Review

On initial Brain Activity Mapping of episodic and semantic 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.

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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 stimuli (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).
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 stimuli or stimulus responses (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 (Buzsáki, 2004; Harris, Henze, Csicsvari, Hirase, & Buzsáki, 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, Cornell, Greger, Scherberger, & Andersen, 2004; Nicoletis & 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 (Buzsáki & Moser, 2013; Kentros, 2006; Lisman & Redish, 2009; McNaughton, Batta-glia, 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 December, 2007 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/ xmld/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 & Buzsáki, 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-C) (Kuang, Lin, & Tsien, 2010). Type-1 and type-2 interneurons were putative basket cells and bistratified cells according the characteristics of these cells (Fig. 1C) (Buzsáki & Edelberg, 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 (Fig. 1C, 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 all
exhibited dynamic relationships with the theta and ripple episodes which provided the characteristic classifications to their putative identities (Klausberger & Somogyi, 2008; Klausberger et al., 2003; Somogyi & Klausberger, 2005). The type-5, type-6, and type-7 interneurons were recorded slightly above the pyramidal cell body layer, namely, in the str. Oriens (often together with O-LM cells) (Fig. 1C), they may correspond to the trilaminar cells, back-projection cells or hippocampo-septal cells (Buzsaki & Eidelberg, 1983; Klausberger & Somogyi, 2008; Somogyi & Klausberger, 2005; Tukker, Fuentealba, Hartwich, Somogyi, & Klausberger, 2007). But their firm identifications remain to be determined (Fig. 1C).

Using the above neuron types as an example, we can ask how many neurons should be recorded simultaneously in order to obtain the first activity map of a CA1 circuit-processing unit (we term it as CPU) that would contain all of the above cell types in conjunction with pyramidal cells in memory processing. In statistics, sampling is concerned with the selection of a subset of individuals from a statistical population to estimate characteristics of the whole population. If assuming small numbers of interneurons have broad control or regulation over large numbers of pyramidal cells (as a basic CPU), one can use parameter estimation method to first calculate joint probability of responsive neurons for classified cell types by maximum likelihood estimate, and then obtain minimum joint probability among all classified cell types for estimating minimum size of recorded unit number. This is similar to the question how to assess all the fish species in a lake. Instead of counting all fish after draining the water from the lake, one use subgroup-sampling methods at multiple locations and depths to obtain the meaningful estimation. This same principle can be applied to Brain Activity Map project, that is, instead of measuring every spike from every neuron, one may reveal the fundamental properties of the neural circuit by performing well designed sampling.

Here we illustrate that minimum size of feature-coding neurons may be estimated from neurons’ distribution in a network population involved in memory processing. As shown in Fig. 1D, \( P(R \cap S) = P(S) \times P(R/S) \)

\[
ns = \frac{1}{\min(P(R|S))}
\]

1,085 cells should be simultaneously recorded to sample most, if not all, CA1 cell types in the pyramidal layers during episodic events.

**Fig. 1.** Diverse neuron types in the hippocampus and theoretical consideration for Brain Activity Mapping. (A) Illustration of diverse neuron types in the CA1, which include Pyramidal cells (pyr), basket cells, bistratified cells, Chandelier cells, O-LM cells, and other unidentified interneuron types. O-LM cell, Type-5, type-6, and type-7 interneurons are located in the str. oriens. Firing temporal rhythms of pyramidal cells and seven distinct interneuron types under ketamine-induced anesthesia. (C) Distinct profiles of distinct CA1 cells in relationship with theta oscillations (the first column of plots from left), ripples (second column), and their autocorrelograms during sleep (third column) and ketamine-induced anesthesia (right column). The figure is partially adopted from Kuang et al. 2010. (D) Joint probability distribution for estimating cell numbers for covering basic CA1 cell types involved in processing fear memory using the Chandelier cell as a low end for estimation. Approximately 1085 neurons in hippocampus CA1 should be ideally recorded simultaneously so that the recorded dataset will contain all most likely responsive neurons of most types, if not all, for the study of encoding of fearful experiences. This is just an example of sketchy estimation, more accurate calculations with confidence levels can be implemented using bootstrapping method. (E) Nyquist–Shannon sampling theorem for estimating the sample speed for detecting various network-level dynamics.
~1.3%, etc.) and \( P(R|S) \) is the probability of the events that recording certain type neuron responding to stimulus (i.e. on average ~20% of pyramidal cells reacted to fearful stimuli, etc.). Minimum size of recording neurons \( n_L \) is defined as the inverse of the minimum \( P(R \cap S) \) among all types of neuron, with the relationship of \( \log n_L \) and \( \min (P(R \cap S)) \) shown in Fig. 1D.

