MedCave Publications
Inviting Scientific Discovery

Annals of Neuropsychiatry

MedCave Publications

Research Aticle Open Access

Associative Memory Cells in Engram Circuits

Jin-Hui Wang

Qingdao University, School of Pharmacy, Qingdao Shandong, China

Corresponding Author: Dr. Jin-Hui Wang, Ph.D. & MD; Distinguished professor in pharmacology, Qingdao University, School of Pharmacy, Qingdao Shandong 266021, China. E-mail id: wangjh@qdu.edu.cn

Received Date: Apr 01, 2019; **Accepted Date:** Apr 18, 2019; **Published Date:** Apr 20, 2019

Abstract

The joint acquisition and integrated storage of multiple exogenous signals are called as associative learning and memory. Endogenous signals that are generated during cognition and emotion based on exogenous signals can be memorized. The integrative storage of these exogenous and endogenous signals is essential for various events in life. In terms of basic units of engrams, associative memory cells are recruited in the brain in learning and cognition. The recruitment and refinement of associative memory cells work for memory retrievals, memory-relevant events and the reorganized learning of unitary signals that have been acquired. Associative memory cells are recruited by generating mutual synapse innervations among coactivated neurons within a single-modality brain area and across multi-modality brain areas. Associative memory cells in engrams are those cells that are able to encode the storage of associatively learned signals and receive synapse innervations carrying these signals. Associative memory cells are generally classified into primary associative memory cells in sensory cortices and secondary associative memory cells in brain areas relevant to cognition and emotion. The axons of primary associative memory cells innervate secondary associative memory cells. Mutual synapse innervations constitute the integrative storage and reciprocal retrieval of associated signals. Convergent synapse innervations to downstream neurons endorse the integrative cognition and emotion, such as associative thinking and logical reasoning. Divergent synapse innervations confer multiple uses of memorized signals. The interconnection between primary and secondary associative memory cells makes sensory sources be included in memory-relevant events. This review presents a comprehensive diagram about the recruitment and refinement of associative memory cells as well as their impacts in physiology, psychology and pathology for the society of memoriology.

Key words: Associative memory cell (AMC); synapse; neuron; learning; memory trace; cognition and brain

Associative learning stands for the joint acquisition of multiple exogenous signals, such as experiences and knowledge, by sensory systems. Associative memory is termed as the integrative storage of these associated signals in the brain, whose formation can be ensured by memory retrievals (recall, representation and recollection) based on speech, writing, gesture, countenance and emotional reactions. Associative learning and memory is a very common approach of signal storage for cognitions in life [1-6] since the acquisition of new unitary signals or the reorganized learning of previously acquired unitary signals are fulfilled in the integrative manner [7]. In learning processes, the associated exogenous signals come from sensory organs and reside into sensory cortices in cross-modal and intramodal styles [7,8]. Coactivations of sensory cortical neurons make their axon projection and synapse innervations mutually, in which these neurons are recruited as primary associative memory cells for the integrative storage of multiple exogenous signals [5,9,10]. The axons of these primary associative memory cells project and make synapse innervations to their downstream neurons in brain areas related to cognition, emotion and behaviors for the storage of endogenous signals generated during these activities [11,7]. Because cognitive processes and emotion reactions can be recalled, the neurons that memorize endogenous signals are named as secondary associative memory cells [7,8]. When the neurons encoding one of associated signals are activated, they can attract axon projection and synapse innervations from the coactivated neurons encoding another of associated signals. After associative memory cells are recruited from the coactivated neurons by receiving the innervation of multiple synapse inputs, their subsequent activities change their excitability and synapse function. The recruitment and refinement of associative memory cells constitute a principle of activity together, connection together, strengthening together and coordination together [7,8]. Therefore, associative memory cells are nerve cells that are able to encode multiple signals associatively acquired as well as receive axon projection and synapse innervations of carrying these signals. Comprehensive cellular architectures underlying associative memory in different periods of the lifespan remain to be revealed in order to better understand memory-related physiology and psychology in the brain. In this review, author focuses on introducing current advances about associative memory cells, the basic units of engrams, which is updated from our previous review [12].

Concepts in associative learning and memory

Learning is defined as the acquisition of new information, knowledge and experiences, which may be new unitary signals or the reorganized unitary signals that are learned previously. Signal acquisition can be classified into associative and non-associative styles [2,6]. Associative learning stands for the joint acquisition of multiple signals that can be sensory signals or sensory signals plus behavioral operations. Their joint acquisitions are featured as the associations of new signals with an innate signal or a previously learned signal as well as the reorganized learning of unitary signals that have been acquired, such as the reorganization of letters into distinct words and phrases [7]. Associative memory to these signals appears emerged if these associated signals can

be retrieved reciprocally by cues or recalled by automatic conversion among sensory modalities. Two physiognomies of associative memory are the integrative storage and distinguishable retrieval of associated signals [5]. On the other hand, non-associative learning is thought to acquire a given sensory signal. For instance, repeated stimulations lead to habituation or sensitization to this sensory signal [2]. However, non-associative learning is not involved in acquiring new information except for repetitive activations in a sensory system for its upregulation or downregulation based on the sensitization or desensitization of sensory receptors and cortical neurons. In this regard, the repetitive activations to a sensory system may fall into the term "review" instead of learning. Thus, the acquisition and storage of almost all of the new signals require them be associated with a signal that has been stored in the brain for the facilitation of their memory [7].

In associative learning, multiple featured signals in each object or an environment are detected by different modalities from sensory receptors to cerebral cortices. These cross-modal signals are integrated for their associative storages. For instance, a fruit is detected by the olfactory system for aromatic odor, the visual system for shape and color, the taste system for sweetness, the auditory system for name and the somatosensory system for its surface sign. After they are jointly memorized, a signal induces the recalls of its associated signals, or the other way around. The recall can also be automatically fulfilled by the signal conversion among different modalities, e.g., image signals are recalled by verbal signals without additional cue. Furthermore, multiple signals with identical natures can be jointly detected by a sensory system, which are associatively acquired in an intramodal manner and primarily stored in one of sensory cortices. Thus, memory traces imprint the joint storage and distinguishable retrieval of multi-associated signals. Primary associative memory cells that encode multiple signals based on the synapses from innate inputs and new innervations from coactivated brain areas have been detected for the integrative storage of associated signals [9,5,13-18].

In addition, logical reasoning, associative thinking, computation and integrative imagination based on those exogenous associated signals that have been stored in primary associative memory cells of sensory cortices may lead to the secondary integrations of those signals for their storage and representation, i.e., secondary associative memory that is essential for cognitions, emotions and behaviors at the high orders under the consciousness condition [7,8]. Although the information can be stored in the prefrontal cortex, hippocampus and amygdala [19-31], the data from these studies do not reveal whether memory is secondary to the information storage in primary associative memory cells from sensory cortices. Currently, secondary associative memory cells are detected in the motor cortex, prefrontal cortex and hippocampus, which reside in the downstream of sensory cortices as well as receive synapse innervations from primary associative memory cells [7,32,33].

Various memory patterns are classified in psychology, e.g., declarative versus nondeclarative memory and episodic versus semantic memory in memory contents as well as sensory versus short-term or long-term memory in temporal feature [34,6]. Declarative (explicit) memory is defined to be the information storage under the consciousness, which includes episodic memory (specific events and contexts) and semantic memory (generalized knowledge and concepts). Nondeclarative (implicit) memory denotes the operations of various skills and procedures without the need of consciousness. There is no clear borderline between explicit and implicit memory. Procedures and skills operated in implicit memory can be consciously stated. Specific events and their contexts after repetitive practices can be executed effortlessly. In neuroscience, memory patterns are classified based on the combination of the location of information storage with the memory of featured signals, for instance, spatial memory in the hippocampus, emotional memory in the amygdala, perceptual memory in sensory cortices as well as prospective, attentive and working memory in the frontal cortex [12,6]. Moreover, memory formation has been suggested to be classified based on cellular mechanisms, such as the different types of associative memory cells in neural circuits (memory traces or engrams) and the sources of memorized signals from cross-modal versus intramodal sensory systems or exogenous versus endogenous resources [8,7].

Associative memory to exogenous signals from external environments refers to the integration and storage of associated signals that are inputted from cross-modal or intra-modal sensory modalities. Associative memory to endogenous signals refers to the integration and storage of associated signals that originate from sensory cortices and regenerate during logical reasoning and associative thinking in cognition- and emotion-relevant brain regions. Intramodal associative memory is related to the integration and storage of associated signals inputted from a single modality, such as a sensory modality or a brain area involved in cognition, emotion or behavior. Cross-modal associative memory is termed as the integration and storage of associated signals that come from different sensory modalities or brain areas relevant to cognitions, emotions or behaviors [8,7].

To better understand the mechanism underlying these memory patterns, we have to figure out basic units in engrams that conduct the integration and storage of associated signals, constitute the foundation of cognitions (logical reasoning, associative thinking, computation, imagination and so on), achieve the integration and storage of endogenous signals generated during cognitions, and control the future presentation of stored associative signals. How the memory is formed in different modalities and encoded under the different states of consciousness, attention and psychological motion remains to be elucidated. Thus, the comprehensive view of cellular architectures relevant to associative memory should be established in the manner of seeing individual trees as well as forests.

Thoughtfulness in the study of memory formation and retrieval

The mechanism underlying learning and memory has been systemically studied for more than one century [35-37,6]. Many observations and concepts have been proved to be solid, however, data inconsistencies and indication controversy still block our clear vision to abstract cellular architectures and molecular profiles. Major reasons for this vagueness may be due to lack of reliable standards to uncover memory cells in neural circuits (basic units in engrams) that encode specific signals stored, to identify molecules in memory cells specifically for their recruitment and to validate behaviors specifically initiated by memory cells. In order to set up reliable criteria for judging whether memory cell ensembles being recruited are correlated to memory formation and retrieval, the changes at the levels of molecules, neurons and behaviors in learning and memory should be precisely estimated.

