patterns, they were not functionally equivalent to the weak code patterns shown in figure 8.

\[ F(3,1682) = 4.18, p < 0.01 \]

Figure 10 also shows an important control for the specificity of MIMO strong code stimulation in which the derived model coefficients of the MIMO kernels (\( 'k' \), in the model equation) were ‘scrambled’, i.e. applied randomly, to individual CA1 neuron firing patterns. These ‘scrambled’ patterns were delivered with exactly the same stimulus parameters (pulse duration and intensity) at the same time during the sample phase of the task and in the same types of trials. The scrambled strong code stimulation patterns did not enhance performance and had essentially no effect \( (F(1,1682) = 2.42, \text{NS}) \) on normal behavior in the same types of trials in which the delivery of the actual MIMO strong code patterns was highly effective (figure 10). The fact that scrambling the strong code MIMO coefficients eliminated performance facilitation with respect to both, (a) the type of trial (object and spatial), as well as (b) particular parameters (delay and number of images) verifies that the strong code pattern of MIMO-derived stimulation, not just electric current, applied during the sample phase was the critical event that facilitated the performance of the DMS task. In addition, the fact that the scrambled strong code patterns did not significantly disrupt normal performance (figure 10) indicates that altering the coefficients in this manner only eliminated a more proficient pattern of CA3–CA1 cell activation, and did not disrupt cell firing enough to produce errors or ‘weak codes’ (figure 8).

Application of MIMO stimulation as a memory prosthesis to enhance hippocampal encoding

From the perspective of recovery of function involving memory deficits in primate brain, these results in which MIMO model-derived stimulation enhanced sample phase encoding in NHPs (figures 9 and 10), provide a basis for the application of this same MIMO model to human disease and brain ageing conditions in which memory is reduced as a result of impaired hippocampal storage and/or retrieval of information (Gemmell et al 2012, Maillet and Rajah 2011, Squire et al 2004, Ta et al 2012, Tubridy and Davachi 2011). The fact that performance as shown in figure 10 was enhanced with respect to the trial parameters of the task, i.e. (1) the number of distracter images \( (F(2,1682) = 7.78, p < 0.001) \) and (2) the temporal delay between information exposure and retrieval \( (F(2,1682) = 9.50, p < 0.001) \), supports the likelihood of the enhancement of a process that facilitates information retrieval irrespective of the item specificity. Activation or improvement of such a hippocampal process would provide recovery under conditions in which information encoding and retrieval was impaired, and as such serve as an effective prosthesis to restore degraded memory capacity in humans, as shown previously in rodents with pharmacologically induced hippocampal malfunction (Berger et al 2011). The presence of similar strong codes (figure 8) and their effectiveness when administered as MIMO-derived electrical stimulation...
patterns under a wide range of memory conditions in all four NHPs (figures 9 and 10) supports the development of the model as a generalized memory prosthesis. Since MIMO stimulation-enhanced information encoding elevated performance relative to non-stimulation trials, the latter were therefore by comparison more difficult (Rolls et al 2005). As such, this application of the MIMO model clearly qualifies as a prosthetic-type influence since performance, deterred by factors that directly affected retention, was improved by strong code MIMO stimulation in the same way in which it would operate if memory was impaired (Berger et al 2011, Hampson et al 2012c).

Discussion

Retention of task-specific information dependent on hippocampal encoding

For a number of years, it has been established that the hippocampus is the primary memory structure in the mammalian brain (Cahusac et al 1989, Malkova and Mishkin 2003, McEchron and Disterhoft 1999, Rolls et al 2005). The basis for this status evolves from both clinical and experimental evidence demonstrating the necessity of normal hippocampal function to provide memory capacity sufficient for daily existence in a complex society (Gold and Shadlen 2007, Pastalkova et al 2008, Smith and Mizumori 2006, Squire et al 2004). However, two important features demonstrated in this study and recent prior studies from this program have not been previously described in the primate hippocampus. The first new insight demonstrated here is the fact that information is encoded during the sample phase, trial—specifically, in the primate hippocampus in a manner consistent with the subsequent operation of the same neurons during the recall of that information in the match phase of the same trial (figures 2–4). Since the same CA1 and CA3 neurons are involved in both phases of the memory process, it is critical to understand how information is encoded by this multi-neuron system such that it can be extracted at a later time for decisions (Hampson et al 2012b). An important outcome in these investigations was that hippocampal cells encoded specific details of information in the sample phase for as long as 40 s prior to utilization (figures 2–4) and facilitated recall impaired with respect to as many as six other ‘distracter’ images (always leaving at least one position blank) during target selection in the match phase (figure 8). Therefore, the manner in which information was encoded, as reflected by the MIMO-derived strong code firing patterns, is a functionally specific feature of hippocampal circuitry that: (1) determines the degree to which other events in the sample phase that are irrelevant to successful selection in the match phase are excluded (figure 5(B)), and (2) provides resistance to the decay of relevant sample-encoded information over the subsequent intervening, variable delay period (figure 5(A)).

