

Organizing principles of real-time memory encoding: neural clique assemblies and universal neural codes

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Recent identification of network-level coding units, termed neural cliques, in the hippocampus has enabled real-time patterns of memory traces to be mathematically described, directly visualized, and dynamically deciphered. These memory coding units are functionally organized in a categorical and hierarchical manner, suggesting that internal representations of external events in the brain is achieved not by recording exact details of those events, but rather by recreating its own selective pictures based on cognitive importance. This neural-clique-based hierarchical-extraction and parallel-binding process enables the brain to acquire not only large storage capacity but also abstraction and generalization capability. In addition, activation patterns of the neural clique assemblies can be converted to strings of binary codes that would permit universal categorizations of internal brain representations across individuals and species.

Introduction

Exciting findings have emerged recently concerning the neural network-level organizing principles underlying real-time memory encoding and processing in the brain. The discovery of memory coding units, termed neural cliques, and their invariant assembly structures is beginning to provide a foundation for direct measurements and universal categorizations of memory codes across individual brains.

At the molecular and synaptic levels, a series of sophisticated molecular and genetic experiments have stringently validated Hebb's learning rule [1–6] and, furthermore, established that the NMDA receptor, which possesses the synaptic coincidence-detection function, is the key molecular switch for the acquisition, consolidation and storage of memories in the mammalian brain [7–12]. To explain how memory might be encoded beyond the level of synapses, Hebb postulated that information processing in the brain could involve the coordinated activity of large numbers of neurons or cell assemblies [1]. This notion, although vague, makes good sense from both

computational and cellular perspectives [2–6,13–15]. The major challenges to date have been to identify the actual activity patterns of a large neuronal population during cognition, and then to extract the network-level organizing mechanisms that enable the brain to achieve its real-time encoding, processing and execution of cognitive information.

Information conveyed by neural activity: rate code, temporal code or population code?

Neuroscientists try to decipher the neural codes of the brain by searching for reliable correlation between firing patterns of neurons and behavioral functions [16–20]. As early as the 1920s, Edgar Adrian in his pioneering recording showed that the firing rate of a frog muscle stretch receptor increases as a function of the weights on the muscle [16], suggesting that information is conveyed by specific firing patterns of neurons. Two leading neural coding theories can be found in the literature: a 'rate code' and a 'temporal code' [21–24]. In the rate code, all the information is conveyed in the changes of the firing of the cell; in the temporal code, information is also conveyed in the precise interspike intervals. However, owing to the large response-variability at the single-neuron level in the brain, even in response to identical stimuli [25,26], these two single-neuron-based decoding schemes often produce significant errors in predictions about the stimulus identities or external information.

A good example is that of the place cells in the hippocampus, which show 'location-specific' firing when an animal navigates through familiar environments [27]. The discharge of place cells is extremely variable during individual passes through their place fields [28]. Moreover, identification of place cells routinely requires additional data manipulations, such as excluding recording files corresponding to periods in which animals do not reach certain running speeds or in which they simply sit at that location. The traditional way to deal with the response variability of single neurons is to average spike discharges of the neurons over repeated trials. Although data-averaging across trials permits the identification of tuning properties of individual neurons, unfortunately

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this practice invariably loses crucial information regarding real-time encoding processes in the brain.

Early efforts in examining population-level mechanisms relied on the ‘reconstructed’ ensembles of neurons from serially, not simultaneously, recorded single-neuron data. Such ‘reconstructed population codes’ can improve the classification and prediction of datasets [29–31] (but see [32]). With technical developments, simultaneous monitoring of activities of many neurons has become more feasible [33–36]. In addition, Georgopoulos and colleagues were among the first to apply a population-vector method to analyze ensemble firing patterns corresponding to arm movements [37]. 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. Subsequently, this population-vector method has been successfully extended to other studies including place cells [38]. However, it is important to be aware that, because the population vectors in those studies were typically constructed from all cells (regardless of their responsiveness or unresponsiveness to stimulus inputs), the underlying assumption is that information is represented by the activities of every cell in the population (this is known as the ‘fully distributed population code’). Recognizing this potential pitfall, researchers have come up with a compromise between the fully distributed population code and the single-neuron code, and the properties of this ‘sparsely distributed population code’ have been explored using computation simulation methods [39].

Measuring neural responses in memory systems

Changes in discharge frequency or latencies of neurons upon learning are well known. Some of the earliest experiments came from *in vivo* recordings in the hippocampus [27,40], which is crucial for memory [41,42]. For example, pioneering studies by Thompson and colleagues show that classical eye-blink conditioning increases neuronal discharges in the hippocampus and cerebellum [40,43,44]. Such a learning paradigm is also reportedly associated with changes in latency responses or membrane potentials [45–47].

Another major focus in the study of hippocampal functions are hippocampal place cells [27,38,48–51]. Experiments suggest that place-cell activities are controlled by complex internal and external inputs and are modifiable by behaviors and long-term potentiation [52–58]. Various models, such as the rate code, temporal code, population code and reverberatory activity hypothesis, have been proposed to test further how the hippocampus might represent and process spatial information [38,59–61].

In addition, learning-related firing changes have also been found in the prefrontal cortex during working-memory-related tests [18–20]. The persistent neural activity has been a subject for much computational modeling, including models of recurrent excitation within cell assemblies, synfire chains and single-cell bistability (reviewed in [62]). Moreover, head-direction cells in the limbic system, which exhibit persistent neural activity in relation to the direction in which an animal is heading in space, have been another focus for both experimental investigation and computational modeling of underlying

mechanisms (reviewed in [63]). Thus, individual neurons in memory systems are clearly responsive to external inputs and have many interesting firing properties. In light of those studies, several fundamental questions arise. What is the network-level memory trace? Can the patterns of memory traces be visualized and decoded? Is there any organizing principle underlying the ability of the brain to achieve real-time memory encoding and processing?

Visualizing network-level memory traces in the brain

Recently, a large-scale ensemble recording technique in mice, coupled with novel categorical episodic memory paradigms and powerful mathematical tools, has been used to investigate the above questions [64]. The large-scale ensemble recordings have revealed that various robust episodic experiences, such as free-fall inside a plunging elevator (‘drop’), a sudden gush of air to the back of an animal (‘air-blow’), or earthquake-like shake of the home cage (‘earthquake’), can evoke diverse changes in the firing of some hippocampal CA1 cells (Figure 1).

