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On brain activity mapping: Insights and lessons from Brain Decoding Project to map memory patterns in the hippocampus

TSIEN Joe Z.[1*], LI Meng[1], OSAN Remus[2], CHEN GuiFen[3], LIN LongNian[4], WANG Phillip Lei[1], FREY Sabine[1], FREY Julietta[1], ZHU DaJiang[5], LIU TianMing[5], ZHAO Fang[1,6] & KUANG Hui[1,6*]

[1]*Brain and Behavior Discovery Institute, Medical College of Georgia, Georgia Regents University, Augusta, GA 30912, USA;*
[2]*Department of Mathematics and Institute of Neuroscience, Georgia State University, Atlanta, GA 30303, USA;*
[3]*Department of Cell and Developmental Biology, University College London, London WC1E 6BT, UK;*
[4]*Shanghai Institute of Brain Functional Genomics, East China Normal University, Shanghai 200062, China;*
[5]*Department of Computer Science & Bioimaging Research Center, The University of Georgia, Athens, GA 30602, USA;*
[6]*Brain Decoding Center, Banna Biomedical Research Institute, Xi-Shuang-Ban-Na Prefecture, Yunnan 666100, China*

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The BRAIN project recently announced by the president Obama is the reflection of unrelenting human quest for cracking the brain code, the patterns of neuronal activity that define who we are and what we are. While the Brain Activity Mapping proposal has rightly emphasized on the need to develop new technologies for measuring every spike from every neuron, it might be helpful to consider both the theoretical and experimental aspects that would accelerate our search for the organizing principles of the brain code. Here we share several insights and lessons from the similar proposal, namely, Brain Decoding Project that we initiated since 2007. We provide a specific example in our initial mapping of real-time memory traces from one part of the memory circuit, namely, the CA1 region of the mouse hippocampus. We show how innovative behavioral tasks and appropriate mathematical analyses of large datasets can play equally, if not more, important roles in uncovering the specific-to-general feature-coding cell assembly mechanism by which episodic memory, semantic knowledge, and imagination are generated and organized. Our own experiences suggest that the bottleneck of the Brain Project is not only at merely developing additional new technologies, but also the lack of efficient avenues to disseminate cutting edge platforms and decoding expertise to neuroscience community. Therefore, we propose that in order to harness unique insights and extensive knowledge from various investigators working in diverse neuroscience subfields, ranging from perception and emotion to memory and social behaviors, the BRAIN project should create a set of International and National Brain Decoding Centers at which cutting-edge recording technologies and expertise on analyzing large datasets analyses can be made readily available to the entire community of neuroscientists who can apply and schedule to perform cutting-edge research.

BRAIN project, Brain Decoding Project, brain activity map, learning and memory, episodic memory, semantic knowledge, imagination, concepts, fear conditioning, earthquake experiences, neural code

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Donald Hebb [1] postulated that information processing in the brain may involve the coordinated activity of large numbers of neurons, or cell assemblies. Brain researchers have been pursuing this idea from the computational and cellular perspective, but the progress has remained embar-

*Corresponding author (email: jtsien@gru.edu; hkuang.y@gmail.com)

rassingly limited [2–9]. The major challenge to date is 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.

Starting in 1920s, brain scientists began to search for reliable correlation between firing patterns of neurons and behavioral functions for many decades [10–14]. Edgar Adrian [10] 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 (which led to his Nobel prize in 1932), 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 [15,16], 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 [17].

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 [18–20]. With technical developments over the past decades, simultaneous monitoring of activities of many neurons has become more feasible [21–24]. For example, Georgopoulos and his colleagues [25] were among the first to apply a population-vector method to analyze ensemble firing patterns corresponding to arm movements of monkeys. 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. This has led to great progress for brain-machine interface-based movement control [26–29]. Similarly, the discovery of place cells in 1970s has prompted many researchers to examine how the hippocampus encodes space [30,31]. Multiple tetrodes techniques have been successfully applied to the study of several dozens of place cells in the rat hippocampus [32]. This has led to extensive knowledge of how the hippocampus may generate perceptual representation of the animal's self-location during spatial navigation [33–37]. Yet it remains controversial as to whether motion-sensitive place cell firing would represent part of long-term episodic memory for which the hippocampus is famously known.

In parallel, molecular genetics became increasingly powerful to the study of genes, circuits, and behaviors, Tsien and his colleagues [38,39] pioneered cre/loxP-mediated region- and cell type-specific genetic technology in mid 1990s. This Cre/loxP conditional method [38] has also become a basic platform for opsin-based optogenetics to manipulate a cell type(s) in the networks. With such genetic tools, our team has provided some of the earliest evidence that memory in mice can be impaired, enhanced, or rapidly erased by genetic means [39–44]. This has led us to ponder some of the more fundamental questions in memory field: what is real-time memory engram? What are the organizing principles for memory-coding cell assemblies in the hippocampus? How does the memory circuit generate not only episodic memory but also semantic knowledge and imagination?

1 Brain Decoding Project Initiative for creating brain activity map of memory engrams

It became apparent that the understanding to the above fundamental questions would require large-scale decoding of brain activity patterns [45]. Thus, in the late 2007, with strong support from Georgia Research Alliance, we have launched the Brain Decoding Project Initiative to identify brain dynamics (http://gra.org/Stories/StoryDetail/tabid/ 622/xmid/632/Default.aspx). The basic idea of our Brain Decoding Project, now similarly expressed behind Brain Activity Map proposal [46], is to investigate and discover the underlying organizing principles by which the brain generates real-time perception, emotion, memory, knowledge, and behavior.