In the study of memory retrieval, the stimulus-induced or cue-induced expression of specific behaviors that have been presented during learning events and memory retrievals are better used to indicate the persistent presence of memory traces. The use of this strategy may have the following pitfalls. Behaviors, perception and cognitions are quickly developed [38,39]. Postnatal developments in perception and cognition versus behavior are not parallel in aspects of their patterns and contents [40-42]. The number of arm/body language patterns is much lower than the number of memory contents and the number of verbal language patterns. Although the number of memory contents is

matched with the number of verbal language patterns, one arm/body language pattern may represent several memory contents, e.g., the thumb-up gesture usually represents memory contents relevant to all positive events. Furthermore, patterns and varieties in sensory input signals, memory contents, cognitive processes or emotional reactions are much enriched in comparison with behavior patterns that are presented by common output pathways, i.e., all of these signals, contents and processes are expressed by behavioral output patterns and pathways in the limit number. For instance, the "OK" gesture is used to express appropriate sensory stimulations, good perception, successful memory retrieval and other good cognitions. In other words, behaviors may not well present the retrievals of specific memory contents, except for verbal language. This limitation of behavioral presentation to memory and cognition may be an issue in the study of memory retrieval based on behaviors in animals. For instance, body freeze and involuntary/voluntary shaking used to signify fear memory can be induced by extreme fear, anxiety, emotional reactions (e.g., anger and fighting) and physiological responses (e.g., hypothermia and hypoglycemia). In addition, the brain in matured human beings and animals is highly wired, and its different areas are interconnected [43]. Stimulations to potential memory trace by electrical, optogenetic or chemogenetic approaches in a site of the brain may indirectly activate other areas connected with this site to evoke memory-relevant behaviors indirectly or behaviors across or similarly to memory retrieval. in other words, the replay of so-called memory-relevant behaviors may not be directly or realistically controlled by particular memory traces.

The learning process includes the associative acquisition of unitary signals and the reorganized acquisition of these unitary signals. At young age, language is learned to be letters and words, and knowledge learning is simple concepts. After these unitary signals are memorized, the advanced learning moves forward to complicated concepts that are various reorganizations of unitary signals, e.g., the acquisition of sentences and articles by the association of letters and words in language as well as the acquisition of principles and theories through the association of various concepts. Unlike verbal presentation, arm/body behaviors are not obviously upgraded to more complicated versions for expressing advanced language and knowledge during postnatal development, such that similar behaviors may represent different contents and knowledge. In other words, memory retrievals represented by similar behaviors may include different contents Thus, the retrievals of stored signals by the replay of similar behaviors may be changeable in their contents spatially and temporally, i.e., behavior replays are unreliable, except for the reoccurrence of cues-induced behaviors [12].

Basic units in the brain are neurons and glia cells. It is important to figure out new features of those neurons that have been recruited as memory cells for storing specific signals, in order to map their working principles during memory formation and retrieval. In addition to their conventional features, such as innate synapse input, synapse transmission, neuron excitability and excitation outputs, memory cells theoretically encode the newly learned signals and receive new synapse inputs that carry these newly learned signals [8]. As the most common style of learning and memory is associative in nature, i.e., the integrative storage of associated signals, associative memory cells recruited should encode both innate signal and new signals as well as receive new axon projection and synapse innervations in addition to innate inputs [7]. In this regard, the detection of new synapse innervations and multiple signal encoding by recording approaches (cell electrophysiology and imaging) is critically important in searching memory traces. Moreover, learning and memory feature the memory of unitary signals in the young and the memory of complicated signals, i.e., reorganized unitary signals, in the later period of development. Individual associative memory cells presumably encode multiple unitary signals, and their assemblies work together to store unitary signals in different reorganizations. In other words, the ensembles of associative memory cells store advanced knowledge contents in specific spatial and temporal patterns [7].

Neuronal excitation is driven by synapse inputs, and neuronal excitability is controlled by spiking threshold [44-47]. Spike patterns and frequencies are influenced by synaptic transmission and spiking threshold. There is a proportional correlation between the intensity of neuronal activities and the strength of synapse inputs, but not the nature of synapse input contents. Similarly, the activity patterns and spiking frequencies of memory cells in engrams denote their activity strength but not memory contents, such that the replay of certain neuronal activity patterns, e.g., spontaneous sharp-wave ripple, indicates the reemergence of neuronal activity strength for memory depth without the necessary indication of memory features and contents encoded. The effort to investigate the correlation of memory cell activity patterns to particular memory contents (memory specificity) [48,49] may not be good practice. Cues-induced neural activity may reflect the retrieval of memory contents. The recording of memory cells plus learning-cues should be used to track the distribution of associative memory cells in the different grades of engram circuits [12].

In order to figure out the features of memory cells and their working principle during memory retrieval, we expect to reveal specific molecules in associative memory cells and be able to label them. The formation of memory cells recruited from neurons involves axon projection and synapse innervation, two nonspecific processes in neurons. In this regard, the elucidation of molecular markers for memory cells is challenge. Immediate early genes have been used to label memory cells [50,51], which is based on a proposal that activated memory cells express immediate early genes [52,53]. Unfortunately, the expression of immediate early genes is proportional to the strength of neuronal activities which are not specific for memory cells. In this regard, the neurons with combo features in the labeling of immediate early genes, the innervation of new synapses and the encoding of new/innate signals are better termed as memory cells.

In summary, neurons that meet all of these criteria, such as cues-induced replay of neuronal activity, new synapse innervations and active molecule labeling, whose emergence is coupled with cues-induced behavior, can be defined as memory cells. Strategies to find out memory traces that meet these criteria are discussed below.

Strategies to trace memory cells

Two issues are important to clearly address the cellular and molecular mechanisms underlying associative memory formation and retrieval, i.e., animal models and strategies for searching cell assemblies in engrams. Based on the studies of learning and memory over centuries, we summarize the animal models and strategies be used.

As associative learning of multiple signals is the most common approach of signal acquisition in life, the mechanisms underlying the integrative storage of these associated signals should be addressed by using appropriate animal models featured by association. A few of animal models have been used to the study of associative learning and memory, such as classical conditioning that includes Pavlov's conditioned reflex, eyeblink conditioning and fear conditioning in rodents and withdraw reflex in Aplysia as well as operant conditioning that includes various types of reward memory (e.g., operation plus reward and place plus reward) in mammalians [54-68,50]. In these models, a stimulus is unconditioned and another stimulus is conditioned. In human beings, the memory of associated signals occurs by the signal inducing the recall of its associated signals, or the other

way around. This reciprocal retrieval of associated signals constitutes the basis of associative thinking, logical reasoning, computation and imagination in forward and backward manners. Therefore, such animal conditioning models do not signify whether air-puffing to the cornea or electric shock to the feet is able to induce the recall of sound signal after the onset of eyelid-blinking conditioning or fear conditioning. That is, these conditioning models may not be ideally used to study associative memory. Moreover, electrical shocks may activate the whole brain by spreading electrical current in the body, such that the association is not region-specific in the brain [7,8]. Compared to electrical stimulations used in the study of fear memory, physical and psychological stresses in social interactions are closer to real life situations [69-71]. Recently, an animal model has been introduced to study associative memory in that the association of whisker and olfactory stimulations in mice leads to odorant-induced whisker motion and whisker-induced olfactory responses, a typical example of reciprocal retrieval of associated signals [9,5,16,10,72,73].

In terms of strategies to study associative learning and memory, theoretical analyses and experimentation *in vivo* are used [74-78]. Theologists in the field of learning and memory focus on drawing potential units for information storage in the brain, such as memory traces, engrams and cell assemblies. Experimenters make efforts to figure out molecular substrates and cellular architectures for memory formation. In order to prove causal relationships between newly formed neuron substrates and memory behaviors, three criteria should be met. The emergence of new substrates and architectures is parallel to memory formation. The downregulation of newly formed substrates and architectures substantially reduces memory formation through the approaches of surgical ablations to brain tissues, pharmacological blockades to neuronal activities and genetic knockout/mutagenesis to molecules in nerve cells or synapses. The upregulation of these newly emerged substrates and architectures significantly facilitate memory formation through the approaches of pharmacological, electrical or optogenetic stimulations to nerve cells and gene overexpression in neurons and synapses [7-9,79].

In addition to the term "memory traces" for information storage coined by ancient Greeks, terms "engram and ecphory" have been suggested by Richard Semon [80], a zoologist and evolutional biologist, especially as renowned theologist in the field of learning and memory. Engram and ecphory correspond to memory traces and memory retrievals, respectively [77,81]. In addition, his view in the relevance of memory retrievals tells that the interaction between engrams and retrieval cues may generate new engrams. As long as an engram-awakening stimulus is similar to an original stimulus, this incomplete retrieval cue is sufficient to activate engrams. Awakening the originally stored engram may generate a new engram relevant to this event. The old retrieved engrams and new engrams become associated by contiguity to strengthen original memory. Moreover, the simultaneous retrieval of multiple engrams with similar contents and their subsequent associations, i.e., resonance among engrams, provides the basis for complicated cognitive events, e.g., abstraction, generalization and knowledge formation [82]. This theory may be the first to hypothesize that awakening engrams is dynamic and use-dependent. Although the engram termed by Semon lacks experimental evidence during that period, his frameworks about engrams are consistent with the features of memory activities. For instance, more representations lead to deeper memory, as well as repeated simultaneous recalls of similar memory contents induce them to be summarized, conceptualized and generalized. His theoretical work has made the engrams as the basis of memory formation.

Donald Hebb [83], another well-known theologist, describes memory traces to be cell assemblies as the basis of memory behaviors. Based on his and Penfield's observation that the destruction of large amounts of cerebral cortices in human beings produces little effect on memory [84], and Lashley's experiments that the ablation of widespread cortices in animals does not induce parallel change in memory behavior [85,86], he has proposed cell assemblies that are the wide distributed neural substrates for memory. Each cell ensemble is a group of cells in that their interconnections are strengthened during their simultaneous activities [87,88]. As these cells are interconnected, the activity in this circuit is maintained briefly after events, i.e., short-term memory. Recurrent activities for a sufficient time in this cell ensemble can induce growth or metabolic change that strengthens those interconnections among ensemble cells, such that short-term memory is converted into longer-term memory [88]. The strengthening of connections between presynaptic and postsynaptic nerve cells in their simultaneous activity confers these neurons a property of firing together and strengthening together. The strengthening of neuron connection has been shown in long-term potentiation of synaptic transmission [89]. The high number of interconnections among cells may allow entire ensembles to be activated if a subset of cells is activated by the process of pattern completion that induces memory retrieval. As Hebb's cell assembly is widely distributed across brain areas, the destruction in a small proportion of cells may not lead to catastrophic memory traces, or graceful network degradation, which may account for Lashley's experimental results. Therefore, Hebb's theory has overlapped multiple spatial scales from the integrated synaptic strengthening (a microscale level) to cell assembly formation (a mesoscale level).

The computational simulation of neuronal substrates for learning and memory has been used to deliver the theoretical model of memory traces, in which the data for modeling is based on experimental results. In the study of neuronal and synaptic architectures for memory traces and memory related behaviors, there are clear indications that show the involvement of neuronal ensemble and synaptic plasticity in processes of learning and memory in spite of a lack of evidences about synapses, neurons and their plasticity specifically correlated to memory formation [90-96].