Based on our recording in the mouse CA1 region during behavior, the joint probability \( P(R \cap S) \) for recorded pyramidal cells, basket cells, bistriated cells, and chandelier cells, responding to fearful stimuli are 6.8%, 1.3%, 1.9%, 0.092%. Using Chandelier cells as the lower end of the population samples (because these cells are more or less located in the same layer with the pyramidal cells where the recording electrodes were inserted), we estimated that approximately ~1085 neurons in hippocampus CA1 should be ideally recorded simultaneously to cover most, if not all, response types for the study of memory encoding. With additional rare types of interneurons to be identified and characterized, the estimations of the size of CA1 neurons within a minimal CPU can be updated correspondingly. It is noteworthy to point out that the size of recorded units will increase significantly for estimating cross-region interactions (i.e. DG-to-CA3-to-CA1).

4. Temporal resolutions of large-scale activity mapping: how fast is fast enough?

The second issue relevant to Brain Activity Mapping is the consideration of temporal resolution for any types of new tools to be developed. The gold standard of neural activity measurement is a variety of in vivo microelectrodes (i.e. in stereotrode or tetrode format) that can offer the state-of-the-art in terms of robust signal quality and fine temporal resolution. In theory, to detect occurrence of the event and avoid signal aliasing between events, minimum sampling frequency of activity mapping techniques can be predicted based on Nyquist–Shannon sampling theorem. In Fig. 1E (the upper drawing), the red curve denote the states in neural population and an event occur beyond the threshold (blue dashed line), and the length of this event is \( T_r \). To detect this hypothetical event or stimulus, the minimum temporal resolution of calcium imaging or other recording methods is the inverse of half \( T_r \), \( f_s = 1/(2T_r) \). The relationship between \( \log f_s \) and \( T_r \), and five examples are shown (Fig. 1E, bottom plot). In the case of detecting two individual neural spikes, because the wave crest of a spike can last ~0.2 ms, a minimum 10 kHz sampling frequency is needed for detecting spike. In this calculation, we only assume to distinguish the occurrence of spikes. But a much higher sampling frequency is required if one wants to reconstruct the whole waveform of neural spike (i.e. 40 kHz at 16-bit resolution in Plexon Omniplex neural data acquisition system). For detecting rapid object categorization from complex natural scenes (which can be achieved ~100 ms in the visual cortex), a minimum 20 Hz sampling frequency is required to measure detailed dynamics. For assessing motor output control of spoken Chinese (the fastest speaking speed for Chinese is ~300 words per minute), a minimum 10 Hz sampling frequency will then be needed to discriminate. Similarly, our memory decoding shows that the shortest time duration of CA1 memory traces is ~0.2 s, thus, sampling frequency should be minimally at or higher than 10 Hz.

At the moment, calcium imaging techniques based on GCaMPs have been promised to study neural activity associated with animal behaviors (Harvey, Coen, & Tank, 2012; Ziv et al., 2013). Yet, the temporal resolution of calcium imaging is mostly at the sampling frequency of 0.1–0.25 Hz, inherently due to variable durations of calcium transient wave which can range from ~4 to 10 s (presumably triggered by multiple action potentials). It will need 40- to 100-fold of improvement in order to reflect many details of memory circuit dynamics. In addition, calcium buffering and potential interferences of intracellular signaling process represents other concerns that will need to be addressed. An alternative is to develop voltage-based imaging methods. Another issue for imaging-based methods is how to simultaneously identify a variety of interneurons types from the imaging view field and how to take advantages of the currently available information in the literature (such as shown in Fig. 1C using microelectrodes based on spike discharge probability and theta or ripples phases).