Over the course of past several years, we have focused our initial efforts on three different but coherently linked aspects: (i) using large-scale neural recording techniques to collect large datasets on memory process in the mouse hippocampus; (ii) using a set of well-designed behavioral paradigms to facilitate the discovery of memory organizing principles; (iii) applying and testing mathematical tools that are suitable for identification of neural ensembles activity patterns and uncovering its underlying cell assembly structures. Here, we share some of the insights and lessons which we believe may be useful to the planning of the BRAIN project that is currently underway.

2 Large-scale neural recording capacity: how large is large enough to get started?

The 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 [46]. Some researchers questioned whether recording all spikes from all neurons in the brain is necessary for studying the brain's emergent proper-

ties [47]. While collecting such complete information would be ideal, the true essence of the BRAIN project is to crack the brain code and establish its organizing principles. How can we estimate the sizes of the recorded neurons that would permit researchers to approach this decoding problem?

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 [48–50]. Little is known about its detailed action on dynamic patterns of hippocampal cells *in vivo*. 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. Based on published criteria, we can classify the recorded interneurons into at least seven major types, including known and unknown types of interneurons, based on their distinct firing patterns and compare with the *in vitro* results (Figure 1A–C) [51].

Type-1 and type-2 interneurons were putative basket cells and bistratified cells according to the characteristics of these cells [48,49,52] (Figure 1C). These cells innervate pyramidal cell somas and dendrites. Type-3 and type-4 interneurons matched well with firing characteristics of

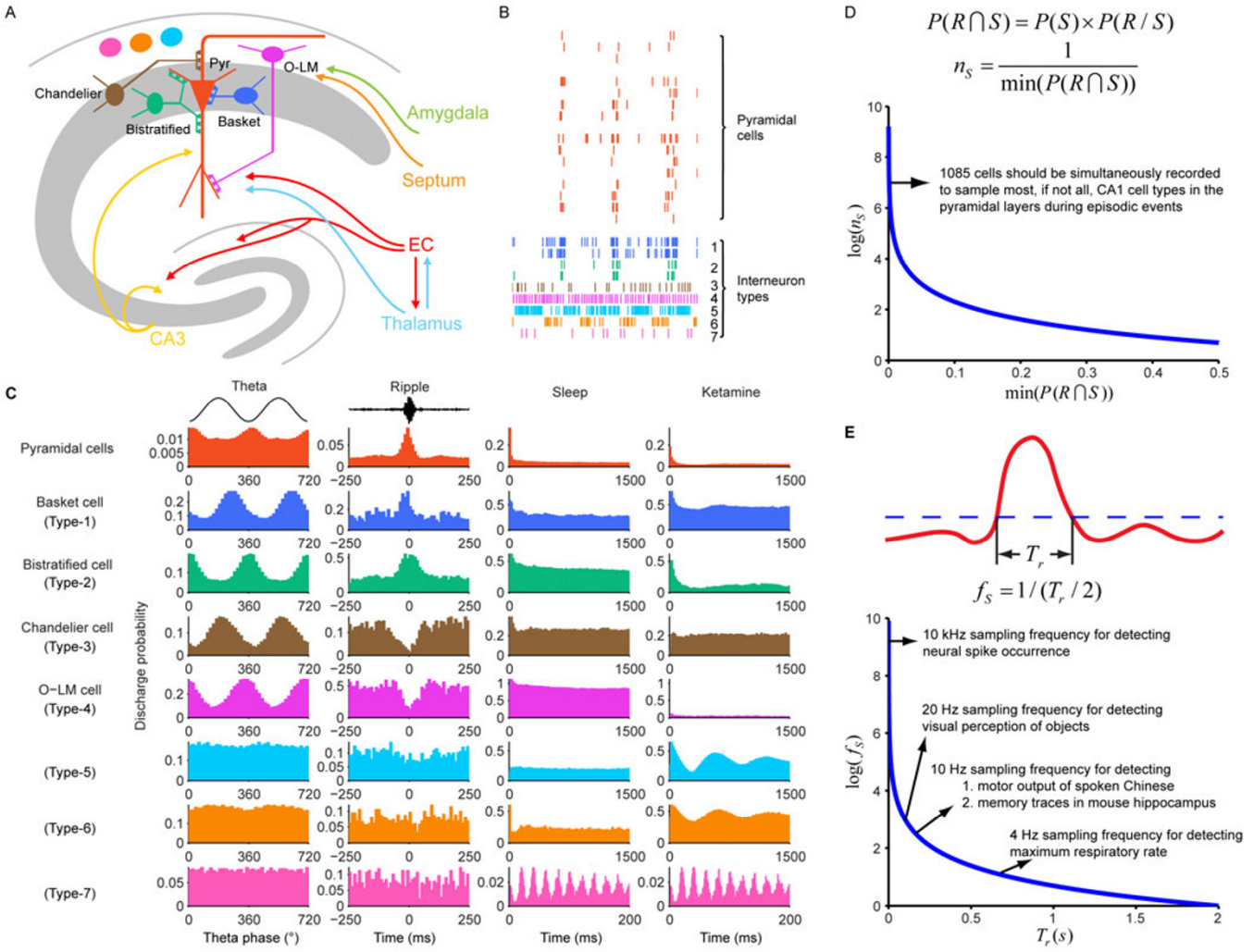

Figure 1 Diverse neuron types in the hippocampus and theoretical consideration for brain activity mapping. A, Illustration of diverse neuron types in the CA1, which include pyramidal cells (pyr), PV-expressing basket cells, bistratified cells, Chandelier cells, O-LM cells, and other unidentified interneuron types. O-LM cell, Type-5, type-6, and type-7 interneurons are located in the str. oriens. B, 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 columns 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. [51]. 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 calculation. 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, 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.