Pattern-classification algorithms, namely multiple discriminant analysis (MDA) and principle component analysis (PCA) reveal that various startle-triggered ensemble responses of CA1 neurons form distinct patterns in a low-dimensional-encoding subspace – mathematical dimensions with the most discriminating features (Figure 2). Further application of a sliding-window technique (sliding through the recorded neural ensemble activity) to MDA or PCA methods enables us to directly visualize and dynamically monitor real-time network memory-encoding patterns (Figure 2a).

Interestingly, post-event processing of newly formed ensemble patterns can also be directly detected and precisely quantified (Figure 2b,c). These spontaneous reactivations of memory traces, represented by dynamic trajectories with similar geometric shapes but smaller amplitudes, seem to occur at intervals ranging from several seconds to minutes after a discrete startling event. Existence of these reactivations suggests that the memory formation is a highly dynamic process, and that the reactivations could be crucial in the immediate post-learning fixation of newly formed memory traces (Figure 2b,c). Previous studies, based on comparing firing covariance values of place cells with overlapping fields between the running sessions and the post-running sleep period, imply that place cells participate in reactivations during sleep [65]. The detection of awake-state reactivations of memory-encoding patterns immediately following the startling events is generally consistent those interpretations, and further illustrates the unprecedented sensitivity of this new decoding method. Thus, the combination of large-scale recording and new decoding algorithms begins to open a door to direct visualization and quantitative measurement of network-level memory traces and their dynamic temporal evolution.

Identification of neural cliques as real-time memory coding units

To characterize further the internal structures underlying the real-time memory encoding, the agglomerative

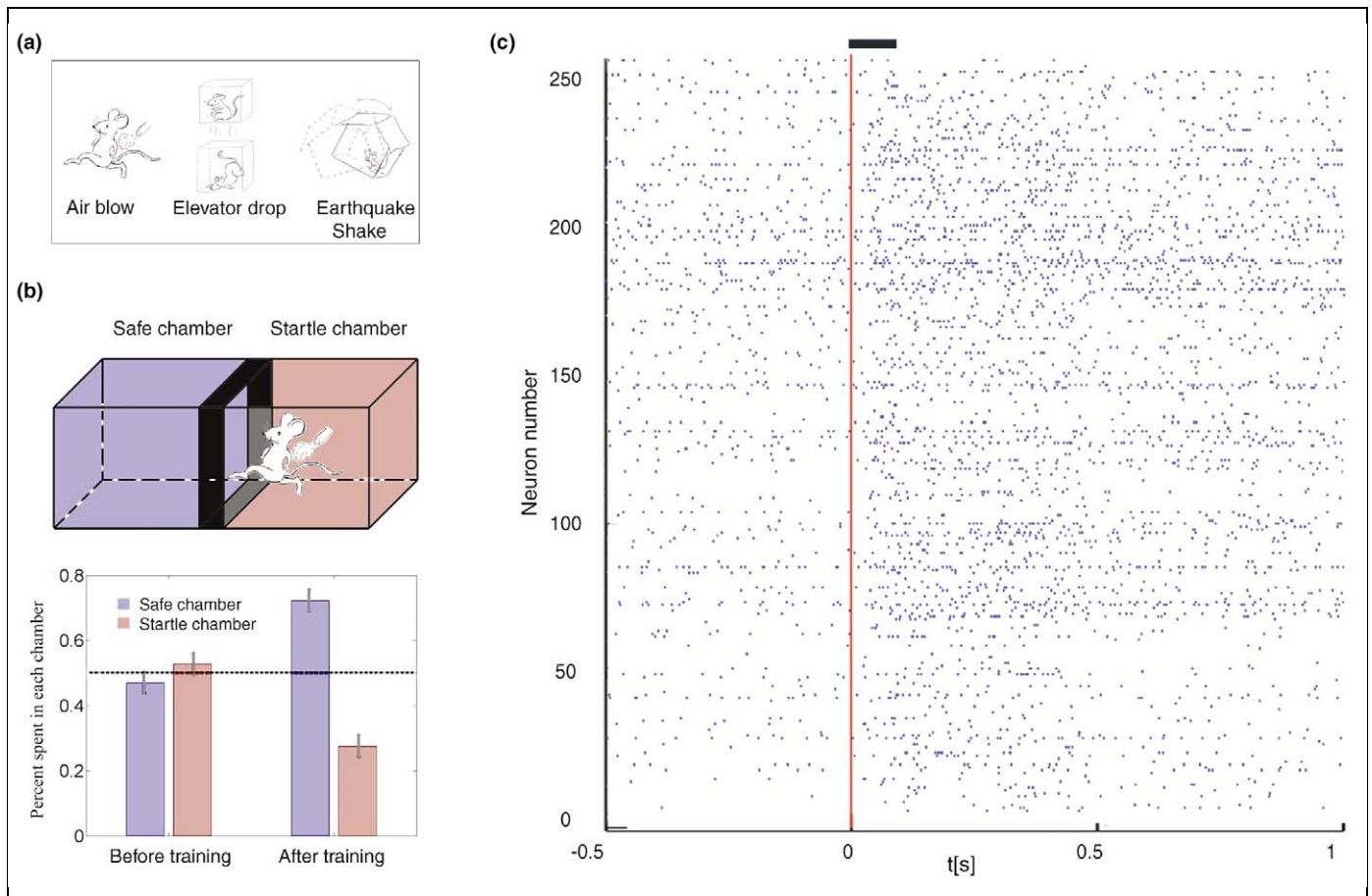


Figure 1. Large-scale simultaneous monitoring of 260 CA1 cells in mice during various mnemonic startling episodes. **(a)** A set of new behavioral paradigms involving categorical variables can create discrete episodic memories for mice: a sudden blow of air to the back (mimicking an owl attack from the sky), a short vertical freefall inside a plunging small elevator, and an unexpected brief earthquake-like shaking of the cage. **(b)** Formation of robust memory about the startling events can be assessed using a place conditioning paradigm. The mice split their time roughly equally between the safe chamber and the startle chamber during the pre-training session, before startle conditioning. However, after startle conditioning the mice spent significantly more time in the unconditioned (safe) chamber, as shown in the 3-h retention test (red bar, 130.1 ± 5.8 s out of the total 180 s; $P < 0.0005$, 14 mice). Adapted from [64]. **(c)** A spike raster of 260 simultaneously recorded single units from a mouse for 0.5 s before and 1.0 s after a single elevator-drop episode [time (t) = 0, vertical red line; x-axis, time in seconds; y-axis, numbers of simultaneously recorded single units ($n = 260$)]. Startle stimulus duration is indicated as a bar above the spike raster.