5. Decoding real-time memory traces of fearful events in the mouse hippocampus

The hippocampus is well known for its role in the formation of emotionally charged episodic memories, such as fear conditioning memories (Clark & Squire, 1998; Davis, Hitchcock, & Rosen, 1988; Kim & Jung, 2006; LeDoux, 1994; Maren, 2001). To investigate what real-time fear memory traces look like in the brain, we use trace fear conditioning protocol which involves a neutral tone followed by a mild foot-shock with a time interval of 20 s in-between. This classical associative memory task produces trace-fear memory as well as contextual fear memory (Biedenkapp & Rudy, 2007; Chowdhury, Quinn, & Fanselow, 2005; Clark & Squire, 1998; Clark & Zola, 1998; Knight, Cheng, Smith, Stein, & Helmstetter, 2004; Matus-Amat, Higgins, Barrientos, & Rudy, 2004; McEchron, Bouwmeester, Tseng, Weiss, & Disterhoft, 1998), and offers an ideal opportunity to study real-time memory engram.

Toward this end, we have employed 128-channel electrode array recording techniques to monitor 200–300 CA1 units simultaneously in mice (Lin, Chen, et al., 2006; Lin et al., 2005). More importantly, we have systematically explored and compared various multi-variant statistics and were able to optimize multi-discriminant analysis (MDA)-sliding window methods to quantitatively measure and intuitively visualize dynamic activity patterns from the recorded large datasets related to episodic memory traces (Osan, Zhu, Shoham, & Tsien, 2007; Tsien, 2007). As a result, we were able to measure and decode, for the first time, real-time memory traces in the hippocampus as mice underwent the acquisition and retrieval of fear conditioning memories (Chen, Wang, & Tsien, 2009). For example, we found that conditioned tone trace can emerge quickly during learning. Moreover, foot shock-triggered ensemble responses, which originally evoked only US-specific simple traces, would turn into the US-to-CS association traces as CS/US pairing was repeated over trial. The emergence of such associative traces suggests that circuitry-level dynamics have captured nicely the CS–US causal relationship. We also found that these CS and US traces reverberated during the learning phase, and more interestingly, the numbers of reverberations increase in proportion to CS/US pairing trial numbers (Chen et al., 2009).

To examine whether these CA1 traces observed during learning represent true memory traces, we asked whether those patterns will re-emerge upon the recall cues during memory retention tests and whether they would precede and correlate with behavioral performances. Indeed, we observed that the first recalled memory trace consistently precedes freezing behavior on the average of 1.4 s (see example of memory traces during contextual recall, Fig. 2A). On average, various CS and/or US memory traces were observed (Fig. 2B-F) and retrieved at a rate of 8–14 times per minute in the mouse hippocampus during the fear memory retention tests (Chen et al., 2009). Importantly, the numbers of retrieved memory traces in the retention tests were tightly correlated with the amount of freezing at both the individual and group levels (Fig. 2H and I). In trace retention test, we further found that upon hearing the conditioned tone, various memory traces re-emerged over the 60 s period, but it was the US memory traces consistently reappeared at the time point of 20 s after the tone (Chen et al.,...
2009), thereby demonstrating that the animals formed the real-time memory trace of time for accurately predicting the anticipated arrival of foot shock, a hallmark feature of real-time hippocampal memory traces for “what” and “when”. Therefore, by using 128-channel recording techniques and appropriate decoding methods, we have revealed, for the first time, that the

![Diagram](image-url)

Fig. 2. Real-time fear memory traces during contextual fear memory recall. (A) At contextual recall test, the mouse entered the freezing state (illustrated by red bar above the local field potential power spectrum) 8 s after entered the conditioning chamber. The observed first retrieved pattern emerged 360 milli-second before the animal froze. During the first freezing epoch (~23 s), eight memory traces were detected (see triangles at the bottom of spike raster, only 105 CA1 units out of 208 simultaneously recorded units were shown here). In the second freezing epoch that lasted about 20 s, another set of trace retrievals (8 trajectories) was observed. These dynamic ensemble traces included CS memory trace (Fig. 2B), US memory trace (Fig. 2C), US-to-CS associative trace (Fig. 2D), and CS-to-US associative trace (Fig. 2E). (F) Correlation between the retrieved memory traces and freezing within the mouse during the contextual retention test. (G) Correlation between the retrieved memory traces and freezing behavior during recall as a group. The figure is adopted from Chen et al. (2009).
coding cell assembly organization