Chandelier cells and O-LM cells (Figure 1C), respectively. These putative Chandelier cells and O-LM cells interneurons tended to fire during the period when pyramidal cells were silent. These four types of interneurons all exhibited dynamic relationships with the theta and ripple episodes which provided the characteristic classifications to their putative identities [48,49,53]. 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), they may correspond to the trilaminar cells, back-projection cells, and hippocampo-septal cells [48,49,52,54]. Their firm identifications, however, remain to be determined (Figure 1A–C).

Using the above neuron types as an example, we can ask how many neurons should be recorded simultaneously in order to obtain the activity map of a CA1 circuit-processing unit 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 we assume small numbers of interneurons have broad control or regulation over large numbers of pyramidal cells, we 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 uses subgroup-sampling methods at multiple locations and depths to obtain the meaningful estimation. This same principle can be readily applied to Brain Activity Map project, that is, instead of measuring every spike from every neuron, we may reveal the fundamental properties of the neural circuit by performing well designed sampling.

Here we illustrate that minimum size of feature-coding neurons can be estimated from neurons' distribution in a network population involved in memory processing. As shown in Figure 1D, $P(R \bigcap S) = P(S) \times P(R/S)$, where $P(R \bigcap S)$ is the joint probability of events that recorded neurons pertain to certain neural types and would be also responding to or encoding a set of given stimuli, $P(S)$ is the probability of the events that recorded neuron pertains to certain neural type(s) (i.e., pyramidal cells, ~63%; basket cell, ~2%, etc.) and $P(R/S)$ is the probability of the events that recording certain type neuron responding to stimulus (i.e., ~20% of pyramidal cells reacted to fearful stimuli, etc.). Minimum size of recording neurons (n_S) is defined as the inverse of the minimum $P(R \bigcap S)$ among all types of neuron, with the relationship of $\log(n_S)$ and $\min(P(R \bigcap S))$ shown in Figure 1D.

Based on our recording in the mouse CA1 region during behavior, the joint probability $P(R \bigcap S)$ for recorded pyramidal cells, basket cells, bistratified cells, busty cells, and chandelier cells responding to fearful stimuli are 6.8%, 1.3%, 1.9%, 1.8%, and 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 our 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 circuit processing unit can be updated correspondingly. It is noteworthy to point out that the size of recorded units will increase substantially for estimating cross-region interactions (i.e., DG-to-CA3-to-CA1). The estimation can also vary greatly depending on the position of electrodes at the different depths.

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

The meaningful brain activity mapping requires high temporal resolution. The gold standard of neural activity measurement is a variety of *in vivo* microelectrodes (i.e., tetrode) 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 Figure 1E (the upper drawing), the red curve denotes the states in neural population and an event occurs beyond the threshold (blue dashed line), and the length of this event is T_r. To detect this hypothetical event, the minimum temporal resolution of calcium imaging or other recording methods is the inverse of half T_r, $f_S=1/(T_r/2)$. The relationship between $\log(f_S)$ and T_r, and five examples are shown (Figure 1E, bottom plot). In the case of detecting two individual neural spike, 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. A much higher sampling frequency, however, is required if one wants to reconstruct the all 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 min^{-1}), a minimum 10 Hz sampling frequency will then be needed. Similarly, our memory decoding shows that the shortest time

duration of CA1 memory traces is ~0.2 s, thus sampling frequency should be ideally at or higher than 10 Hz.

At the moment, calcium imaging techniques based on GCaMPs have been used to study neural activity associated with animal behaviors [55,56]. Yet, the temporal resolution of calcium imaging is very low, at the sampling frequency of 0.1–0.25 Hz (which was inherently due to long durations of calcium transient wave which can be as long as 4 to 10 s, presumably triggered by multiple action potentials). It will need at least 40- to 100-fold of improvement in GCaMPs in order to reveal many valuable details of neural dynamics. Of course, calcium buffering and potential interferences of intracellular signaling process may represent other concerns. One promising direction is the voltage-based imaging techniques. Another unsolved issue is how to simultaneously identify a variety of interneurons types from the imaging view field.

4 Decoding real-time fear memory traces in the mouse hippocampus

The hippocampus is well known for its role in the formation of long-term memories which are usually emotionally charged events, such as memories about a devastating earthquake or a fun tour at Disney World for humans, or in laboratory animals, such as fear conditioning memories [57–61]. To investigate real-time memory traces in the hippocampus, we have used a classical trace fear conditioning protocol by pairing a neutral tone with a mild foot-shock (a time interval of 20 s in-between) [59,62–67]. We employed 128-channel electrode array recording techniques to monitor 200–300 CA1 units simultaneously in mice [68,69]. 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 [45,70]. 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 [71]. We found that conditioned tone trace emerged quickly during learning (Figure 2A and B). More interestingly, as the conditioned tone trace emerged, 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 (Figure 2B). The emergence of such associative traces suggests that circuitry-level dynamics have captured nicely the CS-US causal relationship. More interestingly, these associative patterns required the repetition of CS/US pairings, and can appear as early as the second pairing and become prevalent during the late stage of learning phase in all animals (Figure 2C) [71]. Importantly, memory traces occurrence frequency correlated nicely with the immediate freezing behavior of the animals.