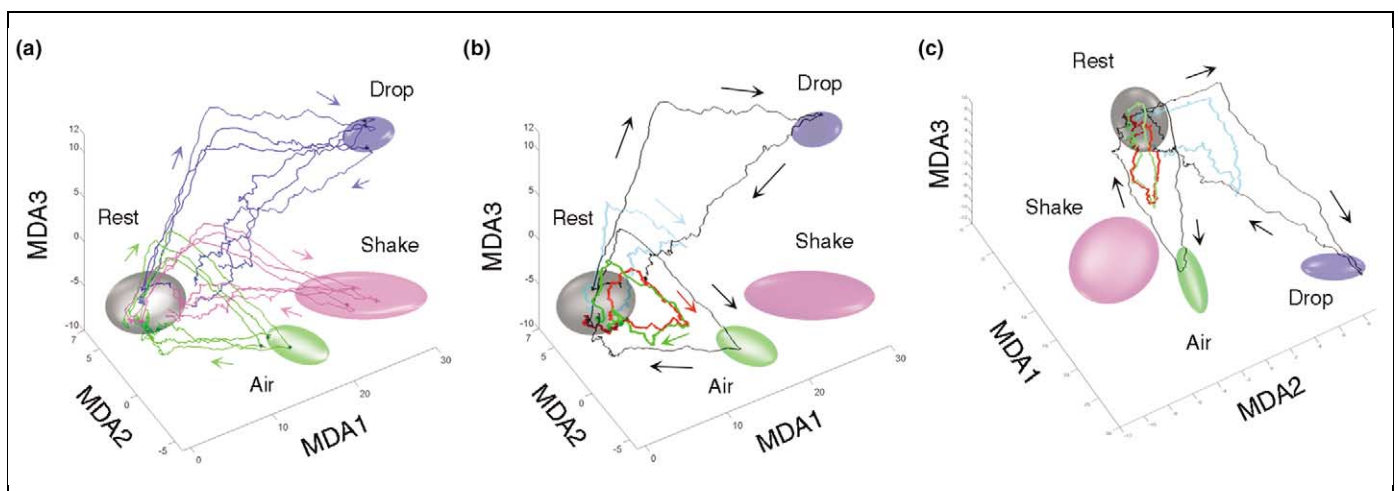


Figure 2. Classification, visualization and dynamic decoding of CA1 ensemble representations of startle episodes by multiple-discriminant analysis (MDA). **(a)** Ensemble patterns during epochs of awake rest (gray ellipsoid), air-blow (green ellipsoid), drop (blue ellipsoid) and earthquake (shake; magenta ellipsoid) are shown in a 3D sub-encoding space obtained using MDA for a mouse in which 260 CA1 cells were simultaneously recorded; MDA1, MDA 2 and MDA3 denote the discriminant axes. Three representative dynamic trajectories of network patterns during encoding are shown for each type of startling event. **(b)** Dynamic monitoring of post-learning spontaneous reactivations of network traces during and after the actual startling events. 3D subspace trajectories of the ensemble encoding patterns during drop and air-blow episodes in the same mouse are shown. The initial response to an actual air-blow or drop event (black lines) is followed by spontaneous reactivations (red and green lines for two air-blow reactivations, and blue lines for drop reactivation), characterized by co-planar, geometrically similar lower-amplitude trajectories (directionality indicated by arrows). **(c)** The same trajectories of reactivation traces after rotation to show that the trajectories are highly specific towards their own startle clusters. These post-learning dynamic trajectories are typically smaller in amplitude than the initial trajectories and take place on the same timescale of those triggered by the actual events. Reactivations within the first several minutes after the startle event seem to number between one and five, with random intervals.

hierarchical clustering and sequential MDA methods have been used [64]. These analyses reveal that the network-encoding power is actually derived from a set of functional coding units in the CA1 cell population; these units are termed neural cliques, and each is a group of neurons with similar response properties and selectivity (Box 1). For example, the 'general startle neural clique' consists of individual cells capable of responding to all types of startling stimuli (including the elevator-drop, earthquake and air-blow), whereas the 'sub-general startle cliques' are neural groups that respond to a combination of two types of, but not all, startling events. In addition, there are neuron groups that exhibit high specificity towards one specific type of startling event, such as elevator-drop (the 'drop-specific neural clique'), earthquake (the 'earthquake-specific neural clique'), or sudden air-blow events (the 'air-puff-specific neural clique').

One can mathematically evaluate the contribution of these neural cliques to the CA1 representations by repeating the MDA analysis while sequentially adding clique members to an initial set of non-responsive neurons. For example, a random selection of 40 non-responsive cells as an initial set provides no discriminating power, yielding only overlapping representations [64]. By contrast, inclusion of the ten most responsive cells from the general startle clique leads to good separation between the rest state and the startle states, but not among startle types. The selective discrimination of 'drop' startle events is obtained by addition of as few as the ten most responsive neurons from the drop clique. Similarly, inclusion of the ten most responsive air-blow-specific clique neurons and the ten most responsive earthquake-specific clique neurons leads to full discrimination between all startle types. Thus, these neural cliques indeed constitute the basic functional units encoding the identity of different startling episodes.

One crucial feature of neural cliques is that the individual neurons of a given clique exhibit 'collective co-spiking' temporal dynamics (Figure 3). This enables the memory coding units to achieve real-time network-level encoding robustness by overcoming the response variability of individual neurons (Figure 3). Moreover, based on the temporal dynamics, neurons within each clique can be further sub-grouped into four major subtypes: (i) transient increase, (ii) prolonged increase, (iii) transient decrease, and (iv) prolonged decrease. The existence of four types of neurons can greatly enhance the real-time encoding robustness and also provide potential means for modifying clique membership via synaptic plasticity. Finally, neural cliques, as network-level coding units, should be less severely affected by cell death than single neurons that function alone, and therefore neural cliques should degrade gracefully during aging or neurodegenerative disease states.