The hippocampus is widely known to be crucial for the formation of declarative memory which can be further divided into episodic memory and semantic memories (Squire & Zola, 1998; Tulving, 1972). The essence of episodic memory is in its specificity in term of representing a specific event in a given time and context (Tulving, 1972), whereas semantic memory is the memory of the personal semantics and world knowledge of facts that are no longer ascribable to any particular occasion in life (Cohen & Eichenbaum, 1993; Squire & Zola, 1998; Tulving, 1972). fMRI studies in healthy humans have shown that the hippocampus is activated during the encoding and retrieval of both episodic memory and semantic memories (Burianova & Grady, 2007; Duzel et al., 1999; Kapur, Friston, Young, Frith, & Frackowiak, 1995; Maguire, Frith, Rudge, & Cipolotti, 2005; McIntosh, Harrison, Forrester, Lawrie, & Johnstone, 2005; Ryan, Cox, Hayes, & Nadell, 2008).

To seek the understanding of the memory organizing principles how the hippocampus encodes and organizes episodic and semantic memories, we designed a set of novel categorical behavioral paradigms to mimic how human would acquire long-term memories (i.e. roller coaster rides, earthquakes, etc.) (Tsien, 2007). By subjecting the mice to these distinct fearful episodic events (such as Drop, Quake, Air-blow), we found diverse changes in the firing of CA1 neuron population (Lin et al., 2005). We show that these episodic events resulted in distinct CA1 ensemble encoding patterns that can be reliably classified (Lin et al., 2005). Similar, these ensemble traces were found to reverberate within seconds after the episodic stimulation (Lin, Osan, et al., 2006; Lin et al., 2005).

To provide an overall view of how CA1 cell populations are organized to process and represent diverse episodic memories, we have employed a pattern classification method known as agglomerative hierarchical clustering which led to the discovery of various cell groups in the CA1 region, invariably ranging from specific to general coding responsiveness (Chen et al., 2009; Lin, Osan, et al., 2006; Lin et al., 2005; Osan et al., 2007 (Fig. 3A)). That is, each group of cells that respond similarly to a select event or feature and thus operate collectively as a robust functional coding unit, termed as neural clique. For example, under the experimental paradigms of subjecting the mice to drop, earthquake, and air-blow, some of CA1 cells exhibit an increase in firing rate to all three types of emotionally charged events, and these cells were termed as general neural clique (Fig. 3A). Other CA1 cells responded to a subset of multiple events (i.e. two events such as Drop/Quake clique, Drop/Air-blast clique, etc.), and they were termed as sub-general neural cliques. Many cells showed firing changes specific to one type of event (i.e. “Air-blow clique”, “Drop clique”, and “Quake clique”) and acted as event-specific neural cliques. Moreover, we found a small portion of the cells which exhibited not only event-specificity, but also context-specific firing changes (e.g. responding only to the earthquake happened in environment-A but not in environment-B) (Fig. 3A). These cells are known as event/context-specific cliques. These event/context-specific cliques encode and integrate specific information about both “what” and “where”, another hallmark feature of episodic memory. Therefore, by designing novel behavioral paradigms coupled with mathematical analyses, we have discovered that each episodic event is actually represented by a set of neural cliques in the CA1 that are invariantly organized from specific to general manner (Fig. 3B).

6. Uncovering of specific-to-general and categorical feature-coding cell assembly organization

This specific-to-general feature coding neural clique assemblies suggest a number of emergent organizing principles that govern memory organization in the brain (Tsien, 2007) (Fig. 3C): First, members of a given clique that share the similar response property and selectivity exhibit collective co-spiking dynamics that enables them to overcome the trial-to-trial response variability of individual neurons as an emergent network-level property. This allows the memory coding units to achieve not only real-time encoding robustness but also be much less vulnerable to the deaths of one or a few member neurons during the ageing process or under disease states.

Second, various neural clique assemblies are further organized in a categorical manner, thereby providing the network-level mechanism for efficiently organizing various memories. Because the memory coding is categorically and hierarchically organized, representing new episodic experiences might simply involve substituting the specific cliques that form the bottoms of the memory pyramids to indicate, for example, that the earthquake took place in Los Angles rather than in Kyoto.