In summary, the study of memory formation by theoretical models has generated great frameworks that can provide useful guideline for revealing cellular mechanisms underlying learning and memory. However, these models about memory traces (or engrams) and cell assemblies have not indicated any insight about the integrative storage of associated signals and need be proved by the experiments. In experimental studies about learning and memory, three strategies can be used to ensure causal relationships between memory traces (cell assemblies) and memory-relevant events. Cell assemblies in memory trace should be detected in memory formation and cue-induced memory retrieval. The downregulation of memory cell assemblies should lead to lack of memory formation in a prevention manner or to interrupt memory previously formed. The upregulation of the memory cell assemblies is able to facilitate memory formation or to strengthen memory previously formed [7-9,79,]. There are two usual methods to track memory traces (engrams) or cell assemblies, i.e., the detection of memory cells during learning and memory and the activation of memory cells to retrieve the memory-relevant behaviors. The detection of memory cells is to see their responses to memory cues by electrophysiological recording and two-photon calcium imaging as well as to localize their distribution through AAV-carried fluorescent neural tracing after memory formation. The activation of memory cells can be done by electrical, pharmacological, optogenetic or chemogenetic stimulations to induce the emergence of memory-related events [7]. It is noteworthy that memory traces are widely distributed in the brain and brain areas are interconnected. These stimulations may lead to the antegrade and retrograde activation of neural pathways. The indirect

activation of memory traces is unable to localize primary versus secondary allocations for memory formation.

In terms of the identification of neurons in a particular engram, their activities in response to specific cues relevant to this memory are expected to detected. Neuronal activities are featured by electrical signals generated on cell membrane as well as calcium signals raised in cells, such that the recording of electrical signals and the imaging of intracellular calcium dynamics can be applied to track cell assemblies relevant to memory formation and retrieval, i.e., the detection of the replays of memory-relevant cells [97]. Electrophysiological recordings by electrodes or electrode array have been used to monitor the replays of neurons in the hippocampus, sensory cortices, amygdala and ventral tegmental areas under different conditions, such as retrieval cues, wakefulness and sleep state [98-112]. For example, the coordinate interactions from hippocampal neurons to prefrontal cortical neurons and associative cortical neurons are involved in spatial memory tasks [113,114]. Cortical-hippocampal-cortical neuronal circuit is critical for memory consolidation [115]. Hippocampal cell assemblies can trigger neuronal activities in the ventral striatum during the replay of place-reward message [116]. The acquisition of associative memory in the hippocampus initiates a gradual-to-stable encoding process in neurons of the medial prefrontal cortex without continued trainings [117]. The representation of emotional memory is associated with the reactivation of in the hippocampus-amygdala system during the sleeping state [118]. These data from functional study are granted by anatomical evidences among the prefrontal cortex, hippocampus and thalamic nucleus [119].

Memory-relevant neurons in a particular engram have been recently identified in cerebral cortices by using two-photon cell calcium imaging *in vivo* [120-122]. For instance, the gradual emergence of neuronal activity relevant to spatial memory in the retrosplenial cortex, which is the major recipient of the hippocampus, depends upon the intact hippocampus. The indirect connections between the retrosplenial cortex and the hippocampus indicate the mutual influence between the hippocampus and neocortex via poly-synaptic neural pathways, i.e., the hippocampus and cerebral cortices include memory-relevant neurons in the widely distributed engrams [123]. Repetitive motor learning induces the formation of new dendritic spines *in vivo* [124]. Associative memory cells in response to retrieval cues are identified in primary sensory cortices, the prefrontal cortex, the hippocampus and the motor cortex [9,5,11,33]. Therefore, memory-relevant neurons or cell assemblies can be tracked by electrophysiological and imaging recordings based on their activities in response to the retrieval cues and during memory-relevant events.

The functional identification of memory-relevant neurons or cell assemblies should be proved and validated by the morphological approach, i.e., their morphology is quantified and their distribution is localized. Two ways can be used for this purpose, the trace of their synapse innervations from axon inputs that are carrying the learnt signals as well as the labeling of memory cell assemblies by molecules specifically relevant to memory. In the identification of associative memory cells about their mutual synapse innervations, the expression of fluorescent proteins mediated by Adeno-Associated Viruses (AAV) in memory relevant neurons and their axons has been conducted by injecting the AAVs tagged with genes of these fluorescent proteins into the source side of predicted memory traces as well as by detecting their axon terminals and target on associative memory cells, or other way around [9,13,72]. Such associative memory cells are characterized by receiving both innate and new synapse innervations. It is noteworthy that the combination of tracing new synapse contact and labeling memory cell assemblies with memory-relevant molecules would be an ideal way to identify memory cell assemblies.

The activity of neurons and synapses can induce the alternation of their included molecules [125-127]. These molecules may be relevant to recruit neurons as memory cells during learning. Thus, these molecules may be used to label memory cells to indicate the allocation of memory cell assemblies. The stimulations to neurons couple with the expression of immediate early genes [53]. Their expression in dendrites is regulated by synapse activities [128]. The immediate early gene Arc is specifically linked to neuronal encoding [129]. Some immediate early genes are widely expressed in the brain after fear memory, in which the number of labeled cells is positively correlated to fear memory [50,51]. There may be the association between the expression of immediate early genes and the active strength of memory cells. Their parallel change leads to a thought that cells labeled by immediate early gene expression are likely engram cells, in which their morphology and function can be studied [130-134]. However, an upregulated expression of immediate early genes is also observed in those neurons with hyperactivity, such as seizure discharge in epilepsy [135-138] and neuron toxicity in brain ischemia [139-141]. In these regards, immediate early genes may be suitable for identifying all of the neurons that have highly active strength. Genes and proteins specifically linked to memory cell assemblies and their memory contents remain to be explored [74,142]. It is noteworthy that there are around ten thousand types of proteins in living cells [143], which is much less than unit signals remembered in life, such as words, unitary images, odorants, and so on. As more than ten billion of neurons reside in the central nervous system, those neurons with synapse interconnection, i.e., associative memory cells, should be the basic units for memory traces, instead of the possibility in a specific protein for a given content of memory.

Because particular memory retrieval may be based on engram cells recruited during learning, the activation of memory cells to induce the emergence of memory-relevant behaviors should be used to study memory formation. This strategy is based on a positive correlation between memory cells and memory behaviors. If some neurons store particular memory contents, the activation of these cells by electrical, pharmacological and optogenetic approaches should induce the expression of memory-relevant behaviors. The electrical stimulation to engram cells in the brain has been used by Penfield who originally expected to localize the source of epilepsy [144]. The stimulation to engram cells in the temporal lobe induced memory recalls in wakeful epileptic patients [145,146]. Pharmacological stimulations to activate serotonin or norepinephrine systems by using these transmitters facilitate memory formation successfully [147,148]. Optogenetic stimulations to activate memory engrams induce the fear memory and false memory [149-153]. There is a positive correlation between engram cells and memory-relevant behaviors. It is noteworthy that direct optogenetic activation to neurons without increases of synaptic strength and dendritic spine density leads to memory retrievals [154], implying nonspecific neuron activation. As engram cells are widely distributed in the brain and the brain areas are interconnected, stimulations may lead to the antegrade and retrograde activation of neuronal pathways as well as the indirect activation of memory cells. The approach in stimulations to those engram cells is unable to localize primary versus secondary allocations for memory formation.

If particular memory contents depend upon memory cells recruited during learning, the downregulation of certain molecules critical for memory cells by pharmacological blockers, gene knockout or optogenetic approaches should prevent or attenuate the emergence of memory-relevant behaviors. This is a common strategy to address the causal relationship among molecular substrates, cellular architectures and memory events. The first use of surgical ablation to search the distribution of engrams was done by Lashley. Although he failed to localize memory traces, his studies imply the wide distribution of

engram cells in the cerebral brain [155-157]. In subsequent studies, the removal of the temporary lobe in human beings leads to the loss of recent memory due to the impairment of the hippocampus [158-161]. In the study of memory cells by pharmacological reagents, recent memory can be blocked by the intracerebral injection of puromycin [162-164], in which Flexner is thought to be a pioneer to study molecular mechanisms, such as protein synthesis, underlying learning and memory. These studies reveal the causal relationship between memory cells in wide brain areas and memory formation though these memory cells specific for content-relevant events remain to be tracked. With the advanced molecular biology, the downregulation of gene expressions by gene knockout [165] and optogenetics [166,167] have been successfully used to find out inverse correlations among molecules, memory cells and behaviors. These studies provide strong evidences for the causal relationships among molecular substrates, cellular architectures and memory formation.

These strategies and approaches to identify memory cells need be evaluated and validated in terms of their advantage and disadvantage. In logical analyses, parallel change, negative correlation as well as positive correlation between functions and changeable factors should be met to ensure their causal relationship. What the manipulations of molecules and/or cells lead to the changes of memory-relevant events in these three criteria should be combinedly used to figure out memory cells recruited during learning, through which consistent results are expected to obtained for the conclusion. However, inconsistent results may occur in these studies. For instance, silencing and stimulating patriate cortical neurons lead to inconsistent results during memory retrieval. Parietal lesions do not normally yield severe episodic-memory deficits, whereas parietal activations are seen frequently in functional neuroimaging studies of episodic memory [168]. These two categories of evidence suggest that an answer to this puzzle requires to distinguish the contributions of dorsal versus ventral parietal areas and the influence of top-down versus bottom-up attention on memory. The natures of memory trace cells identified in these studies include the followings. Engram cells can encode the trained signals, receive synapse inputs and undergo synaptic plasticity [169-172]. The activation of memory cells induces strong memory retrieval. Memory events are upregulated by norepinephrine and serotonin. How the memory traces encode multiple signals associatively learned remains to be reveal (please refer to associative memory cells).

Associative memory cells as basic units in engrams

Associative learning includes the acquisition of associated signals that are unitary natures of various objects, knowledge and experiences as well as the acquisition of complicated signals that are reorganized from those unitary signals in intramodal or cross-modal manner. Associative memory stands for the integrative storage and reciprocal retrieval of these associated signals in neurons. Associative memory cells are presumably basic units to fulfill these processes in associative memory through encoding multiple associated signals and receiving innate and new synapse innervations in the cerebral brain [7,8]. The integrative ability of associative memory cells indicates that activity-dependent synaptic plasticity (long-term potentiation and depression of synaptic transmission) in single neural pathway [173-175] and activity-dependent neuronal plasticity [45,176-180] may not be directly involved in the integrative storage of multiple associated signals though this plasticity may influence memory retrieval [7,8].

In terms of the location of information storages, memory traces appear to be widely distributed in the brain, such as the hippocampus, amygdala, motor cortex, sensory cortices and associative cortices [181-186,3,114,22,23,26,27,30,31]. Memory contents reside hypothetically in cell assemblies by the strengthening of neurons' interconnection that is triggered by their correlated activity in information acquisition [87]. These studies do not explain why cell assemblies are widely distributed and how plasticity at synapses and neurons coordinately integrate associated signals for their storage in primary and secondary manners, i.e., the characteristics and working principle of these neurons that coordinately encode associative memory [7,8]. Neuronal and synaptic plasticity cannot interpret memory patterns, e.g., explicit versus implicit memory, declarative versus non-declarative memory, episodic versus semantic memory and memory transformation among these patterns [34], the temporal features of associative memory as well as the contribution of associative memory to cognitive processes, e.g., associative thinking and logical reasoning. How endogenous signals generated in associative thinking and logical reasoning are memorized for future representation remains unknown. How memory is encoded under different consciousness states needs to be addressed. The natures of these cell assemblies, the patterns of their connection strengthening and the coordination of their encoding memory need to be examined in a comprehensive manner.

