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# Restorative Encoding Memory Integrative Neural Device: "REMIND"

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*Abstract* –**Construction and application of a neural prosthesis device that enhances existing and replaces lost memory capacity in humans is the focus of research described here in rodents. A unique approach for the analysis and application of neural population firing has been developed to decipher the pattern in which information is successfully encoded by the hippocampus where mnemonic accuracy is critical. A nonlinear dynamic multi-input multi-output (MIMO) model is utilized to extract memory relevant firing patterns in CA3 and CA1 and to predict online what the consequences of the encoded firing patterns reflect for subsequent information retrieval for successful performance of delayed-nonmatch-to-sample (DNMS) memory task in rodents. The MIMO model has been tested successfully in a number of different contexts, each of which produced improved performance by a) utilizing online predicted codes to regulate task difficulty, b) employing electrical stimulation of CA1 output areas in the same pattern as successful cell firing, c) employing electrical stimulation to recover cell firing compromised by pharmacological agents and d) transferring and improving performance in naïve animals using the same stimulation patterns that are effective in fully trained animals. The results in rodents formed the basis for extension of the MIMO model to nonhuman primates in the same type of memory task that is now being tested in the last step prior to its application in humans.**

***Index Terms*** **–** Hippocampal Prosthesis, Delayed Memory Task, Ensemble Activity, Nonlinear Model, Stimulation patterns, Memory enhancement and recovery.

## I. INTRODUCTION

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The critical role of the hippocampus in memory formation, translation and retrieval has been established and verified over many decades in all mammalian species [1-4]. The necessity for intact operational circuitry in this brain region has been demonstrated in a wide range of conditions ranging from *in vitro* slices of neural tissue to Alzheimer's Disease patients [5-8]. There have been many theories of how this brain system operates to encode memory and to perform such an important duty in maintaining cognitive capacity [2;5;8-16], however, the precise mechanism by which memories are actually represented by neural elements in this structure has yet to be precisely demonstrated. Prior investigations have demonstrated that the multineuron recordings from hippocampus during performance of a memory dependent task can reflect and predict appropriate behavioral performance [17].

From these studies it has been determined that memory encoding resides in the specific patterns of multi-neuron activity generated within and transmitted through hippocampal circuitry to other brain regions during the performance of a delayed-nonmatch-to-sample (DNMS) task. The value of such findings for potential as a memory prosthesis has been the focus of collaborative investigations in which we have shown that such 'ensemble representations' during encoding can be extracted by a specially designed nonlinear multi-input multi-output (MIMO) model [18-24]. The results provide conclusive examples of how memories are encoded by hippocampal ensembles and demonstrate that reproduction of such patterned firing with electrical stimulation produces functional consequences that are similar if not identical to ensemble patterns generated naturally under the same memory-dependent circumstances. As such these findings provide the basis for several types of brain-based "prosthetic" applications including repair of disrupted circuitry [25;26], correction of inappropriate encoding [27], enhancement of new memory formation [28;29].

The memory task utilized to show these effects requires retention, for later retrieval, of the position of a sample phase lever press, i.e. sample response (SR), across a variable delay period of 1-30s, in order to make the opposite lever choice in the nonmatch phase after the delay times out [30-35]. The

MIMO model used here was developed from nonlinear models successfully employed to predict CA3-to-CA1 spike train transformations in hippocampal slices [36-39]. The successful application of the MIMO model to this well characterized behavioral context provided the basis for testing whether the model could serve as the prototype for a true "cortical prosthesis" [21;40]. This was tested directly by transforming the predicted output pattern of the MIMO model into electrical pulses delivered via a multichannel stimulator to the CA1 electrodes in the recording array [17]. The stimulation patterns were therefore similar to the SR firing patterns recorded from CA1 electrodes and were generated online in both hemispheres by inputs to the MIMO model from the matching sets of CA3 electrodes on the same arrays in each hemisphere [20;22;24]. Stimulation trains delivered to CA1 were timed to arrive when the patterns associated with SR performance were recorded in real-time in CA3 by the MIMO model. Thus when CA3 firing predicated a "weak" SR code in CA1, previously associated with behavioral errors, simulation pulses were delivered to those same electrodes in the "strong code" or successful pattern previously predicated by the MIMO model in prior sessions. There were marked increases in performance on stimulation trials reflecting the influence of MIMO generated SR strong code activation patterns for reversing consequences on trials that were normally at risk for error due the erroneous generation of weak codes on trials that required increased retention (long vs. short delays). Results were compared to trials in which no stimulation was delivered, or trials in which stimulation was delivered in scrambled or reverse patterns.

The specificity of the stimulation pattern with respect to encoding of the SR was provided by the fact that no changes in performance from control levels occurred if the stimulation of CA1 at the same intensities was generated from 1) scrambled ensemble firing patterns with no relation to MIMO derivation, or 2) the same SR stimulation pattern was delivered 3.0 s after the SR. Stimulation intensities (20-100 μAmps) were adjusted to provide indications of extracellular current flow (distinct field potentials) at adjacent CA1 locations on the array. A final control was to reverse the stimulation patterns for Left and Right SRs, which actually reduced performance below control levels, suggesting that the imposed stimulation patterns were utilized as the retrieved information. The results show that functional encoding necessary for successful performance was produced by delivering MIMO predicted CA1 output firing patterns as matching electrical stimulus pulse trains to the same recording loci when the animals required that information to perform the task.