Third, the hippocampus relies on memory-coding neural cliques to not only record and extract specific details, but also to extract sub-common or common features from different events via these general and subgeneral neural cliques. The general clique may encode abstract and generalized knowledge indicating that “the events such as drop, earthquake and sudden air blow are all scary events”; whereas the earthquake/drop-subgeneral clique may encode the semantic knowledge that “those events involve motion disturbances (Fig. 3C). It would be of great interest to define from which brain sub-regions these cells received the common or subcommon input (i.e. amygdala and/or VTA dopamine neurons) (Wang & Tsien, 2011).

For example, Frey and her colleagues described the requirement of specific neuromodulatory inputs to hippocampal neurons to transform a short-term into a long-term memory by means of ‘synaptic tagging’ (Frey & Frey, 2008; Frey & Morris, 1998). Efferent associations to hippocampal neurons – for instance from the amygdala or the VTA within a distinct effective time window – are necessary processes to make a transient memory trace permanent. It was shown that each of these neuromodulators may act as an associative evaluation tool required for the long-term memory formed. A given neuromodulator system is thereby specifically activated in response to and if, for instance, a reward- or novelty- associated stimulus. These brain subregions may thus contribute to evaluate the meaningfulness of an afferent stimulus to a particular glutamatergic synapse population and transform the transient into a permanent memory trace (Frey, Bergado-Rosado, Seidenbecher, Pape, & Frey, 2001; Frey & Frey, 2008; Frey & Morris, 1998). Using more sophisticated techniques – such as VTA-specific optogenetic stimulation – one could study now more specifically the role of a single modulator on hippocampal clique behavior and what “flavor” of memory is encoded by a given neuromodulator within a specific set of neurons.

The notion that the hippocampus encodes generalized semantic knowledge is further supported by our recent finding for the existence of hippocampal cells in encoding of the abstract concepts for nest (Lin, Chen, Kuang, Wang, & Tsien, 2007). These ‘nest cells’ exhibited invariant coding properties during episodic exploration of nest-like objects, over many variations in nest’s shape, material type, color, odor, or locations. Our have shown that these nest cells reply on episodic encounters or experiences to determine the object’s functionality as nest (Lin et al., 2007) In fact, recordings in monkey hippocampus also reported category-encoding cells (Hampson, Pons, Stanford, & Deadwyler, 2004).

7. Parametric analysis of CA1 episode cell assemblies underlying memory consolidation

While our brains can recall a great amount of detail immediately after the event (within the time domain of short-term
memory), there appears to be a gradual loss of many specific details over the long-term memory time domain. To investigate the neural network mechanism underlying this biased consolidation process, we used the same set of fearful events (drop, earthquake, air-blow, etc.) but varied these events' intensities or durations as a way of introducing additional details about these episodes (Osan, Chen, Feng, & Tsien, 2011). For example, we varied drop heights at 5 cm, 13 cm and 30 cm, or air-blow with 200 ms, 400 ms and 800 ms durations. We found that many hippocampal cells (51.3% of all responsive cells) exhibited intensity-sensitive changes, termed as event intensity-sensitive neurons (Fig. 4A and C). In contrast, other CA1 cells (48.7% of all responsive cells) showed similar changes in their firing rates irrespective of the magnitude of the stimulus inputs, and they were termed as intensity-invariant cells (Fig. 4B and C). Non-responsive units are grouped in the bottom half. The color scale bar indicates the normalized response magnitude (1–7). (B) A given episodic event activates a neural clique assembly invariantly organized from specific-to-general. (C) Categorical and hierarchical representation of episodic and semantic information by the specific-to-general feature-coding neural clique assemblies.