Hierarchical organization within memory-encoding neural clique assemblies

Through examining the overall organization of neural clique assembly involved in startle memory encoding, it is clear that the internal CA1 representations of any given startle episode involves a combination of neural cliques,

invariantly consisting of the general startle clique, a sub-general startle clique, a startle identity-specific clique, and a context-specific startle clique [64]. Thus, each clique assembly is organized in a categorical hierarchy forming a 'feature-encoding pyramid' (Box 1). The neural clique representing or extracting the most general features (common to all categories of startle event) is at the bottom, followed by neural cliques responding to less general features (covering multiple, but not all, common categories). Moving gradually upwards the cliques are increasingly specific and discriminating (responding to a specific category), and the most discriminating feature clique (corresponding to context-specificity) is at the top of the feature-encoding pyramid.

According to this hierarchical structure of network-level memory encoding (Box 1), the general startle neural clique represents the neurons engaged in the extraction of the common features among various episodes (e.g. encoding abstract and generalized knowledge that 'such events are scary and dangerous', by integrating neural inputs from the amygdala). Sub-general startle cliques are involved in identifying sub-common features across a subset of startling episodes (e.g. the 'earthquake and drop-specific clique' encoding the semantic memory that both earthquake and drop 'involve shaking and motion disturbances', by integrating inputs from the vestibular system). Startle identity-specific cliques encode discriminative information about startle types (defining 'what type' of event has happened). Startle context-specific cliques provide even more specific features, such as contextual information about 'where' a particular startling event has happened.

This invariant feature-encoding pyramid of neural clique assemblies reveals four basic principles for the organization of memory encoding in the brain (Box 1). First, the neural networks in memory systems employ a categorical and hierarchical architecture in organizing memory coding units. Second, internal representations of external events in the brain via such a feature-encoding pyramid is achieved not by recording exact details of the external event, but by recreating selective pictures based on the importance for survival and adaptation. Third, the structure of the feature-encoding pyramid provides a network mechanism, through a combinatorial and self-organizing process, for creating seemingly unlimited numbers of unique internal patterns that can deal with the potentially infinite number of behavioral episodes that an animal or human might encounter during life. Fourth, in addition to its vast memory storage capacity, these neural-clique-based hierarchical extraction and parallel-binding processes also enable the brain to achieve abstraction and generalization – cognitive functions that are essential for dealing with complex, ever-changing situations.

That the memory-encoding neural clique assembly appears invariantly to contain the coding units for processing abstract and generalized information [66] is interesting. It fits well with the anatomical evidence that virtually all sensory input that the hippocampus receives arises from higher-order, multimodal cortical regions and that the hippocampus has a high degree of sub-regional

Box 1. Categorical and hierarchical organization of the memory-encoding neural clique assembly

The major organizing principle of network-level memory encoding is that memory coding units are organized in a categorical and hierarchical manner. For each neural clique assembly underlying the encoding of a given startling episode, there is an invariant internal organization termed the 'feature-encoding pyramid', with the neural cliques corresponding to the general features at the bottom and neural cliques corresponding to the highly specific features at the top.

Such a feature-encoding pyramid is evident from the hierarchical clustering analysis of responses of 757 CA1 neurons from four mice to the three different types of startling episode (Figure 1a of this box). This reveals the existence of four major neural cliques involved in coding a startle event: (i) the general startle clique, (ii) sub-general startle cliques (e.g. drop-shake clique, air-blow-drop clique and shake-air-blow clique), (iii) startle-type-specific cliques (e.g. drop-specific clique, shake-specific clique and air-blow-specific clique), and (iv) startle-context-specific cliques (e.g. cliques specific for air-blow in context A, air-blow in context B, drop in Elevator A or drop in Elevator B). The color scale bar in Figure 1(a) of this box indicates the normalized response magnitude (1 to 7); neurons that did not respond to any of the startling episodes in this experiment are grouped towards the bottom of the panel. A similar cluster is observed from simultaneously recorded CA1 populations [64].

It is evident that memory coding units are organized in a hierarchical and categorical fashion (Figure 1b of this box), and any given startling episode is encoded by a combinatorial assembly of neural cliques in series, invariantly consisting of the general startle clique, a sub-general startle clique, a startle-identity-specific clique and a context-specific startle clique. In this pyramid of the feature-encoding clique assembly, the neural clique representing the most general, abstract features of all categories of startling event is at the bottom, forming a

common building block for all startle-event encoding. The next layer of the pyramid is made by neural cliques responding to less general features (covering multiple, but not all, categories); these sub-general cliques are present in a subset of the neural clique assemblies. Moving up this feature-encoding pyramid, neural cliques become increasingly specific. The neural clique at the top encodes the most specific and highly discriminate features, thereby defining a particular event or experience. Please note that the number of neurons for each clique does not necessarily correspond to its position in the feature-encoding pyramid. In other words, the neural clique encoding general features does not necessarily have more neurons than the neural cliques encoding more specific features.

This invariant feature structure within each neural clique assembly encoding startling episodes reveals four organizing principles for memory encoding in the brain:

(i) The memory system employs a categorical and hierarchical architecture in organizing memory coding units.

(ii) The categorical and hierarchical organization of memory coding units suggest that internal representations of external events in memory space is achieved by re-creating a selective picture, determined largely by what is important for survival and behavioral adaptation.

(iii) Through combinatorial and self-organizing process, neural cliques can generate vast numbers of unique assembly patterns, thereby providing a network-level mechanism capable of encoding potentially infinite numbers of episodic events.

(iv) Neural-clique-based hierarchical extraction and parallel binding in the memory system can also enable higher cognitions such as abstraction and generalization capacities to emerge during the process.

