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Review

# On initial Brain Activity Mapping of associative memory code in the hippocampus

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ABSTRACT

It has been widely recognized that the understanding of the brain code would require large-scale recording and decoding of brain activity patterns. In 2007 with support from Georgia Research Alliance, we have launched the Brain Decoding Project Initiative with the basic idea which is now similarly advocated by BRAIN project or Brain Activity Map proposal. As the planning of the BRAIN project is currently underway, we share our insights and lessons from our efforts in mapping real-time episodic memory traces in the hippocampus of freely behaving mice. We show that appropriate large-scale statistical methods are essential to decipher and measure real-time memory traces and neural dynamics. We also provide an example of how the carefully designed, sometime thinking-outside-the-box, behavioral paradigms can be highly instrumental to the unraveling of memory-coding cell assembly organizing principle in the hippocampus. Our observations to date have led us to conclude that the specific-to-general categorical and combinatorial feature-coding cell assembly mechanism represents an emergent property for enabling the neural networks to generate and organize not only episodic memory, but also semantic knowledge and imagination.



## 1. Introduction

Aristotle has once pondered the concept of sensation and memory, and how they are produced in the mind. But it wasn't until the end of 19th century neuroscientists, such as Ramon Y. Cajal, had begun to look into how this process may occur at the cellular level. Fifty years after Cajal's observations Donald Hebb postulated that information processing in the brain may involve the coordinated activity of large numbers of neurons, or cell assemblies (Hebb, 1949). This notion, although beautifully vague, makes a good sense both from the computational and cellular perspective (Abbott & Sejnowski, 1999; Bi & Poo, 2001; Bliss & Collingridge, 1993; Malenka & Nicoll, 1999; Sanger, 2003; Shamir & Sompolinsky, 2004; Tsien, 2000; Wigstrom & Gustafsson, 1985). The major challenge to date has been to identify the real-time brain activity patterns and their corresponding cell assemblies, and to understand how such cell assemblies, if any, are organized to generate real-time perception, memory, and behavior.

As early as 1920s, neuroscientists try to decipher the brain codes by searching for reliable correlation between firing patterns of neurons and behavioral functions for many decades (Adrian, 1926; Fuster, 1973; Gross, Rocha-Miranda, & Bender, 1972; Thompson, 2005; Zhou & Fuster, 1996). Edgar Adrian in his pioneering recording showed that the firing rate of a frog muscle's stretch receptor increases as a function of the weights on the muscle (Adrian, 1926), suggesting that information is conveyed by specific firing patterns of neurons. However, due to a large amount of response-variability at the single neuron level in the brain even in response to identical stimulus (Bialek & Rieke, 1992; Lestienne, 2001), single neuron-based decoding schemes often produce significant errors in predictions about the stimulus identities or external information. The traditional way to deal with the response variability of single neurons is to average spike discharge of the neurons over repeated trials. Although the data averaging across trials permits the identification of response properties of the individual neurons, unfortunately, this practice invariably loses crucial information regarding real-time encoding process in the brain (Lin, Osan, & Tsien, 2006).

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Early efforts in examining population-level mechanisms relied on the "reconstructed" ensembles of neurons from serially recorded single neuron data. Such "reconstructed population codes" can improve the classification and prediction of datasets (Eskandar, Richmond, & Optican, 1992; Gochin, Colombo, Dorfman, Gerstein, & Gross, 1994; Miller, Li, & Desimone, 1993). With technical developments over the past decades, simultaneous monitoring of activities of many neurons has become more feasible (Buzsaki, 2004; Harris, Henze, Csicsvari, Hirase, & Buzsaki, 2000; McNaughton, O'Keefe, & Barnes, 1983; Schmidt, 1999). For example, Georgopoulos and his colleagues were among the first to apply a population-vector method to analyze ensemble firing patterns corresponding to arm movements of monkeys (Georgopoulos, Schwartz, & Kettner, 1986). By calculating the mean firing rates for each neuron corresponding to arm movement, a set of population vectors can be obtained that correspond to specific angles of arm rotation and movement (Musallam, Corneil, Greger, Scherberger, & Andersen, 2004; Nicolelis & Ribeiro, 2006; Velliste, Perel, Spalding, Whitford, & Schwartz, 2008). Similarly, the discovery of place cells in 1970s has prompted many researchers to examine how the hippocampus encodes space (O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978). Multiple tetrodes techniques have been successfully applied to the study of several dozens of place cells in the rat hippocampus (Wilson & McNaughton, 1993). This has led to extensive knowledge of how the hippocampal system may generate perceptual representation of the animal's self-location during spatial navigation (Buzsaki & Moser, 2013; Kentros, 2006; Lisman & Redish, 2009; McNaughton, Battaglia, Jensen, Moser, & Moser, 2006; Mizumori, 2006; Oler, Penley, Sava, & Markus, 2008; Redish, 2001; Smith & Mizumori, 2006). Yet it remains unclear as to whether motion-sensitive place cell firing would represent part of long-term episodic memory for which the hippocampus is known.