8. How can we close the knowledge gap between episodic event cells with place cells and time cells?

One of the fundamental questions in the field of learning and memory is to understand how the hippocampus generates long-term memories of what, when, and where. The studies on place cells and grid cells have provided crucial lights on how the where information such as self-location is represented (Buzsaki & Moser, 2013; Kentros, 2006; Lisman & Redish, 2009; McNaughton et al., 2006; Mizumori, 2006; Oler et al., 2008; Redish, 2001; Smith & Mizumori, 2006). Emerging studies have indicated that some of the hippocampal cells encode time information (Chen et al., 2009; Kraus, Robinson, White, Eichenbaum, & Hasselmo, 2013; MacDonald, Lepage, Eden, & Eichenbaum, 2011). Our recent work has shown that the existence of real-time working memory trace for time in the CA1 that predicts the arrival time of foot shock upon hearing the recall tone during trace fear conditioning retention test (Chen et al., 2009). These working memory traces intrinsically captured both the organization of time and event. In addition to our finding of these event-related time cells, Eichenbaum and his colleagues have reported the existence of place-related “time cells” in the CA1. Those cells fire at particular moments during periods when running behavior and location are relatively constant (MacDonald et al., 2011). They recently showed that hippocampal neurons were strongly influenced by time and distance, and less so by minor variations in location (Kraus et al., 2013). They further suggest that hippocampal neuronal networks captured both the organization of time and distance in a situation where these dimensions dominated an ongoing experience. In light of these observations, the above emerging studies collectively suggest that time cells in the CA1 are highly integrated, containing information on either the event and/or distance information.

As to the representation of “what information” in the hippocampus, our recent studies of episode cells responding to earthquake, free fall, and air blast have uncovered how the dramatic
events are encoded and organized in the hippocampus. In addition to study the relationship between episodic memory and semantic memory, one of the major future directions should be to establish protocols and design new experiments that can allow researchers to link these event cells with place cells, two separate yet intrinsically coherent aspects of hippocampal memory engrams.

A recent study from Schnitzer's laboratory used a calcium imaging technique to track activity from more than a thousand CA1 units over the course of a month during repeated exposures to a familiar environment (Ziv et al., 2013). They reported only limited place field overlap between repeated sessions in the same context, and interestingly, almost no cells showed truly stable place fields across more than two exposures. While there are many potential explanations from the purely place cell perspective (i.e. stable place fields), one alternative consideration or interpretation is that activity patterns of many place cells during these daily running sessions may be easily influenced by episode cells which are designed to respond to both specific details and discover generalized episodic information over a month. This is similar to our own experiences when driving to work every day, there is always something different or new to notice or pay attention to along the way.

9. Can the mouse brain study inform us about the human brain?

Our discovery of specific-to-general and categorical feature-coding neural clique assembly in the mouse hippocampus offers a crucial insight how the memory circuit generates both episodic memory and semantic knowledge simultaneously. This explains why humans with hippocampal damage show profound deficits in the acquisition and retrieval of both new semantic and episodic memory (Hodges & Graham, 2001; Messas, Mansur, & Castro, 2008; Tranel, Damasio, & Damasio, 1997; Warrington & Shallice, 1984). Moreover, the significant percentage of general and subgeneral neural cliques in the hippocampus fits well with various anatomical observations that the human hippocampus also receives higher-order, multimodal cortical and subcortical inputs, and is well suited to process abstract memories.

Shortly after our large-scale recording revealed the specific-to-general categorical organization of neural cliques in the mouse hippocampus (Lin et al., 2005), Fried and his colleagues has reported that the existence of cells in the human hippocampus responding to abstract recognition of people identity (Quiroga, Reddy, Kreiman, Koch, & Fried, 2005). For example, they showed that a hippocampal cell from a patient was selectively activated by pictures of the actress Halle Berry, a drawing of her, several pictures of Halle Berry dressed as Cat woman, and even the letter string ‘Halle Berry’, but not by images of other people. This Halle Berry-specific cell apparently encodes the identity about Halle Berry. The same research team later also found another neuron in yet another patient’s hippocampus was activated by pictures of Jennifer Aniston and Lisa Kudrow, both actresses in the TV series ‘Friends’ (Quiroga, Kreiman, Koch, & Fried, 2008), which are clearly
related to the sub-common themes. These human neurophysiological data, although obtained from serial recording from different human subjects, support our conclusion for the existence of the specific-to-general and categorical feature-coding cell assembly organization in the memory system.

