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Research Paper

A cognitive prosthesis for memory facilitation by closed-loop functional ensemble stimulation of hippocampal neurons in primate brain

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ABSTRACT

Very productive collaborative investigations characterized how multineuron hippocampal ensembles recorded in nonhuman primates (NHPs) encode short-term memory necessary for successful performance in a delayed match to sample (DMS) task and utilized that information to devise a unique nonlinear multi-input multi-output (MIMO) memory prosthesis device to enhance short-term memory in real-time during task performance. Investigations have characterized how the hippocampus in primate brain encodes information in a multi-item, rule-controlled, delayed match to sample (DMS) task. The MIMO model was applied via closed loop feedback micro-current stimulation during the task via conformal electrode arrays and enhanced performance of the complex memory requirements. These findings clearly indicate detection of a means by which the hippocampus encodes information and transmits this information to other brain regions involved in memory processing. By employing the nonlinear dynamic multi-input/multi-output (MIMO) model, developed and adapted to hippocampal neural ensemble firing patterns derived from simultaneous recorded multi-neuron CA1 and CA3 activity, it was possible to extract information encoded in the Sample phase of DMS trials that was necessary for successful performance in the subsequent Match phase of the task. The extension of this MIMO model to online delivery of electrical stimulation patterns to the same recording loci that exhibited successful CA1 firing in the DMS Sample Phase provided the means to increase task performance on a trial-by-trial basis. Increased utility of the MIMO model as a memory prosthesis was exhibited by the demonstration of cumulative increases in DMS task performance with repeated MIMO stimulation over many sessions. These results, reported below in this article, provide the necessary demonstrations to further the feasibility of the MIMO model as a memory prosthesis to recover and/or enhance encoding of cognitive information in humans with memory disruptions resulting from brain injury, disease or aging.

1. Introduction

Encoding of memory by brain systems has long been one of the major interests of neuroscience research, since this process allows temporal bridging between events that occur at different times, as well as expectation of future circumstances based on accurate recall of prior experiences (Eichenbaum and Fortin, 2009). Effective memory encoding requires detection, categorization and recognition, in order to allow adequate performance in a number of different circumstances (Davachi, 2006) as indicated most dramatically by Alzheimer's disease in which total memory loss leads to incapacitation and helplessness (Gold et al., 2006). The brain structure most intricately involved in this process is the hippocampus, which exists in all mammalian species and is capable of long-term retention of goal-directed objectives (Eichenbaum et al., 2007; Klausberger and Somogyi, 2008; Manns et al., 2003; Squire et al., 2007). Development of new technologies and brain-behavior assessments has allowed progressive insight into the process of memory formation and retrieval in hippocampus (Eichenbaum and Cohen, 2001; Quirk et al., 1992; Ross and Slotnick, 2008; Rutishauser et al., 2006; Wais et al., 2006; Winters and Bussey, 2005). This has progressed to the extent of making it possible to formulate and test a “device” that can substitute for these functions when they are compromised by damage or disease (Berger and Glanzman, 2005) in the same manner as other neural prostheses (Berger et al., 2005; Hampson et al., 2005; Song et al., 2007a, b).

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In order to understand the neural basis of memory in hippocampus several features of both the context in which encoding occurs as well as the functional aspects of simultaneous multineuron firing patterns, must be identified, interpreted and manipulated, which has been one of the important objectives of the research described here. This entails integrating; 1) an effective operational mathematical model for online prediction of cell discharges in the CA1 field from simultaneously recorded firing patterns of presynaptic CA3 neurons (Marmarelis and Orme, 1993; Song et al., 2007a; Song et al., 2009; Truccolo et al., 2005), together with, 2) obtaining systematic recordings of hippocampal neural ensemble activity in a behavioral task in which trial-to-trial short-term encoding of task features is required for successful performance (Deadwyler et al., 1996; Deadwyler and Hampson, 2006). The combining of these two approaches has involved the analysis and characterization of neuronal firing patterns in CA3/CA1 hippocampal subfields repeatedly subjected to mathematical nonlinear input/output analysis (Marmarelis, 2004; Song et al., 2007a, b; Zanos et al., 2008) in both rodents and nonhuman primates performing a short-term memory task (Hampson et al., 2011; Hampson et al., 2012a, b, c, d; Hampson et al., 2013). The culmination of these investigations (Berger et al., 2011) demonstrated that the "firing codes" extracted online by a custom designed multi-input/multi-output (MIMO) nonlinear model, when reinjected via identical electrical stimulation patterns could 1) enhance performance by changing the strength of encoding required for the memory task and 2) recover the pharmacologically compromised operation of hippocampus by re-inserting electrically-mimicked natural codes in the same animals performing task.