To examine whether these CA1 traces observed during learning represent true memory traces, one need to show those patterns would be retrieved upon the recall cues and whether they would again correlate with behavioral performances. Indeed, we found that these CA1 dynamic patterns observed during CS/US learning phase reappeared at both contextual and trace fear retention tests [71]. On average, various CS and/or US memory traces were observed (Figure 2D and E) and retrieved at a rate of 8–14 times per minute in the mouse hippocampus during the fear memory retention tests [71]. 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 (Figure 2F). In trace retention test, we further found that upon hearing the conditioned tone, various memory traces re-emerged over the 60 s period (Figure 2D), but it was the US, not CS memory traces consistently reappeared at the time point of 20 s after the tone (Figure 2G and H) [71], thereby demonstrating that the animals formed the real-time memory trace of time for accurately predicting or recalling the anticipated arrival of foot shock. This memory trace for "what" at "when" information was detected in all six wild type mice (Figure 2I and J). Therefore, these large-scale recording decoding experiments have begun to uncover the identity and quantity of various real-time fear memory trace contents during learning and recall in the hippocampus.

5 Uncovering of specific-to-general and categorical cell assembly organization in the hippocampus

The hippocampus is widely known to be crucial for the formation of declarative memory which can be further divided into episodic memory and semantic memory [72,73]. The essence of episodic memory is in its specificity in terms of representing a specific event in a given time and context [72], 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 [72–74]. fMRI studies in healthy humans have shown that the hippocampus is activated during the encoding and retrieval of both episodic memory and semantic memories [75–80].