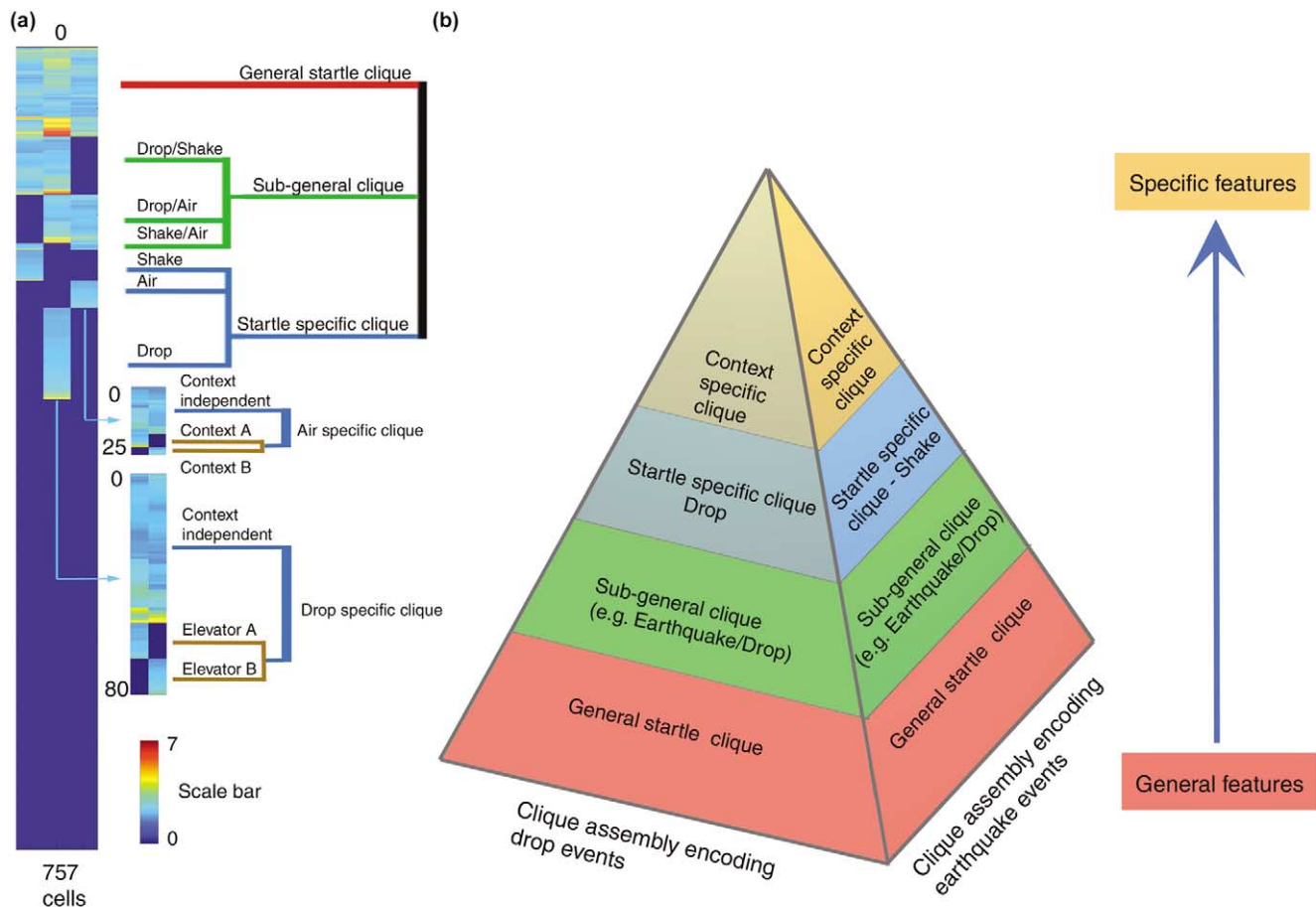


Figure 1. Hierarchical organization of the memory-encoding neural clique assembly. (a) Hierarchical clustering analysis of responses of 757 CA1 neurons from four mice to the three different types of startling episode. (b) Hierarchical and categorical organization of memory coding units into the feature-encoding pyramid.