The extension of these findings to the possible use of the MIMO model as a neural prosthesis to replace damaged brain regions [41] was examined in animals with compromised hippocampal function by infused glutamatergic synaptic blocking agents. Rats previously trained in the DNMS task, were chronically treated with intrahippocampal infusion of the NMDA receptor blocking agent, MK801 [42;43] which markedly impaired performance across all delay intervals and impaired online MIMO derived CA3 predication of CA1 encoding of the SR. However, since the animals were previously trained in the task, MIMO derived successful firing patterns could be imposed by delivering them in the form of electrical stimulation patterns to CA1 at the time of the SR. This procedures markedly reversed the effects of the pharmacological blockade and performance was recovered to 70-75% of normal level [17]. The results showed that activation of CA1 output with effective MIMO derived stimulation patterns was sufficient to partially overcome the compromised synaptic function that was necessary to perform the task.

A further extension of application of the MIMO model to neural prostheses involved the "transfer" of strong codes [44] online from trained (donor) animals to untrained (recipient) naïve animals that were never exposed to delays in the task. The within trial performance of both animals was synchronized with respect to presentation of the sample lever and the occurrence of the SR. Thus, when the MIMO model predicted a strong SR code from the trained "donor" rat as it pressed its lever, the previously established facilitatory stimulation pattern was routed to the same CA1 electrode locations in the delay-naive "recipient" animal while performing its SR in a separate chamber. Next, the naïve recipient animal was exposed to delays of 16-30s that had never been experienced before in the task; performance was compared to trials in which either no stimulation was delivered or the stimulation pattern was scrambled. Naïve recipient animals that received MIMO SR donor stimulation showed higher correct performance on delay trials with "donated" stimulation compared to trials with the same delays and no stimulation. This showed that the MIMO model could extract an effective SR code from a trained rat which could be transferred effectively in real time to a naïve (untrained) rat, attesting to the potential generality of the MIMO derived SR codes for improving memory across animals [44].

The above demonstration provided the basis for a recent accomplishment of generalizing the MIMO model-based neural prosthesis across animals. Rats with similar electrode configurations were trained in same way in the experimental task and MIMO information extracted to allow formulation and application of SR patterns 'derived' across a large number (n=40) of animals. It was possible to construct a mean across animals or "generic" hippocampal MIMO derived CA3/CA1 cell firing pattern and determine whether a 'generic SR strong code stimulation pattern' could also improve performance when administered to trained, as well as naïve animals. Such a generic code may derive from features of the nonlinear interactions between CA3 and CA1 neurons similar to those in the related presentation [45], in which it is shown that the computational complexity of the full MIMO model can be reduced by use of Principal Dynamic Mode (PDM) analyses. Such "reduced" coding may in fact derive from "generic"

codes that incorporate neuron firing that specifically encodes the critical events in the DNMS task. Results showed that a generic code was capable of significantly improving performance in both trained and naïve animals. While not as effective as individualized MIMO codes extracted and tested in the same animals, nevertheless from a neural prosthesis point of view, demonstration of an effective generic code indicates that prior recording of hippocampal neural activity is not necessary to implement a MIMO model-based hippocampal SR stimulation pattern that can enhance performance in the memory task.

The above results demonstrate that functional memory can be mimicked by MIMO model-derived electrical brain stimulation and that information encoded by temporal sequences of individual neuronal spike events in hippocampus can be reconstituted via substitution of stimulus pulses delivered in the same manner [46]. Unlike other forms of effective brain stimulation [28;29], the enhancing effects demonstrated here required that pulses be delivered to the same locations and in the same temporal sequence as the recorded nonlinear firing patterns of hippocampal neurons that were responsible for encoding task-specific events. The demonstration of improved performance under normal, disrupted and even task-naïve conditions, covers all circumstances of prosthesis applications and validates that MIMO derived stimulation was an effective means of enhancing and replacing memory when retrieval of encoded information was required. The fact that stimulation in the patterns that were recorded and extracted by the MIMO model can apparently substitute for normal neuronal ensemble activation patterns is, to some extent understandable [1;2;15;40;47]. The utility of such findings if manifested in neural prostheses could, 1) enhance normal less than optimal task-related neural activity; 2) repair damaged or interrupted brain circuitry, and 3) provide critical task-specific representation of information in the absence of prior behavioral experience. The above demonstrations provide a strong foundation for extending these results to other behavioral contexts, other brain regions and to human circumstances in which cognitive recovery is critical [5;6;8;48].

In the next phase of the program currently under way the MIMO model is being applied to two brain regions in nonhuman primates (NHPs), medial temporal lobe and prefrontal cortex, previously characterized as critical for performance of a multidimensional delayed memory task [49-52]. Current results are consistent with those reported in the rodent in showing that MIMO model derived stimulation in prefrontal cortex (PFC) during the response choice match phase of a delayed match to sample (DMS) task, facilitates performance. The MIMO model is also being elaborated to address other issues in the NHP that might be possible to detect such as neurons that fire exclusively when strong codes are generated. Application of this version of the MIMO model to the primate brain is likely to provide the first instance in which recovery of function is possible using recordings from intact neural systems to trigger information encoding and transmission to disconnected areas that require previously established MIMO recognizable patterned output.


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