Associative memory cells that encode multiple associated signals as well as receive innate and new synapse inputs have been detected to be recruited by the coactivation of cortical neurons [9,5,7,8,73]. The coactivation of sensory cortices evokes their mutual synapse innervations, and recruits associative memory cells to integrate and encode associative signals [5,16,17]. Based on mutual innervations among associative memory cells [9,5,72], the associations of sensory signals for their integrative storages make each signal induce the recall of its associated signals in a reciprocal manner. In the meantime, these primary associative memory cells in the sensory cortices send their axonal projections toward brain areas relevant to cognitions, emotions and behaviors, and undergo synaptic convergences with individual neurons in these areas during logical reasoning and associative thinking to recruit them as secondary associative memory cells [185,7,8]. In this regard, mutual synapse innervations among primary associative memory cells in sensory cortices and their convergence to secondary associative memory cells in brain regions related to cognition, emotion and behaviors constitute basic cellular architectures for the reciprocal recalls of associated signals, the automatic conversion of associated signals during their recalls and the cognitions at the high orders [7,8] (Figure 1). In addition to the learning of associated signals from cross-modal sensory cortices, the acquisition of associated signals can be achieved in one of intramodal sensory cortices, such as the association of letters or words in the auditory cortex, the association of unitary images in the visual cortex, and so on.

Associative memory cells recruited in sensory cortices: Associative learning by paring whisker, odor and tail stimuli in mice leads to reciprocal responses induced by each of these signals, such as odorant-induced whisker motion, odorant-induced tail withdraw, tail-induced whisker motion, tail-induced olfaction response, whisker-induced olfaction response and whisker-induced tail withdraw [9,13,72,5]. Their barrel cortical neurons are able to encode new odor and tail signals alongside innate whisker signal as well as receive new synapse innervations from the piriform and S1-tail cortices besides innate inputs from the thalamus [9,18]. Their piriform cortical neurons encode new whisker signal and innate odor signal, as well as receive new synapse innervations from the barrel cortex alongside innate input from the olfactory bulb [72]. In other words, a portion of the sensory cortical neurons in mice after associative learning become able to encode associated signals as well as receive new synapse inputs based on their mutual innervations alongside innate input, which are named as associative memory cells [13,5,16,17]. These associative memory cells have been assured to include glutamatergic neurons, GABAergic neurons and astrocytes [9,13,72,5,16-18]. Thus, the coactivation

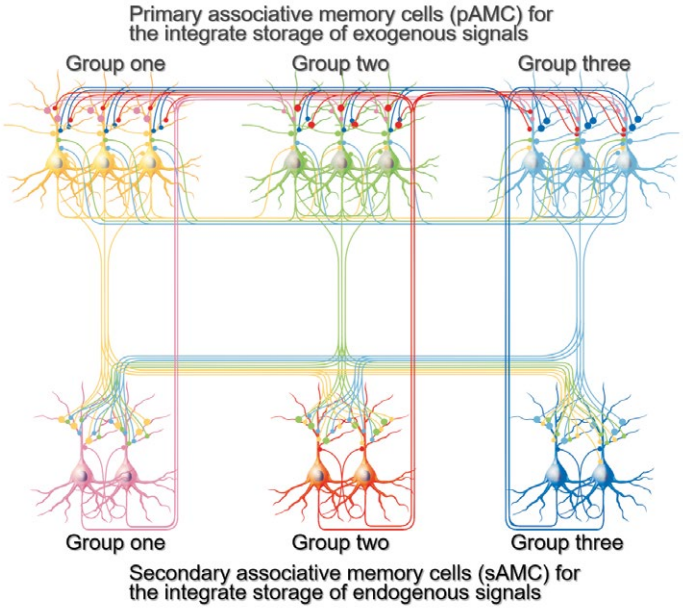

Figure 1: Associative memory cells and their connections. Three groups of primary associative memory cells (blue, green and yellow) in sensory cortices are synaptically innervated. Three groups of secondary associative memory cells (blue, red and pink) in brain areas relevant to cognition, emotion and behaviors are synaptically innervated. Mutual synapse innervations among associative memory cells in each group are intramodal, and mutual synapse innervations among three groups of associative memory cells are cross-modal. The axons of primary associative memory cells convergently and broadly innervate secondary associative memory cells whose axons project back to primary associative memory cells. All of neurons possess innate synapse innervations (yellow axons). The synapse innervations among the functional correspondent groups of primary and secondary associative memory cells are labeled by bigger presynaptic boutons.

or simultaneous activity of sensory cortices can trigger the new synaptogenesis for mutual synapse innervations and the recruitment of associative memory cells for the storage of associated signals. The association of cross-modal sensory signals may occur among all of sensory cortices, such as visual signal with auditory, olfactory, taste and somatosensory signals; auditory signal with visual, olfactory, taste and somatosensory signals; and so on, i.e., primary associative memory cells can be recruited in auditory, visual, olfactory, gustatory and somatosensory cortices by their mutual synapse innervations [7,8] (Figures 2~3).

Associative memory cells recruited through the coactivation of sensory cortices are diversified in their encoding abilities and contents. Some cells encode all associated signals (full associative memory cells) and others encode two or more signals (incomplete associative memory cells), e.g., triple, two or one of odor, whisker and tail signals [9]. If neurons are activated together and wired together, the coactivated strengths among these sensory cortical neurons may be different based on their variable excitability [47]. Neurons that encode one signal are called as new memory cells or innate memory cells [9,5]. The recruitment of diversified populations of associative memory cells in their encoding ability dissects complicated events, objects or images into simple unitary signals for their storages, future retrievals in different patterns and the reorganization of unitary signals in future associative learning [7]. In addition, the repeated coactivations of these sensory cortical neurons can facilitate the recruitment of full associative memory cells from incomplete associative memory cells as well as the formation of more *en passant* synapses among their mutual innervations, so that the number and the activity strength of associative memory cells are upregulated [33]. The proportional relationship among associative memory efficiency, associative memory cells and their plasticity [9,13,14,5,187,188] indicates an activity-dependent positive cycle between the recruitment and refinement of associative memory cells [7].

A feature of associative memory cells is the mutual axon projections and synapse innervations for encoding multiple associated signals. The molecules potentially for axon growth and synapse formation are likely substrates underlying the recruitment of associative memory cells. Current studies indicate that antagomirs for microRNA-324 and microRNA-133a by influencing *Ttbk1* and *Tet3* expressions attenuate associative memory, new synapse innervation and associative memory cell formation [9,79]. The downregulation of miRNA-342 expression and the upregulation of *Nlgn3* and *Nrxn1* expressions are coupled with the recruitment and refinement of associative memory cells [72,18]. These genes and proteins are related to axon prolongation and synapse formation. Thus, the recruitments of synapse innervations and associative memory cells may be based on a chain reaction from intensive neuronal spikes to microRNA-regulated genes and proteins that specifically manage axon prolongation and synapse formation [9,13,79]. In addition, the inhibition of sensory cortices blocks associative memory [13,5] and the injection of microRNA antagomirs into sensory cortices lowers the strength of associative memory and the recruitment of new synapse innervations and associative memory cells [9,79]. Therefore, the primary location to encode associative memory is likely in the sensory cortices, where mutual synapse innervations and primary associative memory cells are recruited [7,8].

The pair-encoding neurons that encode two signals, similar to the encoding property of associative memory cells, have been detected in the animal visual cortex *in vivo* [1,110]. These pair-encoding neurons in intramodal cortices may work for the integrative memory of the associated signals inputted from a single sensory modality, such as associated photon beams in images to the visual system, associated