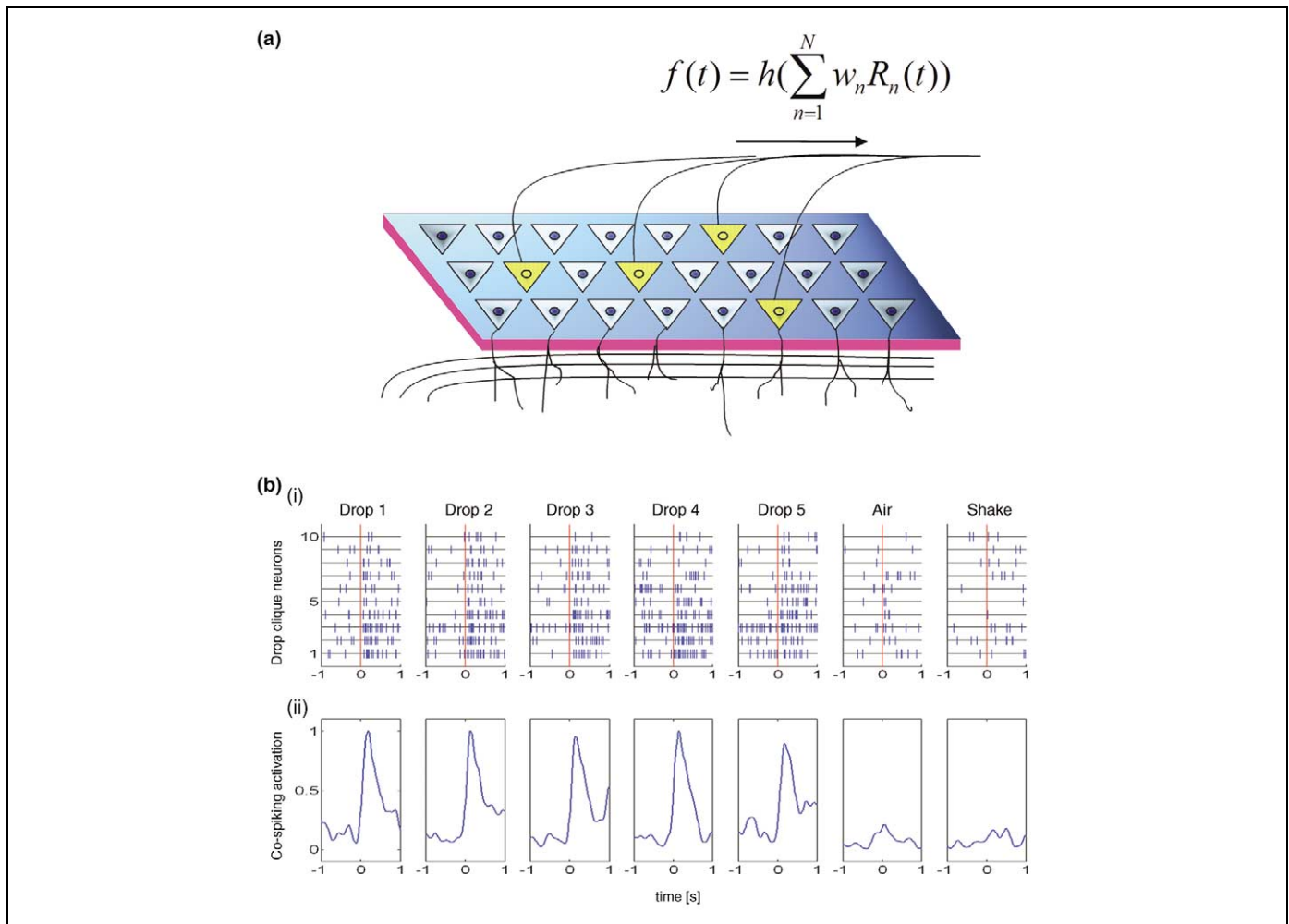


Figure 3. Real-time encoding robustness of memory coding units is achieved through ‘collective co-spiking’ of individual members of each neural clique. **(a)** A neural clique (yellow neurons) in the CA1 network. The activation function of the clique to drive a downstream clique can be mathematically described as a threshold function of the integrated inputs from the upstream clique members, where R is input, w is the weighting factor, h is the threshold function (e.g. sigmoid), and t is time. **(b)** Spike raster plots (i) and weighted responses (ii) of the ten most responsive neurons within the drop-specific neural clique during five elevator-drop events (1 s before and after the startle). Although responses of the individual member neurons vary from trial to trial (i), the consistency and specificity of the collective co-spiking of the clique responses (ii) is evident from each drop episode (five episodes are listed). The drop-specific neural clique exhibited no significant responses to air-blow or shake episodes (right). Note that robust co-spiking of member neurons in the clique is preserved even at time-scales of 20–30 ms, the time window matching the membrane time constant of CA1 pyramidal cells.

divergence and convergence at each loop. This unique anatomical layout supports the notion that whatever processing is achieved by the hippocampus in the service of long-term memory formation should have already engaged with relatively abstract, generalized representations of events, people, facts and knowledge.

The observed feature-encoding-pyramid structure of the neural clique assembly is likely to represent a general mechanism for memory encoding across different animal species. For example, single-unit recordings in human hippocampus show that some hippocampal cells fire in response to faces or, more selectively, to a certain type of human facial emotion [66]; other seems to exhibit highly selective firing in response to one specific person, regardless of how they are recognized (e.g. the ‘Halle Berry cell’ which fires selectively in response to photographs of the actress herself, to photographs of her playing the character ‘Cat-woman’, and even to a string of letters of her name [67]. Although those cells were not recorded simultaneously, the findings are consistent with the

general-to-specific structure of the feature-encoding pyramid. In addition, although some place cells in the rat hippocampus exhibit location-specific firing regardless of whether the animals engage in random foraging or goal-oriented food retrieval (or make a left or right turns in a T-maze), others seem to fire selectively at their place fields only in association with a particular kind of experience [68,69]. Thus, these studies also seem to support the existence of a hierarchical structure involved in space coding. Therefore, the hierarchical organization of the neural clique assembly, revealed through large-scale recording of startling episodes and mathematical analyses, could represent a general feature for memory encoding in the brain. It also suggests that episodic memory is intimately linked with, and simultaneously converted to, semantic memory and generalized knowledge.

Such hierarchical extraction and parallel binding along CNS pathways into the memory system is fundamentally different from the strategies used in current computers,

camcorders or intelligent machines. These unique design principles enable the brain to extract commonalities through one or multiple exposures and to generate more abstract knowledge and generalized experiences. Such generalization and abstract representation of behavioral experiences have enabled humans and other animals to avoid the burden of remembering and storing each mnemonic detail. More importantly, by extracting the essential elements and abstract knowledge, animals can apply past experiences to future encounters that share essential features but vary in physical detail. These higher cognitive functions are obviously crucial for survival and reproduction of animal species.

Universal activation codes for real-time neural representations in the brain across individuals and species

With identification of the neural clique as a basic coding unit and the feature-encoding pyramid within clique assemblies, the distinct ensemble representations observed in a low-dimensional-encoding subspace can be further converted (through matrix inversion) into a string of binary activation codes (Figure 4). This binary assignment, of 1 for the active state and 0 for the inactive state of neural cliques, is based on the idea that the activity state of a neural clique can be monitored by downstream neurons using a biologically plausible binary activation function [70] (Figure 3). This mathematical conversion of

