BRAIN RESEARCH 1621 (2015) 335–344

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Research Report

Neurons and networks organizing and sequencing memories

Sam A. Deadwyler[a,*], Theodore W. Berger[b], Ioan Opris[a], Dong Song[b], Robert E. Hampson[a]

[a]Department of Physiology & Pharmacology, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1083, USA

[b]Department of Biomedical Engineering, Viterbi School of Engineering, University of Southern California, 1042 Downey Way (DRB140), Los Angeles, CA 90089-1111, USA

ARTICLE INFO

Article history:
Accepted 17 December 2014
Available online 29 December 2014

Keywords:
Hippocampal neurons
Memory
Hierarchical encoding
Retention and retrieval
Nonlinear hierarchical model
Nonhuman primates

ABSTRACT

Hippocampal CA1 and CA3 neurons sampled randomly in large numbers in primate brain show conclusive examples of hierarchical encoding of task specific information. Hierarchical encoding allows multi-task utilization of the same hippocampal neural networks via distributed firing between neurons that respond to subsets, attributes or "categories" of stimulus features which can be applied in events in different contexts. In addition, such networks are uniquely adaptable to neural systems unrestricted by rigid synaptic architecture (i.e. columns, layers or "patches") which physically limits the number of possible task-specific interactions between neurons. Also hierarchical encoding is not random; it requires multiple exposures to the same types of relevant events to elevate synaptic connectivity between neurons for different stimulus features that occur in different task-dependent contexts. The large number of cells within associated hierarchical circuits in structures such as hippocampus provides efficient processing of information relevant to common memory-dependent behavioral decisions within different contextual circumstances.

This article is part of a Special Issue entitled SI: Brain and Memory.

1. Neurons and networks

1.1. *Requirements for neural encoding*

Individual neurons change their firing activity based on the nature of the synaptic inputs they receive which could be related to the nature of the transmitter involved, or frequency of membrane depolarization from repetitive single, or temporally convergent multiple, synaptic inputs. The resulting long-term potentiation (LTP) from such repetitive synaptic activation provides the primary basis for sustained increases in firing tendencies, under the same circumstances, at the single neuron level (Abraham, 2003; Bliss and Collingridge, 1993; Lynch, 2004; Lynch et al., 2014). An established feature of

*Corresponding author. Fax: +1 336 716 8628.
E-mail address: sdeadwyl@wfubmc.edu (S.A. Deadwyler).

http://dx.doi.org/10.1016/j.brainres.2014.12.037
0006-8993/

neuron encoding (Cox et al., 2014) is modulation of neuronal efficacy in response to single or convergent synaptic inputs, dependent upon whether such inputs exhibit higher firing rates during critical events. However, from the perspective of circuit operation and large scale information integration, if firing of the involved neural cells is not synchronized in a spatiotemporal manner, adequate recruitment and altered responsiveness is not likely to happen (Hampson et al., 1999; Brasselet et al., 2012; Lynch et al., 2013).

1.2. *Relation to organized circuit operation*

Synchronized synaptic inputs and firing frequencies are primary factors in coordinating connections between neurons in the same functional circuits. Factors such as LTP promote the chance that groups of neurons with multiple synaptic connections will tend to fire in coordinated spatiotemporal patterns that underlie information processing for specific sensory events when frequently repeated. In previous investigations a nonlinear multi-input multi-output (MIMO) math model was employed to analyze cell firing across large neuron populations in the same structures (Berger et al. 2011; Hampson et al., 2012b; Hampson et al., 2012c). In those studies it was demonstrated that the derived spatiotemporal firing patterns across all cells in the population were hierarchical, and provided important information-specific "firing codes" during performance of complex memory tasks. This convergence of synaptic inputs from two or more *Simple* neurons that encode item-specific information, onto other single neurons at the next stage of input–output circuit transmission through the structure, provides "*Conjunctive* neurons" for functional hierarchical circuits. Firing of only a few *Conjunctive* cells can therefore reflect several different task features dependent of the temporal synchrony of inputs from different convergent *Simple* cells activated by specific task-related events. Hence, it is likely that functional hierarchical circuits are the bases for the spatiotemporal firing patterns that represent effective task-related performance codes developed in brain areas that process information required for complex decision-making situations.

1.3. *Categorization-constraints and plasticity*

As mentioned with respect to the role of neuron population encoding in task-dependent circumstances, it is assumed that hierarchical formats of multi-neuron connectivity are what logically encodes features related to memory demands and cognitive processing. New hierarchical neural networks therefore are required to be constructed for encoding additional task-dependent features that were previously not relevant to successful performance. However, the evolution of successful hierarchical encoding depends to a large extent on frequent re-exposure to task events that can be categorized via specific firing of directly responsive "*Simple*" cells for eventual selective increased synaptic connectivity with "*Conjunctive*" and "*Trial Type*" (*TT*) cells (Marmarelis et al., 2013; Hampson et al., 2012c; Deadwyler and Hampson, 2004; Hampson and Deadwyler, 2003; Hampson et al., 2001). The resulting outcome of such hierarchically controlled plasticity is faster processing of previously unfamiliar information due to the sharing of some of the same *Simple* and *Conjunctive* cells in a previously hierarchical circuit established for other circumstances.

2. Neural dynamics of memory formation and retrieval

2.1. *Pattern identity and extraction*

There are several studies which have established the features of pattern identification by brain processes (Kaliukhovich and Vogels, 2013; Beyeler et al., 2013; Safaai et al., 2013; Cerda and Girau, 2013; Brasselet et al., 2012). In order to extract spatiotemporal patterns of multi-neuron firing that have specificity for cognition and memory in primate brain requires that the patterns be obtained within subareas representative of input–output flow of information through the structure which has been previously shown for hippocampus and prefrontal cortex (Hampson et al. 2012b. 2013). Inherent anatomic distributions of cells and intrinsic connectivity within such cell groupings are defining factors as to where and how such hierarchical information processing circuits are formatted. In classic cortical structures where pyramidal cells communicate via columnar connectivity, this micro-anatomic substrate serves as the basis for information segregation, derivation and transmission. However, in structures that do not have such detailed anatomic microcircuit capacity the only way of processing information within or across cell layers in a proficient input–output manner, is via hierarchical encoding of item specific information. Such encoding is produced via spatiotemporal convergence of synaptic inputs across *Simple*, *Conjunctive*, and one or two *TT* neurons within a time frame required to satisfy the event-specific constraints of the memory demanding circumstances.

2.2. *Temporal dynamics*

Maintained temporal relations between the firing of individual neurons is critical for preserving appropriate information processing in hierarchical circuits. Spatiotemporal firing patterns have been extracted by the experimental diagnosis of nonlinear "input–output" characteristics of multi-cell firing recorded from synaptically connected neurons to reveal hierarchical encoding of information during cognitive processing (Safaai et al., 2013; Mathis et al., 2012; Brasselet et al., 2012; Hampson et al., 2012c; Hampson et al., 2004; Hampson and Deadwyler, 2003; Hampson et al., 2001). Temporal specificity is a key element in terms of the critical (postsynaptic) outputs that results from specific (presynaptic) input patterns, which is required for effective hierarchical coding. Fortunately, as shown below, employment of nonlinear multi-input multi-output (MIMO) models can reveal the spatiotemporal dynamics critical for effective operation of hierarchically organized neural systems (Berger et al., 2011; Berger et al., 2012; Hampson et al., 2012b; Hampson et al., 2013).

2.3. *Specificity of neural representation*

The nature of neural representation described above involves continuous dimensional and categorically defined formatting of information that provides the means to relate, extract, infer, or even reconstruct events via temporally congruent firing in