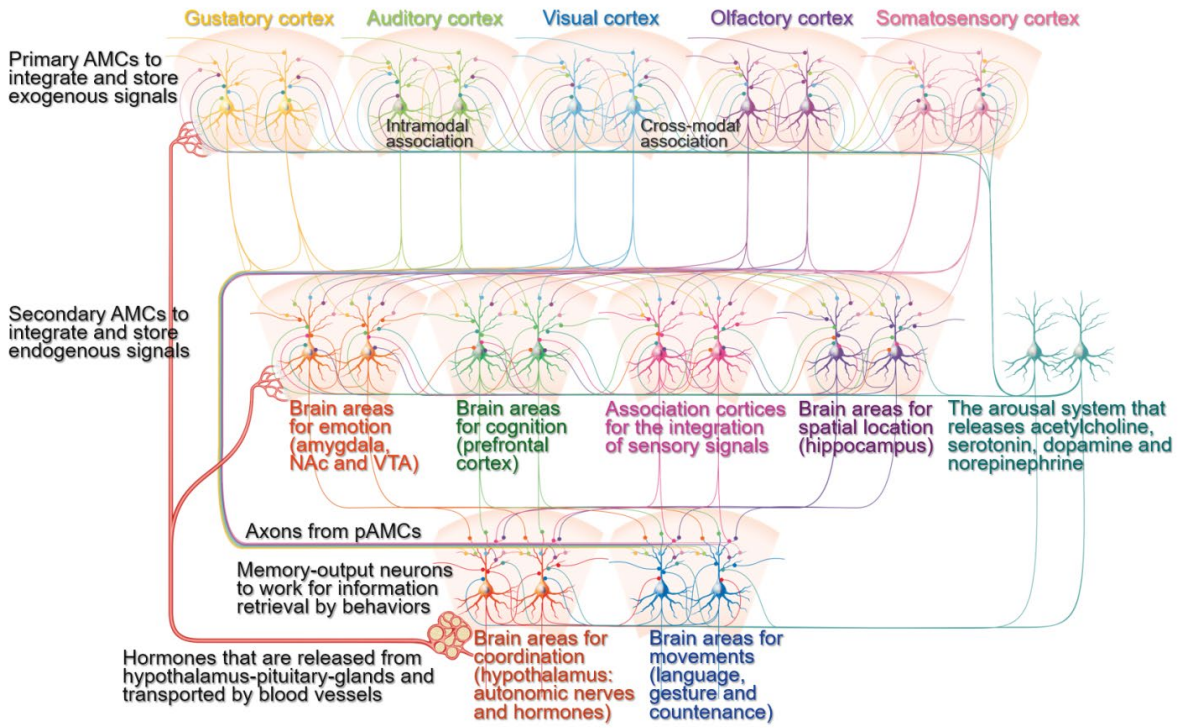

Figure 2: Associative memory cells and their working principles in the memory, cognition and emotion. Associative learning and memory include the acquisition of associated signals, the integration and storage of exogenous signals, the integration and storage of endogenous signals as well as the memory retrievals through behavioral presentation. Associative Memory Cells (AMC) are classified into primary AMCs in sensory cortices including visual, auditory, olfactory, gustatory and somatosensory cortices for the integrative storage of exogenous associated signals as well as secondary AMCs in brain areas related to cognitive processes (logical reasoning, associative thinking, computation, imagination, concept, judgement conclusion, decision and so on in the prefrontal cortex), emotional reactions (fear, aversion, happiness, angry and so on in the amygdala, Ventral Tegmental Area (VTA) and nucleus accumbens (NAc)), sensation integration (understanding and perception in association cortices) as well as spatial localization in the hippocampus. pAMCs are mutually connected through cross-modal and intramodal synapse innervations for the integrative storage and the reciprocal retrievals of associated signals. The axons of pAMCs convergently innervate onto sAMCs for cognitions, emotion and spatial localization. sAMCs are mutually connected through their synapse innervations for the integrations of cognitions, emotion, perception, localization and so on. All of these primary and secondary associative memory cells will send their axons toward brain areas relevant to behaviors (language, gesture and countenance in motion cortices) and their coordination (the systems for maintaining internal environment, e.g., the hypothalamus to control autonomic nerves and hormones). Cross-modal associative memory cells are recruited by mutual innervations among sensory cortices or between cognition- and emotion-relevant brain areas. Intramodal associative memory cells are recruited by mutual innervations among the neurons in single-modality sensory cortex, cognition brain area or emotion brain area. In addition to the activation by innate input and new synapse innervation from the coactivated brain regions to integrate and encode associated signals, associative memory cells are activated by the arousal system including the ascending reticular activating pathway in the brain stem and thalamus as well as the ascending activating pathways from the cholinergic nuclei, midbrain raphe nuclei, locus coeruleus and substance nigra that release acetylcholine (ACh), serotonin (5-HT), norepinephrine (NE) and dopamine (DA), respectively, which can maintain well wakefulness, permit normal consciousness as well as grant specific alertness and attention. In addition, associative memory cells are regulated by hormones that are released from the hypothalamus-pituitary-glands. The upregulations of AMC number and activity strength can facilitate memory to be impressive, or vice versa. The function downregulation of motion-relevant brain regions leads to the inability of memory retrieval and presentation.

odor signals to the olfactory system, associated letters and words to the auditory system and so on (Figure 2). It should be emphasized that the morphological evidence about mutual synapse innervations among the pair-encoding neurons in single modality cortices remains to be indicated.

As nerve cells, associative memory cells recruited in sensory cortices have specific features for associative memory and general features for neurons, in which specific features are used as criteria for identifying whether the neurons detected are associative memory cells. As the coactivation via the synchronous activity of cortical neurons triggers their mutual synapse innervations and recruits them as associative memory cells, the specific features of associative memory cells include the followings [7,8]. Associative memory cells receive new synapse innervations from coactivated sensory cortical neurons for their mutual connections alongside innate sensory input. Associative memory cells encode new and innate signals for their integrative storage. Their axons project to and synapse on the neurons in brain areas relevant to cognitive processes, emotional reaction and behaviors. Their recruitment is controlled by microRNA-regulated genes and proteins for axon projections and synapse formations [9,13,79]. Mutual synapse innervations among associative memory cells confer the reciprocal

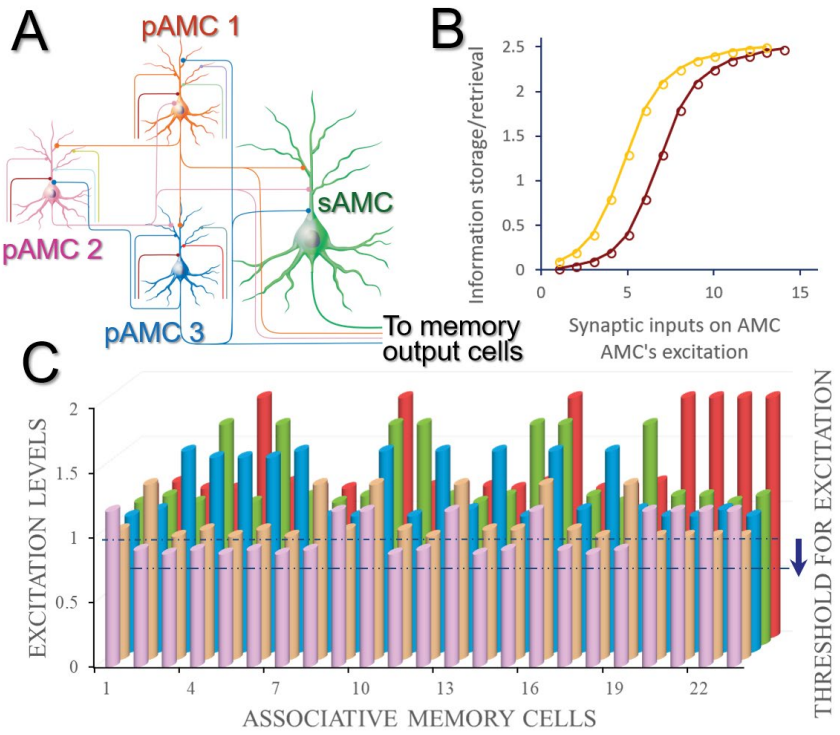

Figure 3: Associative memory cells and their functional states play the critical role in the integrative storage and the reciprocal retrieval of specific associated signals. **A)** A basic neural circuit (memory trace) for associative memory includes Primary Associative Memory Cells (pAMC) and Secondary Associative Memory Cells (sAMC). Each of these primary associative memory cells receives synapse innervations from the innate inputs (their colors correspondent to those for cell bodies), the input from the arousal system (dark red) as well as the mutual synapse innervations among them (i.e., from other primary associative memory cells). These primary associative memory cells send their axons convergently to secondary associative memory cells (green) and make synapse innervations. All of these associative memory cells send their axons to Memory Output Neurons (MON). **B)** The relationships between the excitation state of associative memory cells and the strength of memory formation/retrievals. The excitation state of such associative memory cells is influenced by the number and the function state of their synapse inputs and by their own excitability. If the excitability of associative memory cells rises, their relationship curve (dark red) shifts toward left (yellow) and the efficiency of learning and memory increases. **C)** denotes the relationship between different associative memory cells and their excitation levels. If the threshold to fire spikes (excitation) decreases, the relative excitation levels of associative memory cells increase as well as more neurons will be coactivated for the recruitment and refinement of associative memory cells in memory formation and retrieval.

recall of associated signals and the conversion of signal retrieval among different modalities, such as visual signals in images are presented by verbal language and verbal signals in stories are presented by visual diagrams. Their synapse convergences onto downstream neurons and the activation of associative memory cells grant logical reasoning, associative thinking, computing and so on. Therefore, the synapse innervations determine the specificity of memory contents. To general features for neurons and functional outcome, the number and the functional state of associative memory cells influence memory strength and maintenance. The recruited number of associative memory cells is proportional to the number of their mutual synapse innervations produced by neuronal coactivation strength and repetitive coactivations during learning as well as is influenced by development stages [9,5]. The functional state of associative memory cells is influenced by the strength of innate and new synapse inputs, their ability to convert synaptic analogue signals into digital spikes as well as their ability to output spikes [47,189-191]. In addition, glutamatergic associative memory cells will suppress the activity of other neurons via GABAergic associative memory cells and lateral inhibition to have themselves to be dominantly active for memory contrast [16,18].

Synapse innervations to associative memory cells determine memory specificity. The number and function state of associative memory cells as well as the connection and activity strengths in their synapse inputs and axon output partners influence memory power and persistence [9,14,79,188]. For instance, barrel cortical neurons receive new synapse innervations from piriform cortical neurons after associative learning alongside innate inputs from the thalamus. Synapse activity in the pathway of odor signal will drive barrel cortical neurons toward spiking threshold under the basal activity of thalamic inputs. Once spike threshold reaches, their spikes trigger downstream motor cortical neurons for odorant-induced whisker motion. With the associative memory cells in sensory cortices [9,79,5], their axon-innervated downstream neurons are able to encode these associated signals [24,28,29,18,32,192,193]. Stimulations to any of these areas in neural circuits from sensory cortices to behavior- and emotion-related brain nuclei induce memory retrieval [22,23,26,27,30,31]. It should be noteworthy that there are around ten thousand types of proteins in the living cells [143], which is much less than unitary signals remembered in life, such as words, unitary visual signals, odorants, and so on. As more than ten billion of neurons reside in the central nervous system,

those neurons with synapse interconnection, i.e., associative memory cells, should be the basic units for memory traces, instead of the possibility in a specific protein for a given content of memory.

Associative memory cells recruited in cognition-, emotion- and behavior-relevant brain areas: In addition to primary associative memory cells in sensory cortices to encode the integrative storage of exogenous associated signals, secondary associative memory cells that integrate and store endogenous signals may be recruited during the cognition, emotion and behaviors [8]. Contents, processes and outcomes generated from logical reasoning and associative thinking can be remembered. Emotional reactions to various stimulations and operations can be recalled. All of these specific events in mind may be generated based on the associative storage of learned exogenous signals in sensory cortices, such as images, stories, tastes and odors, and can be memorized in brain areas relevant to cognition, emotion or behaviors in the integrative manner for subsequent retrievals. In terms of cellular substrates, the reorganized association of stored signals in sensory cortices may make primary associative memory cells to strengthen their mutual synapse innervations and convergent innervation on downstream neurons as well as to receive feedback synapse innervations during cognitive processes and emotional reactions. These downstream neurons become able to encode the associated signals and are recruited to be secondary associative memory cells that memorize specific contents generated in associative thinking and logical reasoning [11,33]. The feedforward and feedback interaction among primary and secondary associative memory cells make associative thinking and logical reasoning with the inclusion of sensory origins [7,8] (Figures 1~2).

In terms of brain areas to produce secondary associative memory [7], prefrontal cortical neurons demonstrate a sustained activity after pair stimulations [117,29]. Cue-response neurons in the inferotemporal cortex are detected after associative learning [24]. Neurons in response to conditioned and unconditioned stimulations and their response transformation are seen in the amygdala [194]. Neurons in the hippocampus and amygdala are involved in contextual fear memory [195]. Memory cell assemblies for temporal signals are overlapped and recorded in the hippocampus [19]. The activation of engram cells in the amygdala or the hippocampus is sufficient to induce fear responses [22,23]. These data imply that memory cells are generated in the prefrontal cortex, hippocampus, amygdala and associative cortices for memory retrievals [196,27]. Whether these memory cells are synaptically innervated by primary associative memory cells in sensory cortices remains to be examined.