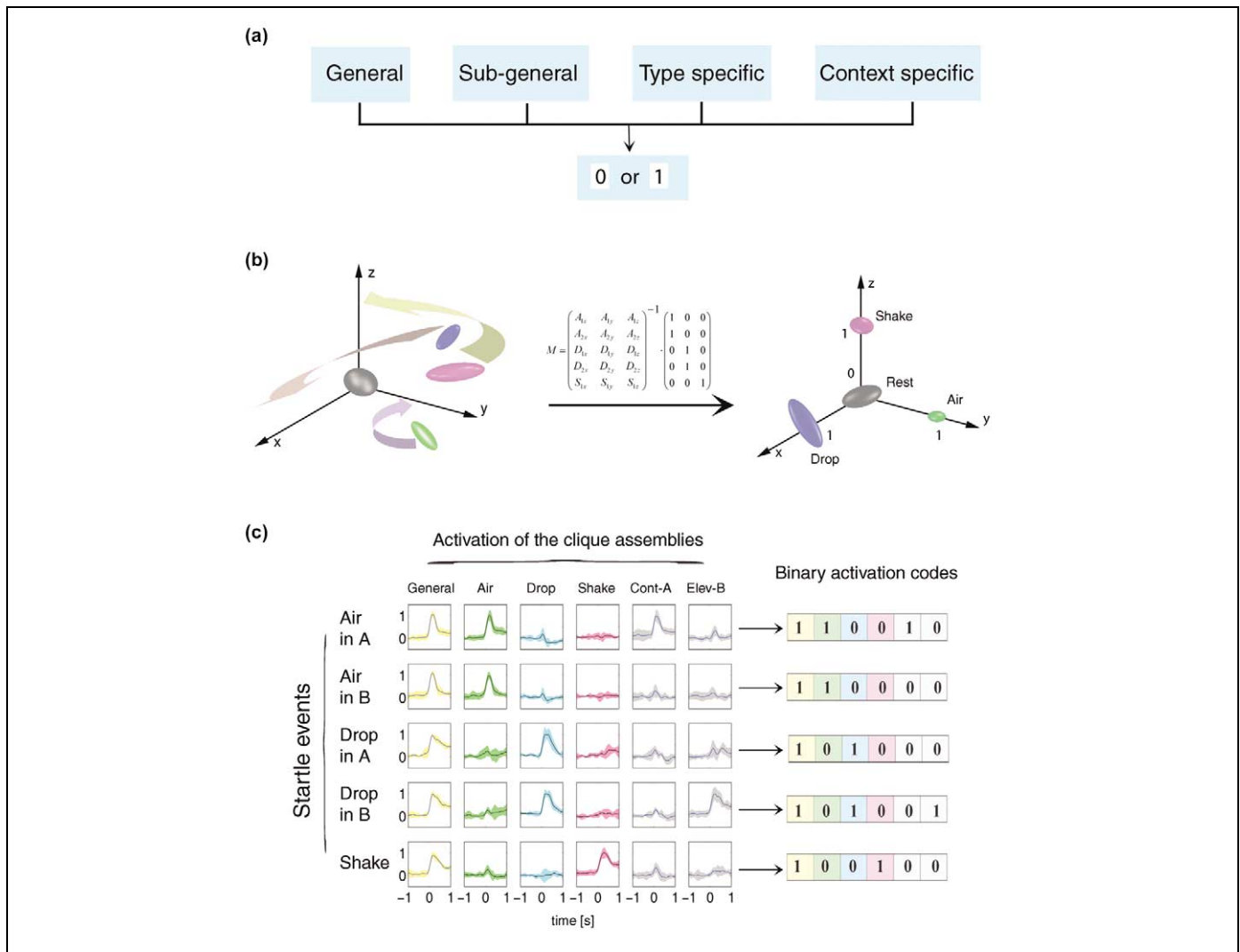


Figure 4. Conversion of activation patterns of neural clique assemblies into a binary code. (a) Activation states of a neural clique assembly (consisting of cliques of four different levels: general, sub-general, type-specific and context-specific) encoding a single type of startling event is converted into binary digits 1 or 0. (b) Mathematical transformation of multiple-discriminant analysis (MDA) patterns into a startle-type-specific binary encoding system. Although the MDA method provides an efficient separation of the startle episodes, each discriminant axis at the MDA-encoding subspaces (left) no longer corresponds to functional meaning. Thus, matrix inversion was used to translate the ensemble patterns into a startle-specific encoding coordinate system (right). This assigns new positions for the cluster centers so that they are linearly mapped into a 'clique-space', where each axis directly corresponds to a particular clique, thus projecting specific activation patterns to 1 and the absence of activation to 0 (a). This mathematical operation enables us to map the encoding subspace into one where the startle representations can directly correspond to neural clique activity patterns and, subsequently, to translate the collective activity patterns of neural clique assembly into unique and efficient network-level binary activation codes as a string of binary digits (1s and 0s). (c) Conversion of activation patterns of multiple neural clique assemblies into real-time binary codes. Responses of neural cliques are illustrated on the left in different colors. Rows correspond to the different startling episodes, and columns indicate the different neural cliques (general startle, air-blow, drop, shake, air-blow in context A, and drop in elevator B). The activation function of a given clique at each network level can be mathematically described [64]. Binary activation patterns corresponding to each event can be converted into a set of binary codes (shown on the right following the sequence of the cliques on the left). As such, the clique activation codes are: 110010 for air-blow in context A; 110000 for air-blow in context B; 101000 for drop in elevator A; 101001 for drop in elevator B; and 100100 for shake. This binary code enables us to predict the behavioral experiences accurately by sliding through the recorded neural population activity and calculating the hit ratio of matching those binary codes with the occurrences of each startling event. Panel (c) is adapted from [64] © (2005) National Academy of Sciences, USA.

the activation patterns of the neural clique assembly into a code of 1s and 0s creates a simple and convenient way for universally comparing and categorizing network-level representations from brain to brain.

Such a universal binary code can provide a potentially unifying framework for studying high cognition even across animal species. For example, should a mouse, dog and human all experience a sudden free-fall in a plunging elevator, the activation patterns of the general startle neural clique, drop-specific clique, air-puff clique and earthquake clique in their brains would produce an identical real-time binary activation code (1100, according to the aforementioned permutation and arrangement of the coding-unit assembly). Yet because the mouse, dog and human might perceive other subtle information differently during the incident, the subsequent digits might differ. For example, perhaps the dog would sense a trace smell of burning wires, whereas the human would see erratic flicking of elevator buttons, and the mouse would have a flying candy wrapper hit its face. As such, the binary activation codes would permit the universal measurement and categorization of neural representations between those three species, with the initial four digits defining the common experience of free falling, and with the subsequent digits corresponding to different subtle details.