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., Tower of Terror

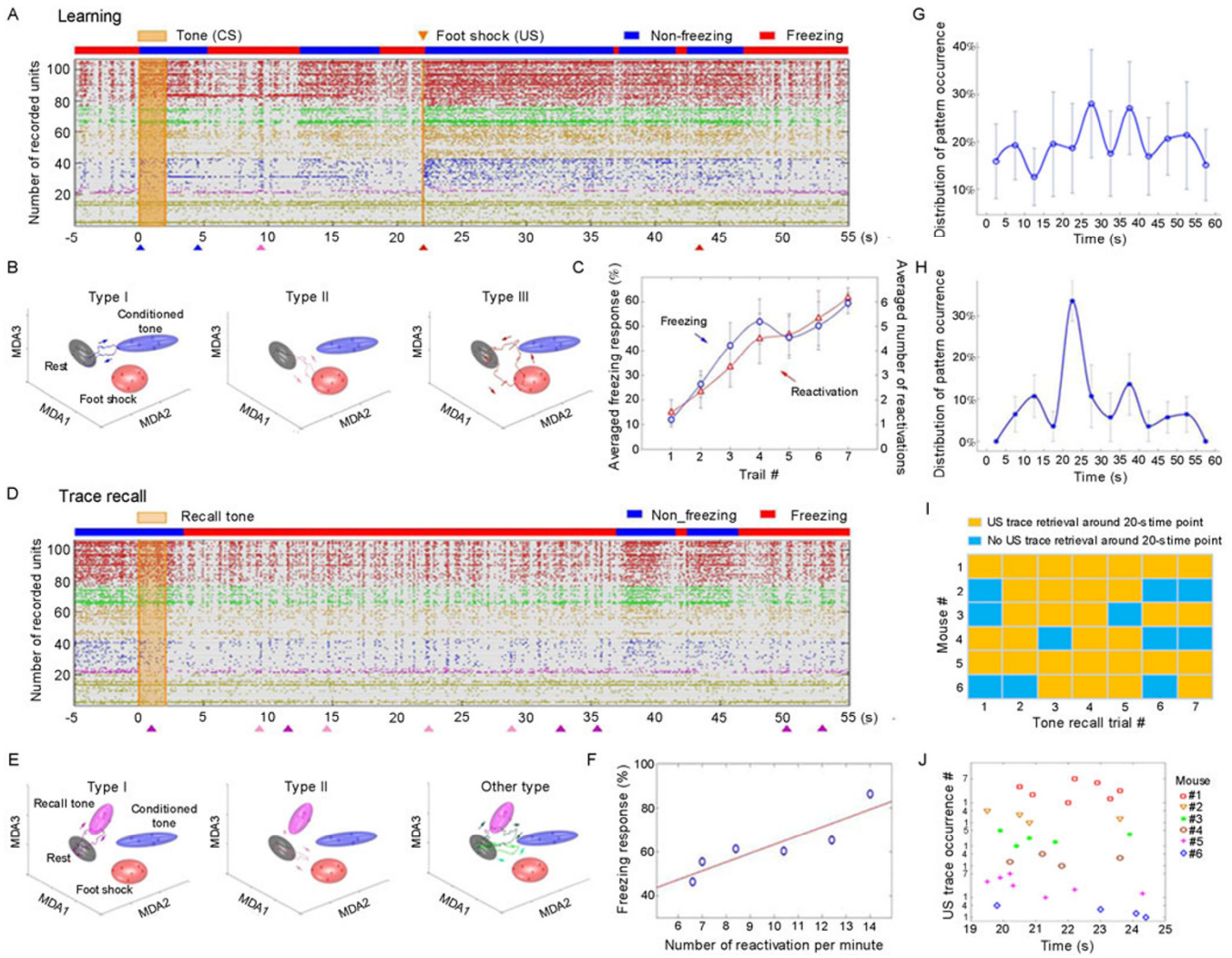

Figure 2 Real-time fear memory traces in the hippocampal CA1 region during learning and trace recall. A, Spike rasters of a selective set of CA1 units during the first CS-US pairing (105 units shown out of 208 simultaneously recorded units from a mouse). The different colors represent several groups of cells with different response properties. The units listed at the bottom were selected from the non-responsive group. The blue and red bars above the raster indicate the time period during which the mouse was in the non-freezing state or freezing state, respectively. Triangles at the bottom of the raster plot indicate the occurrences of various real-time memory traces during learning. Five traces were detected in this trial. B, The trajectories of three types of CA1 ensemble traces: CS trace (Type I), US trace (Type II) and US-to-CS associative trace (Type III). C, Learning trial-dependent increases in the number of memory trace reverberations and immediate freezing. D, The spike raster of the same set of CA1 units during the trace retention test. Presentation of the conditioned tone resulted in recalling a string of memory traces (shown at the bottom of the raster plot). Ten traces were retrieved in this recall trial. E, The trajectories of three types of memory: CS trace (Type I), US trace (Type II) and associative traces (other type). F, Correlation between the memory traces and freezing behavior during retention test. G, Time distribution of the averaged occurrences of ensemble tone traces over seven recall-trials in one representative mouse. Time zero indicates the moment when the recall tone was delivered. H, Time distribution of the averaged occurrences of ensemble shock traces over seven recall-trials in the same mouse. Time zero indicates the onset moment when the recall tone was delivered. The same analysis reveals a salient peak in the occurrences of the US trajectories around the traced interval time point which is around the 22 s. I, The color matrix shows the retrievals of the US ensemble traces in six individual wild-type mice around the traced interval time (20±2.5 s after the offset of the recall tone) at each of the seven trials. Yellow squares represent the occurrences of the correct US ensemble patterns, whereas blue squares indicate the absence of US patterns at the time point of this trace interval. J, The exact time distribution of the 31 correct US pattern retrievals around the traced interval time in all six mice. Please note that the 22-s time point is from the onset of the recall tone (which lasts 2 s). The figure is adopted from Chen et al. [71].

ride, earthquakes, etc.) [45]. Thus, we designed a set of distinct fearful episodic events (such as free fall Drop, Quake, Air-blow) to mimic such experiences. Our thinking-outside-of-the-box designs of episodic events such as earthquake and drop was highly risky at the time because the microdrive headstage fixed on thin mouse scalp may fall off or the electrode's stability may be compromised. With trial and error, we were able to stably record 200–300 of neurons and found diverse changes in the firing of CA1 neuron population [68]. We show that these episodic events resulted in distinct CA1 ensemble encoding patterns that can be reliably classified [68,71]. Similar, those ensemble traces were found to reverberate within seconds after the episodic stimulation [17,68,71].

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, invariantly ranging from specific to general coding responsiveness [17,68,70,71] (Figure 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 (Figure 3A). Other CA1 cells responded to a subset of multiple events (i.e., two events such as Drop/ Quake clique, Drop/Air-blow 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) (Figure 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 mathematic 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 (Figure 3B).

This specific-to-general feature coding neural clique assemblies suggest a number of emergent organizing principles that govern memory organization in the brain [45] (Figure 3C): First, members of a given clique that share the similar response property and selectivity exhibit collective co-