After associative learning by pairing whisker, odor and tail signals, neurons that encode three signals are detected in the motor cortex, prefrontal cortex and hippocampus [11,32,33], in addition to the barrel and piriform cortices [9,79,5]. The responses of the neurons in the prefrontal cortex, the hippocampus and the motor cortex to the signals are attenuated by inhibiting barrel or piriform cortical functions. Their responses and plasticity are sustained in the barrel cortex for long-term and are decayed in the motor cortex after the pair training ends. Individual neurons in the prefrontal cortex, motor cortex and hippocampus receive synapse innervations from the coactivated sensory cortices after paired stimulations [11,32,33]. These results provide functional and morphological evidences for the recruitment of secondary associative memory cells in the prefrontal cortex, the hippocampus and motor cortex through their coactivity with primary associative memory cells in sensory cortices [8].

Whether memory cells in the downstream of sensory cortices undergo cross-modal connections, similar to primary associative memory cells [8], appears indicated by recent studies. The pathway from the ventral hippocampus to the nucleus accumbens is involved in social memory [25]. Engrams in the prefrontal cortex emerge after receiving inputs from the hippocampus and amygdala in contextual fear memory [21]. Axon projection from the prefrontal cortex and hippocampus to the amygdala is formed during fear memory [197]. The pathway from the prefrontal cortex to the striatum plays a crucial role in reward memory [26].

The characteristics of secondary associative memory cells in cognition- and emotion-related brain areas and association cortices are given below. They receive new synapse innervations from primary associative memory cells in coactivated sensory cortices in convergent and divergent manners during cognitive events and emotion reactions. They encode endogenous associated signals from sensory cortices for integrative storage. Associations of cognition events and emotion reactions induce mutual synapse innervations among these secondary associative memory cells. Their axons project to memory-output cells in behavior-relevant brain areas for memory representation by language, countenance, gesture and writing. The recruited number of secondary associative memory cells is proportional to the mutual synapse innervations evoked by coactivation strength and repetitive coactivations during cognition as well as is affected by development stage. The function state of secondary associative memory cells is influenced by synapse input, their ability to convert synaptic analogue signals into digital spikes and their ability to output spikes that drive memory-output cells. Synapse innervations onto secondary associative memory cells determine the specificity of memory contents during cognition and emotion. The number and excitability of secondary associative memory cells as well as their connection and activity strengths set up memory persistence and power. Activations to secondary associative memory cells confer the rehearsal of associative thinking, logical reasoning and emotional reactions. It is pointed out that the outputs of secondary associative memory cells innervate brain areas, such as the hypothalamus and extrapyramidal system, to influence sympathetic/parasympathetic balance, temperature set-point, food ingestion and hormones to be involved in emotional reactions and behaviors [12,7].

Associative memory cells detected in cerebral cortices include glutamatergic neurons, GABAergic neurons and astrocytes [9,13,79,5,16-18]. The connections between glutamatergic neurons and GABAergic neurons is mutually upregulated after memory formation [79,18]. These data indicate that all of these memory cells constitute the basic units to store specific associated signals. The activation of glutamatergic associative memory cells will cause them to be excited and their neighboring neurons to be inhibited by GABAergic associative memory cells and lateral inhibition, so that the memory of associated signals is maintained in a contrast manner. In the meantime, these glutamatergic associative memory cells can limit themselves so not to become over-excited through GABAergic associative memory cells and recurrent inhibition [7]. In terms of interactions among associative memory neurons and astrocytes, the working load of associative memory neurons can be supported by associative memory astrocytes that transfer nutrients and waste products between neurons and blood vessels [9,5,7].

In addition to associative memory cells in cross-modal sensory cortices or among cognition- and emotion-related brain areas, associative memory cells can be located in intramodal cortices, such as associated photon beams in images to the visual system [1,110], associated odor signals to the olfactory system, associated letters and words to the auditory system and so on (Figures 2~3). Neuronal afferent pathways for associated signals in a single sensory modality may innervate multiple groups of neurons, in which neurons in each group encode one of these associated signals. For instance, different

groups of auditory cortical neurons receive neural afferents carrying different frequency sounds in a point-by-point manner and each group of neurons encodes one of specific frequency sounds. Different visual cortical neurons receive synapse innervations from different retina cone cells in a point-by-point manner. The coactivation of the neurons that encode different intramodal signals can induce their mutual synapse innervations, such that associative memory cells in a single modality of sensory cortices are recruited. Associative memory cells in a given sensory cortex are recruited to memorize intramodal signals with different features, strengths and locations of input signals. With associative memory cells in intramodal sensory cortices, intramodal memory to associated signals is formed, e.g., image one induces image two recall, odor one induces odor two recall and word one induces word two recall, or the other way around [7]. There is the time delay among intramodal signals, in which activity persistence in different sets of neurons in a given sensory cortex may grant the partially temporal overlap of their coactivity to recruit intramodal associative memory cells. The different proportions, activity strengths and connections of intramodal associative memory cells are responsible for the storage and retrieval of intramodal signals with different features [12,97]. Intramodal associative memory cells may also be recruited within one of brain areas relevant to cognitions and emotions [8].

In terms of the relationship between primary and secondary associative memory cells in engrams and their role in memory-relevant events, our proposed model is given below. Basic architectures for their working together include mutual synapse innervations among primary associative memory cells in sensory cortices and their axon convergence onto secondary associative memory cells in brain areas relevant to cognitions, emotions and behaviors. Each set of primary associative memory cells reciprocally connects one set of secondary associative memory cells, whose functions are closely related (Figure 1). The axons from all of these associative memory cells terminate onto motor neurons for memory output (memory output cell) and innate reflex (Figure 2). Mutual synapse innervations among primary associative memory cells constitute the interaction circuits for the reciprocal retrieval of associated signals by each of the sensory cues and the automatic conversion retrieval of associated signals among different modalities [9,79,5,18]. Convergent synapse innervations from primary associative memory cells to secondary associative memory cells (Figure 1) confer logical reasoning, associative thinking and other integrative cognitions (such as abstraction) induced by one of cues [11]. As showed in Figure 1, one of secondary associative memory cells is convergently innervated by three sets of primary associative memory cells that carry three kinds of signals, which maintain basal activity in this secondary associative memory cell. When an input cue activates three sets of primary associative memory cells by their mutual synapse innervations, these primary associative memory cells can convergently activate this secondary associative memory cell, in addition to its activation through the dominantly innate chain from one set of primary associative memory cells onto one set of secondary associative memory cells. In other words, three kinds of signals triggered by one of these cues drive this secondary associative memory cell to achieve the integration of three associated signals for associative thinking and logical reasoning. This integration is also facilitated by the mutual synapse innervations among secondary associative cells that contribute to interactions of the higher order cognitions and emotions. The divergent synapse innervations from primary associative memory cells in sensory cortices to secondary associative memory cells in the prefrontal cortex, the hippocampus and other areas [11,32,33] (Figures 1~2) make the associated signals to be stored in several brain areas for persistent maintenance with less chance being loss, to be used for different cognitive events and emotional reactions as well as to be generalized in concepts and knowledge [11,7]. The functional compatibility between presynaptic and postsynaptic partners [189] plays a critical role in their coordination for memory formation and decay in the multiple uses. In addition to this feedforward innervation from primary to secondary associative memory cells, there may be feedback connection from secondary associative memory cells to primary associative memory cells, by which the learned exogenous signals automatically initiate cognitions and emotions as well as endogenous signals generated from cognitive events and emotional reactions contain sensory signal origins [7] (Figures 1~2).

Plasticity at associative memory cells

Cell assemblies formed by their connection strengthening through their correlated activities, especially the coincidence activity of presynaptic and postsynaptic cells, presumably work for learning and memory [87]. This hypothesis is well matched by synaptic and neuronal plasticity [198-200,75], e.g., long-term potentiation and depression in synaptic transmission [173,175] or neuronal excitability [29,180]. Many studies about synapse and neuron plasticity are not carried out in memory cells despite brain areas presumably relevant to memory. Tetanus-induced LTP that expresses in a bundle of axons and their innervated synapses may be due to the decrease of their spike threshold, instead of the expression at individual synapses. If the strengthening of synaptic transmission expresses in a given neural pathway, this potentiation cannot explain the integrative storage of associated signals carried from their correspondent inputs in associative memory cells. Moreover, tetanus-induced LTP usually cannot express at synapses in unmatured animals, such that it is not relevant to learning and memory in early life when the learning is efficient and memory is impressive. Long-term depression at synapses is induced by low frequency stimulation, in which 1 Hz stimuli do not mimic any physiological spiking in the neurons, as well as results from the extensive depletion of presynaptic vesicles, especially at synapses in young animals. The association of potentiation in some neural pathways and depression in other pathways [45] may be relevant to the contrast in memories [12]. These uncertainties questions how these data about plasticity are written in the profile of cellular mechanisms underlying associative memory.

The potentiation of synaptic transmission may be caused by the conversion of developmentally unmatured synapses into natured synapses, the conversion of silent synapses into function synapses, the conversion of inactive synapses into active synapses, the upregulated compatibility between presynaptic and postsynaptic partners. During postnatal development, the formation of glutamatergic synapses is featured by the emergence of NMDA receptors in the central area of postsynaptic density and the subsequent insertion of AMPA receptors around [201-203]. The complete form of glutamatergic synapses includes the embedding of NMDA and AMPA receptors in the postsynaptic density, i.e., matured glutamatergic synapses that are critical for the fulfilment of synapse plasticity. Even though both NMDA and AMPA receptors are localized in the postsynaptic density, their functions appear sequentially to be different, in which AMPA receptors are activated by glutamates for fast synaptic transmission and the membrane depolarization facilitates the activation of NMDA receptors to mediate slow synaptic transmission [204]. With this complete form of glutamatergic synapses, they possess a nature in the conversion of silent synapses into functional synapses during synaptic plasticity, in which membrane depolarization activates NMDA receptors and subsequently AMPA receptors to have synapses be converted from silence to function. In fact, even though synapses include both kinds of receptors, they remain to be inactive. Once calmodulin-dependent protein kinase II is activated in postsynaptic neurons, these inactive synapses are converted into active synapses, especially this process

is matured during the postnatal development [205]. As this kinase plays a critical role in LTP induction and maintenance [206,207], the conversion of inactive synapses into active synapses is a mechanism underlying synaptic potentiation. Finally, there is a functional compatibility between presynaptic and postsynaptic partners [189]. The upregulated compatibility between presynaptic and postsynaptic partners may be critical for the refinement of synapses.

Based on current studies, there are two forms of plasticity in associative memory cells, i.e., the refinement during their recruitment for them to coordinate each other and the refinement induced by cues to recall specific signals, both of which are activity-dependent based on coactivations among neurons [9,13,79,72,5,33,18], i.e., recruitment-relevant refinement and activity-dependent plasticity.