The proposed binary codes, derived from the activation

patterns of the neural clique assembly, offer a concise way to categorize the neural representations of cognition in all brains. However, it is important to note the fundamental differences between neural clique pattern-based brain codes and nucleotide-based genetic codes. Specifically, neural-clique-based brain codes have at least four distinct properties:

- (i) They are not heritable. Genetic codes are directly transferred through reproduction whereas brain codes are not usually inheritable and can be acquired only through experiences (perhaps with exceptions of neural codes for controlling primitive functions such as breathing, heartbeat and the knee-jerk reflex, which might be genetically programmed).
- (ii) They are self-organizing. Genetic codes act as pre-determined scaffolds, providing blueprints for the development and basic functionality of the organism; brain codes are dynamic and self-organizing, arising out of internal structures and connectivity of neural networks upon behavioral experiences.
- (iii) They vary in size. Numbers of genes are exactly fixed for each individual and species, whereas the number of brain codes is highly variable in each brain; in theory, it is limited only by the network capacity (which is

Box 2. Neural clique code-based real-time information processes in the brain

Through a series of hierarchical-extraction and parallel-binding processes, the brain achieves coherent internal encoding and processing of external events (Figure 1 of this box). For example, when a person experiences a sudden earthquake, neural cliques in the vestibular nuclei detect sudden motion disturbances, whereas neural cliques in the primary visual cortex (V1) and area V2 encode decomposed features about edge orientation and movement, and those in cortical areas V4 and V5 encode shapes of visual objects. As information is processed along pathways into deeper cortical areas such as the inferior temporal cortex (IT), neural cliques begin to encode complex features, such as houses. When the information reaches high association cortices such as the hippocampus (HP) and temporal medial cortex (TMC), the neural clique assembly encodes the

earthquake experience and its location, with a selective set of 'what and where' information. At this level, abstract and generalized information such as semantic memories of 'the earthquake is dangerous and scary' emerge. As information is further processed into other cortical regions involving decision-making and motor-planning, a series of phased firing among various neural clique assemblies leads to adaptive behaviors such as screaming and running away from the house, or hiding under a dining table. As illustrated, the activation patterns of neural clique assemblies in each brain region can be converted into a binary code for universally comparing and categorizing network-level representations from brain to brain. Such universal brain codes can also potentially allow brain-machine interface communications.

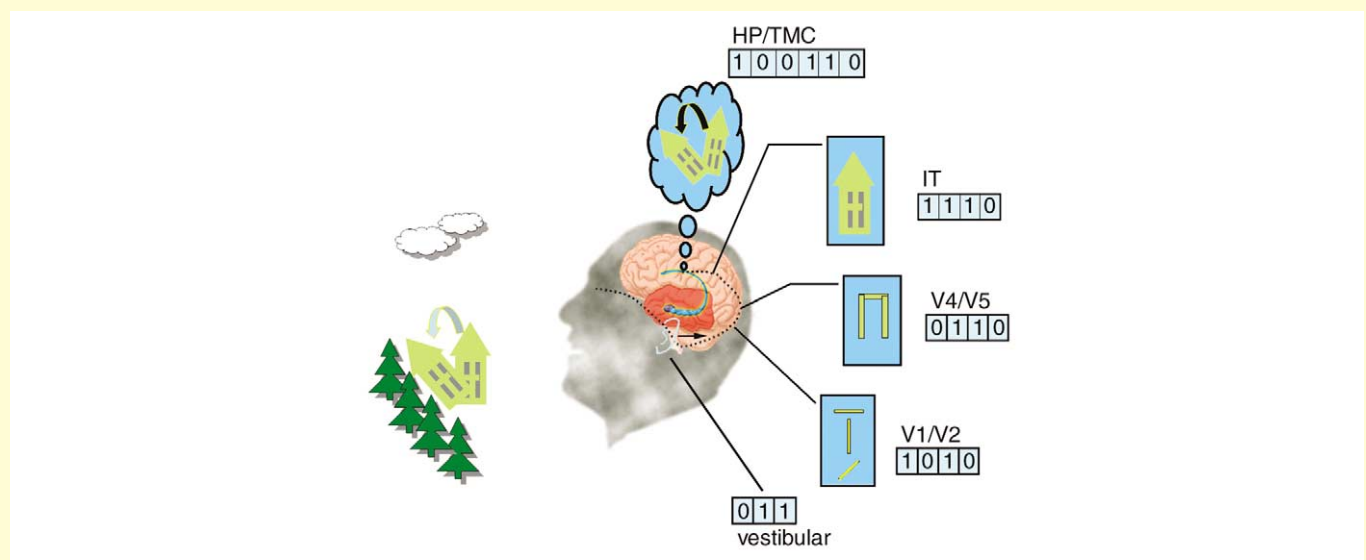


Figure 1. Hierarchical extraction and parallel-binding processes lead to coherent internal encoding and processing of external events such as a sudden earthquake.

determined by convergence and divergence in connectivity) and by the number of behavioral experiences that an individual encounters.

- (iv) They are modifiable. Unless mutated, the genetic code remains static, whereas membership of individual neurons within a given neural clique is modifiable by experience-dependent synaptic plasticity or disease states.

Identification of neural cliques as memory coding units in the hippocampus suggests that the concept of neural cliques as basic, self-organizing processing units could apply to many, if not all, neural networks in the brain. Under this neural clique code model (Box 2), the functionality implemented by neural cliques in a given network depends on the specializations of the corresponding regions. In primary sensory regions, neural cliques (perhaps organized in cortical columns) encode piecemeal information by decomposing external events into various basic features (e.g. the primary visual cortex for detecting edge-orientation, color or size of visual objects, or the vestibular nuclei for detecting motion) (Box 2). As information is further processed along its pathways into deeper regions, neural cliques (although no longer organized in their anatomically distinguishable maps or columns) start to encode more complex features (e.g. shapes and complex objects such as houses and faces in the inferior temporal cortex). When high association cortices such as the hippocampus are reached, neural cliques have already contained both specific and generalized mnemonic information about events, places and people with a significant amount of abstraction and generalization (Box 2). Eventually, the brain areas involved in decision-making, executive function and motor-planning can begin coherent and phased firings among various neural cliques, thereby generating behaviors.

In summary, recent identification of neural cliques as the basic coding units in the brain has provided crucial insight into the network-level organizing principles underlying real-time memory encoding. Neural cliques are self-organized in a combinatorial fashion to form a memory-encoding assembly that has an invariant hierarchical structure. This feature-encoding structure immediately suggests a network mechanism for the brain to achieve both large memory storage capacity and higher cognitive functions such as abstraction and generalization.

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