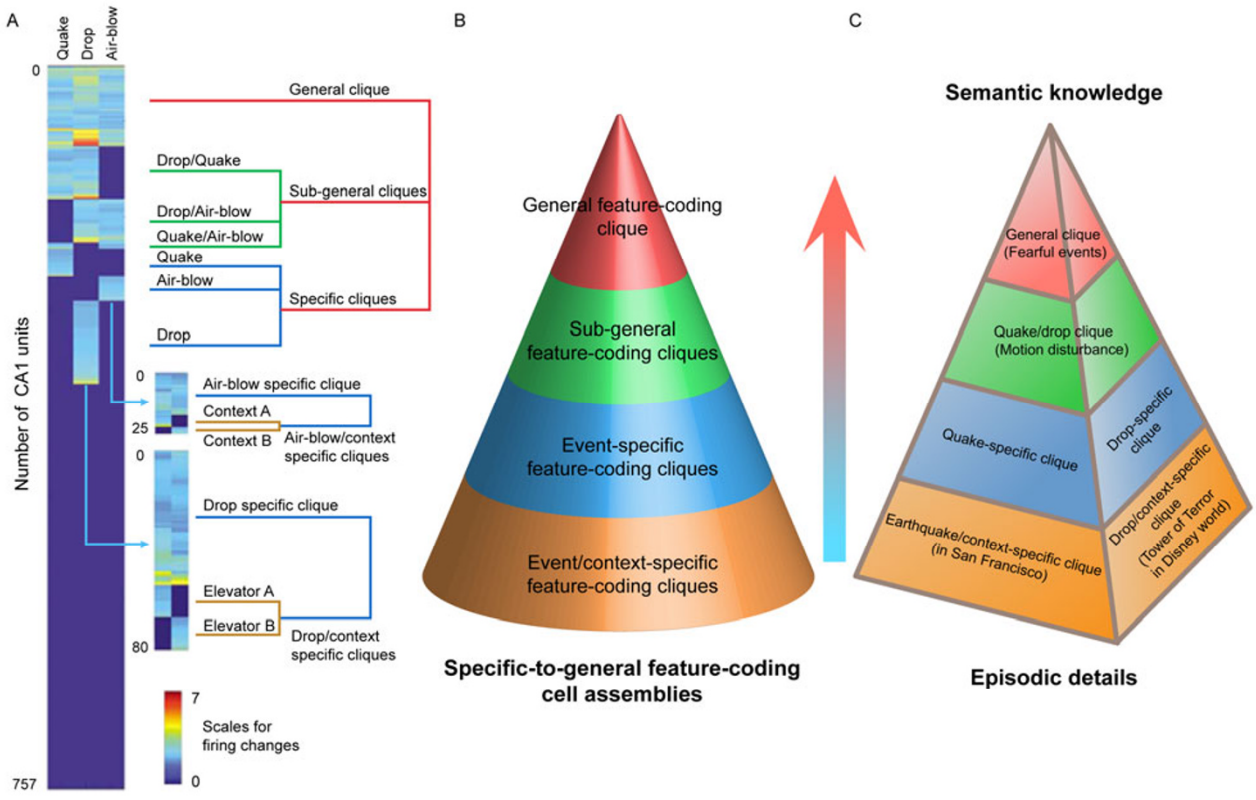

Figure 3 Categorical and hierarchical organization of the memory coding neural clique assembly. A, The hierarchical clustering analysis of responses of a total of 757 CA1 neurons from four mice to the three different types of startling episodes reveals the existence of seven major neural cliques (A): General responsive clique, sub-general cliques (Drop-Shake clique, Air blow-Drop cliques, Shake-Air blow clique), event-specific cliques (Drop-specific clique, Shake-specific clique, and Air blow-specific clique), and event/context-specific clique (Air-blow in context A-specific clique, Air-blow in context B-specific clique, Drop in Elevator A-specific clique, and Drop in Elevator B-specific clique). 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, Combinatorial and hierarchical representation of episodic and semantic information by the specific-to-general categorical feature-coding neural clique assemblies.

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 subcommon 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 (Figure 3C). It would be of great interest to define from which brain subregions these cells received the common or subcommon input (i.e., amygdala and/or VTA dopamine neurons) [81]. For example, Frey and her colleagues [82,83] 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'. 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 evaluating the meaningfulness of an afferent stimulus to a particular glutamatergic synapse population and transform the transient into a permanent memory trace [82–84]. 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.

Thus, 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 [85]. 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. We have shown that these nest cells reply on episodic encounters or experiences to determine the object's functionality as nest [85]. In fact, recordings in monkey hippocampus also reported category encoding cells [86].

6 Parametric analysis of CA1 episode cell assemblies for 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 [87]. For example, we varied drop heights at 5, 13 and 30 cm, or air-blow with 200, 400 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 (Figure 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 (Figure 4B and C). Interestingly, our detailed examinations using shuffling techniques suggested that post-learning pattern reverberations were primarily driven by event intensity-invariant cell groups, not by the intensity-sensitive cells (Figure 4D–I). Reduced participation by event intensity-coding cells in post-learning period may provide a mechanism for explaining why some parametric details may not be equally retained in the long-term memory domain [87].

7 Can the mouse brain study inform us about the human brain?

In general, our previous discovery of specific-to-general and categorical feature-coding neural clique assembly in the mouse hippocampus provided important insights into how the memory circuitry generates both episodic memory and semantic knowledge. For instance, this offers a new perspective about why human subjects with hippocampal damage exhibit profound deficits in the acquisition and retrieval of both newly obtained semantic and episodic memory [88–91]. In addition, the significant percentage of general