Successful performance related to hippocampal encoding of task-relevant information

It is clear therefore that CA1 and CA3 firing in the sample phase was the primary controlling factor in task performance; hence, the detection of the pattern of SR firing associated with successful trials provided a means of predicting and facilitating memory encoding during the task. The MIMO model accomplished this by detecting and classifying strong codes for supporting successful performance on the same trial as shown in figure 8. The direct relationship between these MIMO extracted codes and task performance is exhibited in another conclusive manner by the relative interactive nature of strong codes for different types of trials as shown in the supplementary figure (A) (online supplementary data available from stacks.iop.org/JNE/10/066013/mmmedia) (NHP1) in which ‘weak code’ patterns on incorrect object trials resembled ‘strong code’ patterns on successful spatial trials. Therefore, in addition to the difficulty incorporated by the increased number of images and longer delays, retention was also required for the type of trial (object or spatial) designated by the TS signal at the start of the sample phase of the task (figures 1 and 2), and this also appeared to be incorporated in MIMO-derived CA3–CA1 sample encoding patterns. The fact that animals had to deal with a large number of different types of trials randomly presented within the same session supports the possibility that extracted weak code patterns that caused errors were the result of ‘mis-encoding’ with another strong code pattern for either (a) a different type of trial or (b) mis-anticipated parameters.

MIMO model-induced enhancement of memory encoding under difficult circumstances

What is presented here is the first application of the MIMO model to a primate hippocampus, which is an extension of the application of the same model as a prosthesis to other primate brain areas, previously shown to be critical in controlling decision making in the match phase in this same DMS task (Hampson et al 2012a, 2012b). However, a previous successful application of a MIMO model prosthesis to disrupted hippocampal neural processing in rodents (Berger et al 2011, Hampson et al 2012a) was the basis for developing a hippocampal neuroprosthesis for NHPs (Berger et al 2011, Hampson et al 2012a, 2012c, 2012d). In contrast to the application of MIMO model stimulation to the rodent hippocampus (Berger et al 2011, Hampson et al 2012a), the extent and range of effectiveness in improving cognitive performance in this NHP memory task was more indicative of application to humans (figures 9 and 10). However, what is of major importance with regard to this demonstration of neuroprosthetic capability is the fact that, as in the rodent model (Berger et al 2011), effective CA1 stimulation parameters had to mimic those derived by the MIMO model during strong encoding of trial-specific sample information. This was confirmed by stimulating the same CA1 location with scrambled strong code patterns at the same intensities (figure 10) which did not facilitate performance. The strong code patterns extracted by the MIMO model were not only effective because they mimicked firing in successful trials, they also were capable of increasing performance above control levels via delivery on trials in which ineffective (weak) encoding (errors) occurred (figures 9 and 10). Hence,
these results demonstrate the potential for MIMO stimulation delivered to the primate hippocampus, to not only facilitate but also recover memory in subjects, including humans, impaired by pathological events such as brain damage, or possibly even brain ageing where memory disruption is more or less permanent (Carmichael et al. 2012, Gemmell et al. 2012, Maillet and Rajah 2011, Riddle and Lichtenwalner 2007, Ta et al. 2012).

Conclusions

These unique results are the first to show that interactions between CA3 and CA1 hippocampal neurons in the primate brain that encode information relevant to the successful performance of a memory-dependent decision making task (Deadwyler et al. 2007, Porrino et al. 2005) are capable of being extracted and re-introduced via the application of a MIMO model neuroprosthesis (Berger et al. 2011, Hampson et al. 2012a). The neural basis for effective performance in this task likely relates to significantly increased synaptic transmission from CA3–CA1 in the hippocampus (Song et al. 2007, 2009) to encode proper information during the sample phase (figures 8 and 9). Therefore, interposing a MIMO model to control such processing provides a means of reducing random fluctuations in performance under normal conditions (figures 5 and 8) and/or to recover performance when retention is reduced or impaired (figures 9 and 10). In addition to providing potential insight into other types of cognitive impairments involving decision making and executive function in the human brain as a result of disease or injuries (Gold and Shadlen 2007, Graybiel 2008, Wang et al. 2011), these results provide confirmation that a MIMO-based functional device, integrated physiologically with hippocampal operation will improve and even recover lost memory capacity in humans.

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