In the recruitment of associative memory cells from cortical neurons through their coactivation and mutual synapse innervations, the number of excitatory synapses and the transmission strength at each of these synapses on glutamatergic and GABAergic neurons are enhanced; the output of glutamatergic neurons is enhanced and the output of GABAergic neurons is weakened [193,72,187,18,188]. In addition, the active intrinsic property of glutamatergic associative memory cells is upregulated and the excitability of GABAergic associative memory cells is downregulated [72,187,18,188]. Mutual synapse innervations among the associative memory cells are increased [187,18]. Increases in the driving force from excitatory synapses and in the excitability of memory cells as well as decreases in the driving force from inhibitory synapses shift the balance of these cortical neurons between excitation and inhibition towards excitation. Their high activity can attract more synapse innervations, recruit more glutamatergic/GABAergic associative memory cells, promote their function state to an optimal level for information storage and facilitate the activation of these associative memory cells for retrievals of associated signals [13,14,5,18]. The increased number and function of excitatory synapse inputs in associative memory cells strengthen their encoding ability and precision [47,190,191] for efficient memory formation and precise retrieval. If excitatory associative memory cells are over active, they activate neighboring inhibitory neurons to prevent the hyperactivity by recurrent negative feedback [45,208,47].

There are two forms of neuronal excitation plasticity to interpret how neuronal refinements are involved in the formation and the retrieval of associative memory, i.e., the downregulation of threshold potential to fire spikes and the upregulation of spiking ability to fire more sequential spikes. The intensive activity of cortical neurons by high frequency stimulus, similar to neuronal coactivation during associative learning, shifts spike threshold potential toward the resting membrane potential, so that the firing of neuronal spikes is facilitated [180]. The intensive neuronal activity also upregulates the capacity to fire sequential spikes [75,29]. Both mechanisms elevate the neuronal capability to encode digital spikes, which strengthens a chain reaction from spikes to microRNA-regulated expression of genes and proteins that facilitate the recruitments of new synapse innervations and associative memory cells [9,79,72,5,18] as well as the retrieval of the associated signals (Pignatelli et al., 2018). These changes have been detected in associative memory cells [72,18,188]. Thus, plasticity in neuronal excitability may play one of central roles in learning and memory, which is reiterated by a current review [209].

In the study of memory cells, synaptic potentiation has been seen at engram cells in slices of the prefrontal cortex, hippocampus and amygdala [154] as well as the excitation enhancement of B51 neurons is isolated from Aplysia [210]. In the study by using cues to sensory inputs *in vivo*, activity-dependent potentiation in response to associated signals is induced at input pathways in the active group of primary and secondary associative memory cells, and activity-dependent conversion from silent into active neural pathways in response to associated signals is initiated in the inactive group of associative memory cells [11,7,33]. This activity-dependent upregulation in response to associative signals in the given group of associative memory cells allows them to become more excited than their neighboring neurons and to be highly sensitive to the excitatory driving force from sensory cues, such that more associative memory cells in response to all associated signals are recruited by their increased mutual synapse innervations [72,18]. Moreover, activity-dependent potentiation in response to associated signals can be induced *in vivo* at homosynaptic and heterosynaptic pathways [33], which facilitates the reciprocal recall and logical reasoning of associated signals. Activity-dependent potentiation at associative memory cells in response to associated signals inputted through new synapses may be mechanistically caused by the enhancement of individual synapses and/or the conversion of inactive or silent synapses into active synapses [204,205], since new mutual synaptic innervations have been formed among these associative memory cells [9,79,72,5,11,7,33,18]. In terms of function impacts, activity-dependent potentiation at primary associative memory cells may facilitate the memory retrieval of exogenous associated signals. Activity-dependent potentiation at secondary associative memory cells facilitates the memory retrieval of endogenous signals generated during cognitive processes and emotional reaction. Thus, the spontaneous or cue-induced recalls of these signals are emerged for the rehearsal of cognitions and emotional pulses. Recruitment-relevant neural potentiation and activity-dependent neural potentiation are supported by a fact that the enhancement of neuronal excitability is multi-grades in nature [180].

Recruitments of primary associative memory cells in sensory cortices and of secondary associative memory cells in cognition/emotion-relevant brain areas endorse the specificity of the stored associative signals [9,13,79,72,5,8,18]. The number and function state of associative memory cells influence memory strength and maintenance as well as memory retrievals [7,13,14,79]. Structural and functional plasticity at subcellular compartments of associative memory cell influences whether they sensitively integrate associated signals, precisely memorize these signals and efficiently trigger their target neurons for memory retrievals [72,18]. The maintenance of activity-dependent refinement at associative memory cells supports the period for them to be sensitive to the cue for memory retrieval. It is emphasized that both recruitment and refinement of associative memory cells depend on their simultaneous activity [9,13,72,5,18]. The activities of associative memory cells as central point comprise coactivity-dependent positive cycle in their recruitment and refinement, i.e., activity together, mutual innervation together and strengthening together. Highly active neurons while receiving associated signals are recruited as associative memory cells and are functionally upregulated. The upregulated population and function state of associative memory cells during repeated learning processes recruit more associative memory cells and upregulate their active state further [7]. Activity-dependent positive cycle in the recruitment and refinement of associative memory cells, which is based on the function compatibility between neuronal partners [211], can interpret realistic practices under conditions of normal consciousness and well attention, i.e., the more learning times is, the more associative memory cell recruitment/refinement is, and the more impressive memory is. It should be pointed that associative memory cells fall into the active group of neurons in the brain, but active neurons labeled by non-specific immediate early genes may not be memory cells.

In terms of the functional states of primary and secondary associative memory cells influenced by synapse inputs, the number and strength of the inputted synapses are proportional to the excitation

levels of these associative memory cells [9,14,79,187,188]. The increase of synapse inputs that carry specific memory contents and their upregulation from receiving repeated cues drive associative memory cells to become more excitable for the retrieval of this specific memory and the full recruitment of memory cells. The increased activity of synapse inputs from the arousal system boosts associative memory cells to become more excitable for the retrieval of memory contents in a nonspecific manner. Moreover, the increase of excitability or the decrease of spiking threshold in associative memory cells will make them be easily activated for the retrieval of memory contents nonspecifically and the recruitment of more associative memory cells [72,18]. A theoretical illustration of associative memory cells driven by synapses and neuronal excitability is given in Figure 3.

The neurons in the central nervous system that are dominantly recruited as associative memory cells need be identified. Based on a principle that the simultaneous coactivation of cortical neurons and the activity-dependent positive cycle between the recruitment and refinement of associative memory cells are primary driving force for the neurons being recruited as associative memory cells [7], we assume that the neurons with high levels of excitation and synapse inputs are preferentially are recruited as associative memory cells. In other words, cortical neurons, which possess a lower spiking threshold caused by their activities and the stronger synapse inputs driven by attention calls from previously learned relevant associated signals carried by the synapses formed in those events or by the consciousness level maintained by the arousal system plus memory, are favorably recruited as associative memory cells. The dominant active neurons are always recruited to be associative memory cells at the first grade, their activation and recruitment trigger the neighboring neurons via their synapse connections to be more active and become associative memory cells in the second grade and so on. This preferential grade in the recruitment of associative memory cells leads to a time sequence for the groups of cortical neurons to be recruited as associative memory cells when multiple associated signals are exposed to learners sequentially, such as words by words in sentences or articles and images by images in visual or video views [7].

There are a few interesting observations about the recruitment and refinement of associative memory cells. The establishment of associative memory has development dynamics, i.e., memory formation shows initial increase and then decrease in aging [5]. Synapse and neuron plasticity matures in postnatal development [205,180]. These studies indicate dominant roles of recruitments versus refinements of associative memory cells in memory formation and retrieval during different developmental stages. The activity-dependent recruitment of associative memory cells may play the dominant role in associative memory during early and young age, while the activity-dependent refinement of associative memory cells works dominantly after these stages. The knowledge learned in young age is relatively simple unitary signals whereas the knowledge learned in matured age is complicated or those reorganized unitary signals. In this regard, associative memory cells recruited in young age store unitary signals, and associative memory cells refined in matured age work for learning reorganized unitary signals [7].

Associative memory cells are modulated by the arousal system

In addition to specific new synapse innervations and innate inputs on primary associative memory cells for the integrative storage of associated signals as well as the convergent and reciprocal innervations on secondary associative memory cells for logical reasoning and associative thinking (Figure 1), these associative memory cells may receive other synaptic inputs and neurotransmitters for the modulation of their functional state [7]. In the central nervous system, the arousal system that include the ascending reticular activating pathway [212,213] and the ascending activating pathway from the neuronal axons of the locus coeruleus, midbrain raphe nuclei and cholinergic nuclei [214-217] widely innervates cerebral neurons to maintain wakefulness and to grant consciousness. Their released transmitters including acetylcholine, serotonin and norepinephrine theoretically modulate the functional states of ready-recruited neurons and associative memory cells. The activity of this arousal system confers the coactivation of cortical neurons for their recruitment to be associative memory cells as well as maintains the basal activity of primary and secondary associative memory cells (Figure 2). In other words, the alert and reward facilitate the recruitment and refinement of associative memory cells [7].

It has been suggested that learning and memory are modulated by neurotransmitters, such as acetylcholine, norepinephrine and serotonin [148,218-221], which are localized in the arousal system [214-217]. For instance, a direct activation of acetylcholine M1-type receptors on hippocampal interneurons facilitates learning process and memory formation [222]. The infusion of norepinephrine or adrenoceptor agonists into the amygdala or the prefrontal cortex enhances memory formation, which coordinates with the action of stress hormone [223]. The augmented and reduced activities of serotonin neurons lead to bidirectional influence on memory and cognition [224,225]. The application of dopamine to activate their type-I and type-V receptors in the forebrain and the hippocampus plays critical role in spatial learning and memory [226,227]. There is a coordinated strengthening effect of serotonin and norepinephrine on associative memory cells to facilitate associative learning and memory [33]. These data provide evidences for acetylcholine, serotonin, norepinephrine, dopamine and stress hormones to modulate learning and memory. How these molecules act onto the presynaptic inputs of associative memory cells to influence their neurotransmitter release or the bodies of associative memory cells to regulate their excitability remain to be addressed.

It has been found that serotonin facilitates the neuron excitability and neuron responses to synaptic inputs [228,229], and that the activation of dopaminergic neurons facilitates synaptic bouton formation and postsynaptic neuron activity in their target regions [230]. The plasticity of these monoaminergic neurons may modulate the recruitment and refinement of associative memory cells, and in turn influence memory formation and memory-related cognitions. This modulation supports the fact that the high levels of wakefulness, consciousness, attention and motivation based on the active monoaminergic and cholinergic neurons elevate the efficiencies of associative learning and memory retrieval.