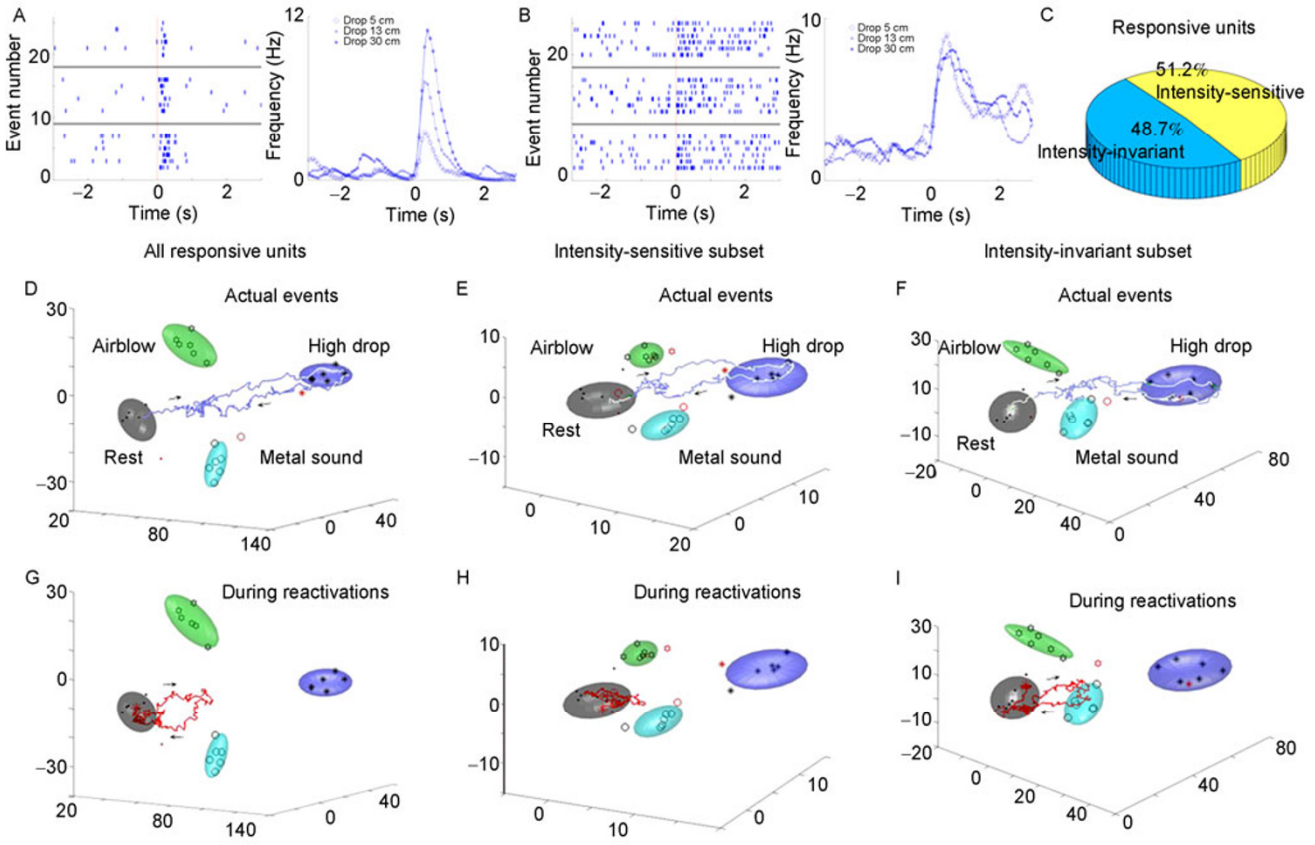

Figure 4 Pattern reverberations are mainly driven by the fearful event intensity invariant cell subpopulation, but by intensity-sensitive cell subpopulation. A, A representative CA1 unit encoded event-intensities through its increased firing changes to different drop heights from 5, 13 and 30 cm (upper, middle and lower raster, respectively). Time is represented on the horizontal *X*-axis (–3 to 3 s) and the trial number is listed on the vertical *Y*-axis. The vertical red line indicates *t*=0. B, A representative CA1 unit did not encode event intensity as it maintained firing rate monotonically in response to changes in drop heights. C, Percentage of event intensity-sensitive and intensity-invariant cells in the simultaneously recorded CA1 cell population. D, A typical trajectory during a drop event from 30 cm is plotted in MDA subspaces. E, Activation dynamics can be also observed in the MDA encoding subspaces which used only the event intensity-sensitive subpopulation of cells. F, Activation dynamics can be further observed in the MDA encoding subspaces constructed from the intensity-invariant subpopulation only. G, A typical reactivation trajectory is detected in whole population activity. H, However, at this time point little reactivation is observed in the intensity-sensitive subpopulation. I, In contrast, the intensity-invariant responsive subpopulation exhibits a significant reactivation. Please note that the directionality of trajectory towards the drop cluster and away from the air-blow cluster or acoustic metal sound is confirmed in other rotated 3-D dimensions. The figure is adopted from Osan et al. [87].

and subgeneral neural cliques in the hippocampus are consistent with various neuroanatomical observations that the human hippocampus also has higher-order, multimodal cortical and subcortical inputs, and is suitable to process abstract memories.

In a closely related study, Fried and his colleagues reported the existence of cells in the human hippocampus responding to abstract recognition of people identity [92], shortly after our large-scale neural recording data demonstrated the specific-to-general categorical organization of neural cliques in the mouse hippocampus [68]. For instance, they demonstrated that a hippocampal cell from a patient was selectively activated by the pictures of the actress Halle Berry, such as a drawing of her, several pictures of Halle Berry dressed as Cat woman, or even the letter string 'Halle Berry', but not activated by the pictures of other people. This Halle Berry-specific cell clearly encodes the identity of Halle Berry. Interestingly, the same research team later found another neuron in yet another patient's hippocampus that was activated by the pictures of Jennifer Aniston and Lisa Kudrow, both actresses in the TV series 'Friends' [93], which are clearly related to the sub-common themes. These human neurophysiological data, although obtained from serial recording from different human subjects, lend support to our conclusion about the existence of the specific-to-general and categorical feature-coding cell assembly organization in the memory system.

Recently, more and more data from human neuroimaging studies on cortical connections demonstrated the strikingly common structural and functional cortical architecture across individuals and populations. By using diffusion tensor imaging (DTI) techniques, Tianming Liu and his col-

leagues at the University of Georgia reported a dense and consistent map of 358 cortical landmarks, namely, Dense Individualized and Common Connectivity-based Cortical Landmarks (DICCCOL) (Figure 5). Each DICCCOL landmark is defined by group-wise consistent DTI-derived white-matter streamline fiber connection patterns [94]. Remarkably, these DTI-derived 358 DICCCOL landmarks are quite reproducible and predictable over more than 200 human brains, and exhibit accurate and robust intrinsically-established structural and functional cross-subject correspondences. For instance, the fear network in the human brain includes 14 nodes (including the amygdala and insular cortex, etc) in the brain atlas space that were activated by task-based fMRI (Figure 5A). It is interesting that these DTI-derived fiber connections exhibit diverse yet distinct convergent patterns across those corresponding brain regions [94,95] (Figure 5B). It is postulated that such conserved structural and functional architectures would possibly offer neural substrates for the specific-to-general feature processing cell assemblies at each node (Figure 5C). Encouragingly, our finding of specific-to-general cliques seem to map nicely onto the recently published fMRI findings from Schacter group in linking hippocampal activation with recombination of episodic elements using an 'experimental recombination task' [96]. This human fMRI study provides some arguably direct and striking empirical evidence in support of our proposed cellular organizing mechanism.