In the studies reported here four additional features of the MIMO model extracted firing patterns of hippocampal neural ensembles are shown that provide further support for its application as a memory prosthesis. First, the actual basis of the utility of ensemble spatiotemporal firing patterns detected by the MIMO model is revealed in terms of the degree to which encoding of specific task events reflects the level of performance on a given trial. Second, it is shown that if given repeatedly on specified trials within the testing session, MIMO model electrical stimulation patterns also enhances performance on trials without stimulation delivered in the same sessions, and, that such enhancement persisted even after the stimulation trials were terminated in the session. Third, it has been shown that similar types of hippocampal encoding patterns exist across different animals tested in the same task. Finally, it is revealed that ensemble firing patterns extracted online by the MIMO model conform to the synchronized firing of cells in the ensemble that naturally and successfully encode task features (Hampson et al., 2008). Collectively these findings support the feasibility of applying the current prosthetic device (Hampson et al., 2013) to 1) repair damaged or disrupted brain-memory processes, and/or 2)

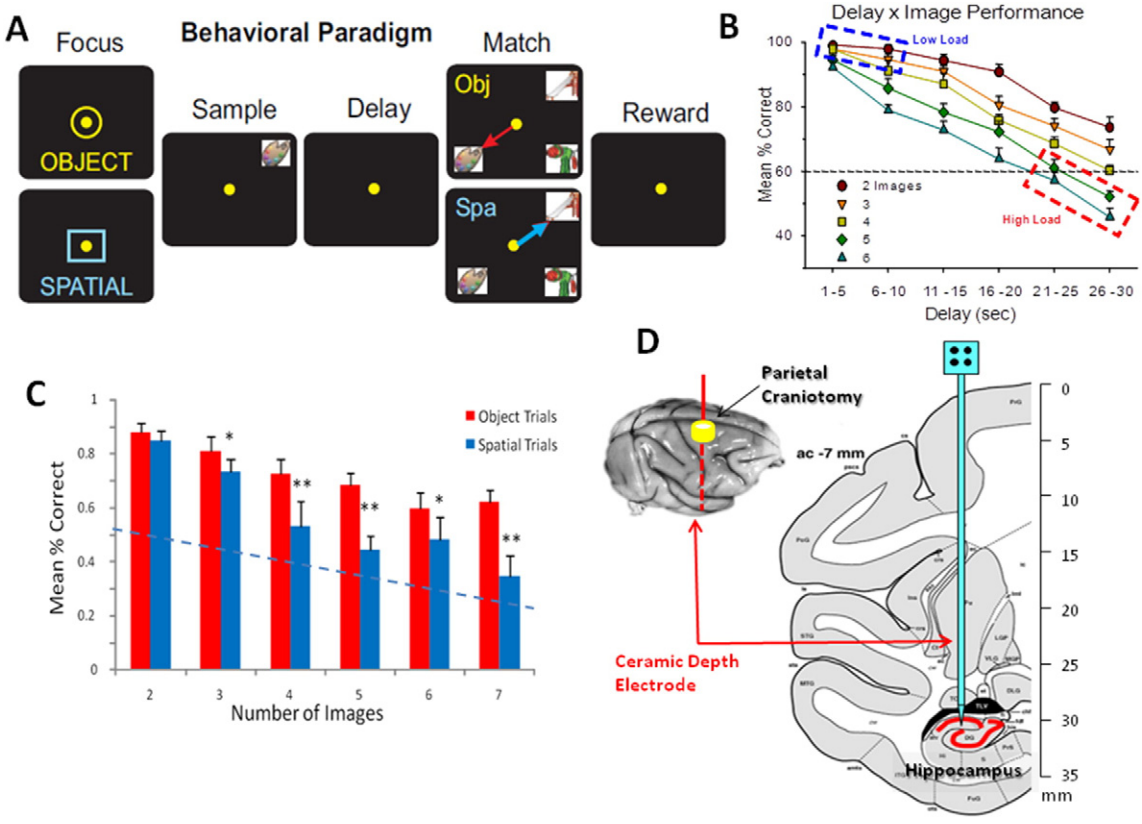

Fig. 1. Illustration of DMS behavioral task and localization of hippocampal recording electrodes. A: Behavioral paradigm showing the sequence of events in the DMS task with correct cursor movement (yellow dot) indicated for each phase of the task: (Berger et al., 2005) Trial initiation 'start signal' (to maintain subject attention and signal the start of a new trial. Signal consists of yellow circle (upper) or blue square (lower) signaling an object or spatial trial, respectively. Placement of the cursor into the start signal initiated the Sample Phase of the trial. (Berger and Glanzman, 2005) Sample Presentation (SP) of a clip-art image in one of eight different spatial locations on the screen. The Sample Response (SR) consisted of movement of the cursor onto the presented sample image, which ended the Sample Phase and initiated the Delay Phase. (Chapin, 2004) Variable Delay consisted of randomly-selected 1–60 s interval with only a black screen showing. When computer determined that Delay interval had timed out, the Match Phase was initiated independent of any subject response. (Davachi, 2006) Match Presentation (MP) consisted of display of Sample image in a different location from Sample Phase, along with 1–7 Non-match distracter images. Match response (MR) consisted of cursor movements onto same image (for Object trials, red arrow) or same position (for Spatial trials, blue arrow) as in the Sample Phase. (Deadwyler et al., 1996) Correct MRs were rewarded by delivery of a squirt of juice reward (Reinf.). 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: Overall performance averages showing the interaction of interposed delays with number of images presented in Match Phase. High and Low Cognitive Load conditions indicated by dashed outlines. C: 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. $^{*}p < 0.01$, $^{**}p < 0.001$ Object vs. Spatial. D: Diagram of NHP brain in cross-section showing hippocampal tetrode tracks through temporal lobe and placement in the CA3 and CA1 cell layers.