In parallel, development of region- and cell type-specific cre/loxP conditional transgenic methods in mid 1990s has opened a new door to studying gene, neural circuits, and behavior (Tsien, Chen, et al., 1996; Tsien, Huerta, & Tonegawa, 1996). This Cre/loxP method has also provided a useful platform for opsin-based optogenetics to restrict its manipulation to a given cell type within a given region. We have provided some of the earliest evidence that memory in mice can be impaired, enhanced, or rapidly erased by genetic means (Cao et al., 2008; Cui et al., 2004; Shimizu, Tang, Rampon, & Tsien, 2000; Tang et al., 1999; Tsien, Huerta, et al., 1996; Wang et al., 2011). Because the hippocampus is widely known for creating long-term memory of what event, when it happened, and at where, this has led us to focus on the following questions: what are real-time memory engrams underlying dramatic events or emotional experiences? Can real-time memory traces be mathematically described and decoded at any given moment? What are the organizing principles for memory-coding cell assemblies in the hippocampus? How does the memory circuit generate not only episodic memories but also semantic knowledge and imagination?

## 2. Brain decoding project initiative for creating brain activity map of memory engrams

To approach the above fundamental questions, it is obvious that it would require large-scale decoding of brain activity patterns. Over the course of past several years, we have focused our initial efforts on three different but coherently linked aspects: (1) To employ large-scale neural recording techniques to collect large datasets on memory process in the mouse hippocampus; (2) To use a set of innovative behavioral paradigms to facilitate the discovery of memory organizing principles; (3) To develop and apply mathematical tools that are suitable for identification of neural ensembles activity patterns and uncovering its underlying cell assembly structures.

Based on our initial success in decoding event-related neural patterns in the mouse hippocampus (Lin, Osan, et al., 2006; Lin et al., 2005; Tsien, 2007), in 2008 we have obtained strong support from Georgia Research Alliance and launched the Brain Decoding Project Initiative to identify neural dynamics in the memory circuits (http://gra.org/Stories/StoryDetail/tabid/622/xmid/632/Default.aspx). The basic idea of our Brain Decoding Project, now similarly expressed by Brain Activity Map proposal (Alivisatos et al., 2012), is to investigate and discover the underlying organizing principles by which the brain generates real-time perception, emotion, memory, knowledge, and behavior. Here, we share some of the insights and lessons from our brain decoding project effort which we believe may be useful to the planning of the BRAIN project that is currently underway:

## 3. Large-scale neural recording capacity: how large is large enough to get started?

Any brain decoding or activity mapping effort will face the question of how many neurons should be recorded in order to decipher the real-time brain code and more importantly to understand the basic designing principles. One of the grand claims in the Brain Activity Map proposal is to measure every spike from every neuron (Alivisatos et al., 2012). This has raised some theoretical questions as to whether the brain's "emergent properties" can only be studied by recording all spikes from all neurons in the brain (Mitra, 2013). While collecting such complete information would be ideal, it may take more than fifteen years (the presumed time frame of the BRAIN project) before every spike of every neuron from a brain region of mammal species, say the hippocampus of freely behaving mice, can be achieved. Because the ultimate goal of the BRAIN project is to crack the brain code and establish its organizing principles, researchers may approach it with more practical question as to what the sizes of the recorded neurons should be recorded to get this decoding problem going.

In the case of the CA1 region of the hippocampus, it is known that pyramidal cells and diverse interneurons compose the intricate hippocampal circuits and are involved in various firing patterns. Much of current knowledge has been obtained from studies of *in vitro* brain slices (Freund & Buzsaki, 1996; Klausberger & Somogyi, 2008; Somogyi & Klausberger, 2005). Little is known about its detailed action on dynamic patterns of hippocampal cells during learning and memory. By taking the advantage of 96- or 128-channel *in vivo* neural recording technique, we are allowed to monitor many pyramidal cells and interneurons from the CA1 of freely behaving mice. Although the interneuron types identified *in vitro* or anesthetized state may not map clearly to those in freely behaving state, for simplicity we used these classification terms and identified at least seven major interneurons types, including known and unknown types of interneurons, based on their distinct firing patterns and compare with the *in vitro* results (Fig. 1A).

Type-1 and type-2 interneurons were putative basket cells and bistratified cells according the characteristics of these cells (Buzsaki & Eidelberg, 1983; Klausberger & Somogyi, 2008; Somogyi & Klausberger, 2005). They were made of nearly half of recorded interneurons. These cells innervate pyramidal cell somas and dendrites. Type-3 and type-4 interneurons matched well with firing characteristics of Chandelier cells and O-LM cells, respectively. These putative Chandelier cells and O-LM cells interneurons tended to fire during the period when pyramidal cells were silent. Cross-correlation analyses confirmed their negative dynamic correlation with pyramidal cells. These four types of interneurons



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