Based on the specific-to-general feature cell assembly architecture across many different cortical sites, it is postulated that the brain can possibly use a combinatorial activation strategy to generate an almost unlimited number of global patterns representing both specific memory and generalized knowledge such as events, object, people, and environments [45]. More importantly, the same mechanism can be potentially employed to create the infinite number of fictitious or future events, actions, or experiences during imagination (Figure 5D). In the conceptual level, this combinatorial strategy is akin to the way that DNA uses combinations of four deoxynucleotides (A, T, G, C) to encode diverse genetic information or the immune system uses combinatorial rearrangement of immunoglobulin gene segments to produce diverse antibodies to deal with various antigens. Similarly, under the abnormal conditions (i.e., genetic mutations affecting connectivity patterns in schizophrenic patients), wrong combinatorial activations of the neural clique assemblies would possibly lead to delusional thoughts or nightmares (Figure 5E).

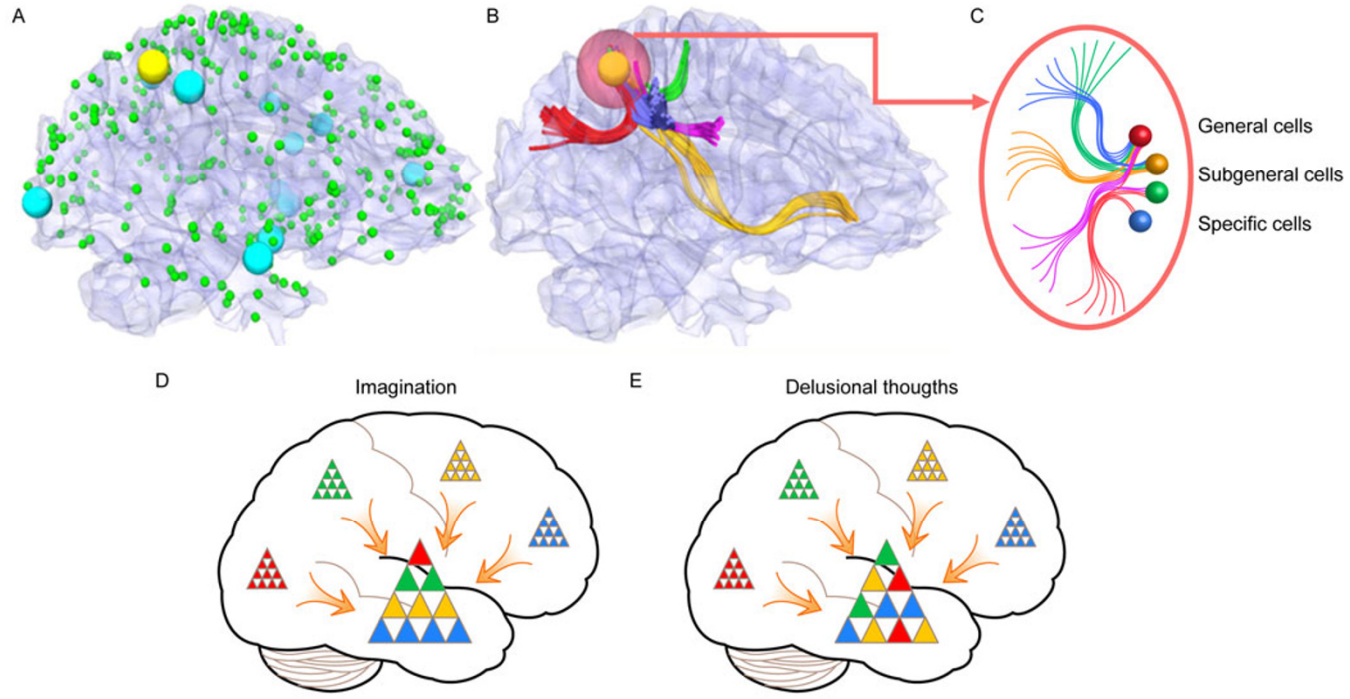

Figure 5 Specific-to-general cell assembly architecture for building other high cognitions in the brain. A, Fear network in the human brain mapped by fMRI. The cyan spheres represent the fear network activated by task-based fMRI (a total of 14 nodes is identified). The green spheres are 358 DICCCOL (dense 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. [94]. 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. [94]. D, Imagination 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.

8 Conclusion and future direction

Innovative behavioral paradigms and appropriate mathematical analyses of the large datasets 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 human brain generates episodic memory, semantic knowledge, and imagination. By developing various innovative techniques called by BRAIN project, scientists will be in a great position to map neural activity in a brain-wide fashion for uncovering many additional emergent properties underlying real-time perception, memory, knowledge, and behaviors.

As complex as each unique subject and subfield in neuroscience, it is not realistic to expect a small number of well-equipped and well-funded laboratories are going to have all the knowledge and expertise to solve all the brain problems. Our own experiences in hippocampal memory research suggest that the bottleneck of the BRAIN Project is not merely at developing additional new technologies, but can also be due to lack of efficient avenues to disseminate cutting edge platforms and decoding expertise to broad neuroscience community. Therefore, we propose that in order to harness unique insights and extensive knowledge from various investigators working in diverse neuroscience subfields, ranging from perception and emotion to memory and social behaviors, the BRAIN project should create a set of International and National Brain Decoding Centers at which cutting-edge recording technologies and expertise on analyzing large datasets analyses can be made readily available to individual neuroscientists who can visit and schedule to perform cutting-edge brain research.

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