Moreover, emerging data from human neuroimaging study on cortical connections show the strikingly common structural and functional cortical architecture across individuals and populations. Using diffusion tensor imaging (DTI) techniques, Tianming Liu and his colleagues have reported a dense and consistent map of 358 cortical landmarks, named Dense Individualized and Common Connectivity-based Cortical Landmarks (DICCCOL) (Fig. 5). Each DICCCOL is defined by group-wise consistent DTI-derived white-matter fiber connection patterns (Zhu et al., 2013). Remarkably, these 358 landmarks are reproducible over more than two hundred human brains, and possess accurate intrinsically-established structural and functional cross-subject correspondences. For example, the fear network in the human brain contains 14 nodes (including the amygdala and insular cortex, etc.) in the atlas space that were activated by task-based fMRI (Fig. 5A). These DTI-derived fiber connections show diverse yet distinct convergent patterns across these corresponding brain regions (Yuan et al., 2013; Zhu et al., 2013) (Fig. 5B). Such conserved structural and functional architecture would provide neural substrates for the specific-to-general feature processing cell assemblies at each node (Fig. 5C). Encouragingly, our finding of specific-to-general cliques seem to map on nicely to the recently published fMRI findings from Schacter group in linking hippocampal activation with recombination of episodic elements using an ‘experimental recombination task (Addis, Pan, Vu, Laiser, & Schacter, 2009). This human fMRI study provides some fairly direct and striking empirical evidence in support of our proposed cellular organizing mechanism.

With this specific-to-general feature cell assembly architecture across many different cortical sites, the brain can use a combinatorial activation strategy to generate an almost unlimited number of global patterns representing both specific memory and generalized knowledge of events, object, people, and environments. More importantly, the same mechanism can be employed to create the infinite number of fictitious or future events, actions, or experiences during the imagination (Fig. 5D). This combinatorial strategy is similar to the way that DNA uses combinations of four deoxyribonucleotides (A, T, G, C) to encode diverse genetic information or the immune system uses combinatorial rearrangement of immunoglobulin gene segments to generate diverse antibodies for dealing with various antigens that the animals may encounter in life. Likewise, under the abnormal conditions (i.e. genetic mutations affecting connectivity patterns in schizophrenic patients), incorrect combinatorial activations of the neural clique assemblies would lead to delusional thoughts or nightmares (Fig. 5E).

10. Conclusion

Innovative behavioral paradigms and appropriate mathematical analyses of large datasets obtained from neural ensemble recordings have enabled us to decode real-time associative memory traces in the hippocampus. It also led to the discovery of specific-to-general feature-coding and categorical cell assembly organization in the memory system which can explain how the brain generates not only episodic memory, but also semantic knowledge and imagination. By mapping neural activity in a brain-wide fashion, scientists should uncover many more emergent properties of the neural networks that generate real-time perception, memory, knowledge, and behaviors. Moreover, by comparing the brain

Fig. 5. Specific-to-general cell assembly architecture for building other high cognitions in the brain. (A) Fear network in the human brain mapped by fMRI. The cyan spheres represent the fear network activated by task-based fMRI (a total of 14 nodes is identified). The green spheres are 358 DICCCOL (dense individualized and common connectivity-based cortical landmarks) landmarks. The cyan and yellow landmarks represent the fear network activated by task-based fMRI. They are located in the Brodmann areas 2, 7, 9, 10, 19, 21 and 43. The green spheres are other DICCCOL landmarks. Additional information is referred to Zhu et al. (2013). (B) The consistent DTI-derived fiber connections to the yellow cortical landmark are shown in color curves. (C) Schematic illustration of general, subgeneral and specific cells that compose the yellow cortical landmark in B. Additional details of the fMRI task design and landmark mapping are in Zhu et al., 2013, Cerebral Cortex. (D) Imagination and creative thoughts can be generated from coherent combinatorial co-activation of various neural cliques from different cell assemblies. (E) Delusional thoughts or nightmares can be produced by inappropriate combinatorial co-activation of various neural cliques from various cell assemblies.
activity patterns between the normal and the mutant mouse models and dysfunctional human brains, scientists can further discover aberrant circuitry dynamic patterns underlying various brain diseases including schizophrenia and posttraumatic stress disorder. Such knowledge should lead to better and more efficient development of novel treatment for these brain diseases in future.

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