Associative memory cells versus engrams

Whether associative memory cells are the basic units in memory traces or engrams needs to be figured out, though these studies above may issue a positive answer. Table 1 presents the data from the studies in these fields to conduct the comparison between associative memory cells and engrams. Similarities between associative memory cells and engrams grant a possibility that basic units in engrams, which encode associated signals, are associative memory cells.

The role of associative memory cells in physiology and psychology

Associative memory cells are essential for memory formation, memory retrieval, cognitions and emotional reactions [9,79,187,72,5,33,32,188]. The nature and work principles of associative memory cells can be used to construct a working map (Figures 1~3) relevant to associative memory by cross-modal or intramodal manner,

Table 1: Associative memory cells versus engrams.

	Associative memory cells (AMC)	Memory traces or engrams
Classification in neural networks relevant to memory formation	Primary associative memory cells (pAMC) in sensory cortices and secondary associative memory cells. (sAMC) in cognition- and emotion-relevant brain areas. AMCs include glutamatergic cells, GABAergic cells and astrocytes.	Engrams are widely distributed in the brain, such as the hippocampus, the amygdala, association cortices, sensory cortices and so on.
Dendritic synapse innervations	pAMC: newly formed mutual synapse innervations among sensory cortical neurons for the reciprocal retrieval of associative signals. sAMC: synapse innervations from pAMC in convergent and divergent manners. Their mutual innervation for integrative cognition and emotion.	Engrams in the hippocampus or the amygdala receive axon inputs from the auditory cortex in fear memory.
Encoding signals	pAMC: multiple associated signals in sensory cortices. sAMC: integrative signals from sensory cortices.	Signals by trained cues.
Axon projections	pAMC: axons project toward sAMC and motor cortical neurons. sAMC: axons project to motor cortical neurons.	Engram cells project to various brain areas.
Neuronal circuits for memory traces	pAMCs in mutual connected sensory cortices convergently innervate onto sAMCs in the prefrontal cortex, hippocampus, amygdala, nucleus accumbens and association cortices. They innervate the motor cortex.	The wide interconnection among engrams.
Molecules	miRNAs: miRNA-324-5p, miRNA-133a-3p and miRNA-342-5p Genes and proteins: *Ttbk1*, *Tet3*, *Nlgn3* and *Nrxn1*.	Engrams are labeled by immediate early gene and transcription factor CREB, as well as regulated by epigenetic process.
Mechanisms	A chain reaction: intensive spikes in the coactivated neurons, miRNA-mediated epigenetic processes (+), up-/down-regulated genes and proteins for new axon prolongation and synapse formation.	Numerous intracellular signaling pathways, such as protein kinases.
Modulations	Serotonin, norepinephrine, dopamine and estrogen.	Serotonin, norepinephrine, dopamine and others
Animal models	Associative learning and memory in a reciprocal manner.	Fear memory by the association of electrical shock and sound.

which includes the efficiency of associative learning, the integrative storage of multiple signals, the strength and preservation of associative memory, the efficiency of memory retrieval, the transformation of simple to complex information storage, the temporal sequence of learning and memory to multiple signals, the correlation of associating memory to cognitive events and emotional reaction and so on. This working map of associative memory cells also assists interpreting memory patterns, e.g., declarative (explicit) versus nondeclarative (implicit) memory, episodic versus semantic memory and transformation between such patterns under the conditions of consciousness and attentions.

The simultaneous activity of the neurons among different brain areas is essential for recruiting new synapse innervations and associative memory cells. The coactivity of sensory cortical neurons by cross-modal or intramodal manner induces their mutual synapse innervations, so that these neurons become able to encode multiple associated signals, i.e., these neurons are recruited as associative memory cells [9,79,5,18]. The coactivation of these primary associative memory cells also drive their axon prolongation and convergent synapse innervations onto the neurons in cognition and/or emotion-relevant brain areas, recruiting them as secondary associative memory cells in logical reasoning and associative thinking [193,11,32,33,7]. Associative memory cells based on their synapse inputs and mutual synapse innervations constitute memories specific to those associated signals. Activity-dependent positive cycle in the recruitment and refinement of associative memory cells will recruit more associative memory cells to strengthen memory depth and maintenance [7]. These studies provide new insights for memory formation, suggesting that mutual synapse innervations among primary associative memory cells endorse a reciprocal retrieval of associated signals and that secondary associative memory cells based on synapse convergences from primary associative memory cells work for associative thinking and logical reasoning. These results in activity together, connection together and strengthening together also upgrade

a hypothesis by Hebb that the repeated coactivation of interconnected cells evokes the strengthening of neural wire to form cell assemblies for memory [87].

Associative memory formed by the association of multiple signals from cross-modal sensory modalities is commonly seen in life, such as the association of visual and auditory signals. Memory retrievals can be achieved by the automatic conversion of visual signals into verbal signals, or other way around, as well as the reciprocal retrieval induced by either cues of associated signals [7]. For instance, images in movies or videos can be recalled and represented by verbal styles. Contents in verbal stories can be recalled as diagrams. Primary associative memory cells by mutual synapse innervation among cross-modal sensory cortices may contribute to the reciprocally induced retrievals and the automatically conversional retrievals of associated signals among cross-modal sensory modalities. Similarly, the intramodal association of multiple unitary signals is commonly seen, e.g., the association of different objects in a single view or different parts in an object in the visual system as well as different letters or words in single sentence in the auditory system. Intramodal associative learning refers to the association of unitary signals in a single sensory system. Primary associative memory cells through mutual synapse innervations [7] and pair-encoding [1,110] in the single sensory cortex endorse memory retrievals in a picture-by-picture or word-by-word manner. It is noteworthy that signals in the visual system and the auditory system are usually complicated. An image consists of numerous photon beams with various light strengths and colors. Each sentence consists of many words and letters. Images that consist of numerous photon beams with different spatial distributions and light strengths are detected by different cone cells in the retina, which transmit these photon signals via visual nerves to visual cortical neurons in the point-by-point manner. Sound wave frequencies from words and letters are detected by hair cells in different segments on cochlea base membrane, where hair cells are stimulated and their electrical signals are transmitted via auditory nerves to auditory cortical neurons in a point-by-point manner [231]. How these unitary signals included in an image or a sentence are reintegrated and specifically memorized in cerebral cortices is largely unknown [7].

In line with the principle of activity together, connection together and strengthening together [7], the coactivation of auditory cortical neurons, which receive synapse inputs from hair cells on cochlea base membrane and encode words or letters with different sound frequencies, induce mutual synapse innervations among these neurons to recruit intramodal primary associative memory cells that store these unitary sound signals in early life. As cortical neurons possess a few folds in the difference of their excitability [7,232], it is postulated that neurons with the highest excitatory state are dominantly activated. The afterdischarge of the neurons initially activated by the first letter or word coincides with the discharge of the neurons activated by the second ones, the afterdischarge of the neurons for the second letters or words coincides with the discharge of neurons for the third ones, and so on. The coactivation of these neurons induces their mutual synapse innervations, which constitutes the integrative storage of letters in a word or words in a sentence. In repeated learnings of this sentence or word, this group of auditory cortical associative memory cells is strengthened in their mutual synapse innervations and activities. The recruitment and refinement in this group of auditory cortical associative memory cells confer the consolidated memory of this word or sentence for subsequent retrievals. In the subsequent lifespan, sound signals to the auditory system become complicated, which are the reorganization of unitary sound signals including letters and words. The learning of these reorganized unitary signals will strengthen the activities of their correspondent associative memory cells that have stored unitary sound signals via their synapse innervations and excitability. The upregulation of these associative memory cells will encode the newly listened words and sentences, which are preferentially activated in memory retrievals [12]. Moreover, glutamatergic associative memory cells suppress the activity of other neurons by GABAergic associative memory cells and lateral inhibition to have themselves activated preferentially for the retrieval of memorized words or sentences [16,18].

The coactivity of visual cortical neurons that receive point-by-point synapse innervations from retina cone cells in early life evokes mutual synapse innervations among these neurons in order to recruit intramodal associative memory cells that store unitary signals (photon beams with different intensity and color) in visual images. There is a proportional relationship between neural activity strength and stimulus intensity [18], such that the neurons receiving the light beams with stronger intensity and more fresh colors in a visual image are more active. In line with the principle of neurons that are active together, connecting together and strengthening together [7], mutual synapse innervations are formed dominantly among more active neurons. These highly active neurons are recruited to become a group of intramodal primary associative memory cells that are interconnected to fulfill the integration and storage of light beams with strong intensity and fresh color in this visual image. So, this visual image in the front of eyes is converted to a neural image in the visual cortex based on a local neural network that consists of associative memory cells in an engram particular for this visual image, though the light beams in this visual image are dissected by retina cone cells and transmitted by visual nerves to visual cortical neurons in a point-by-point manner in medium steps [12]. In the meantime, the axons of these primary associative memory cells may project to visual association cortices [233,234] and make the convergent synapse innervations onto their neurons to recruit secondary associative memory cells [33]. This process from primary to secondary associative memory cells fulfills the transferring of image signals, especially strong photon beams in this visual image, into the integrative storage at the secondary level as well as allows primary associative memory cells in the visual cortex to be able to receive new signals. As the neurons in the visual cortex correspond to the retina cone cells in a point-by-point manner, intramodal primary associative memory cells in the visual cortex receive major and minor synapse innervations based on their activity strength stimulated by signals from cone cells. Secondary associative memory cells in visual association cortices mainly receive convergent synapse innervations from active primary associative memory cells with major synapse innervations and active synapses converted from silent synapses, such that major features in the visual image can be integrative storage and subsequent retrieval [12]. Our suggestions are supported by a current report that visual association areas are recruited during memory formation [235]. In subsequent associative learning based on the reorganization of unitary signals in various new images, the portion of associative memory cells reactivated by those reorganized unitary signals will be integrated together through the conversion of inactive/silent synapses into active synapses among them to fulfill the integrative storage of new associated signals [12,205].

In practice, intramodal and cross-modal associative learning and memory occur simultaneously, especially the association of visual and auditory signals. For instance, unitary signals in visual images are associated to verbal signals during social activities, such as family activities, personal communications and classroom studies, in which each feature of a visual image is given clear definition by words or sentences. During social interactions, numerous associations are established between unitary signals from the visual modality and words/phrases from the auditory modality. These associations at unitary levels confer the learning of complicated signals based on the reorganization

of these unitary signals and the reorganized integration of associative memory cells. After cross-modal associative learning, individuals are able to fulfill the reciprocal recall of the associated signals, i.e., a signal evokes the recall of its associated signals, or other way around, as well as the automatic recall of signals in one modality that have been learned through another modality, i.e., a view of images is converted into verbal recall, or other way around [7]. There are two mechanisms involved in these events. In early life, the learning of associated signals from two or more modalities coactivates sensory cortical neurons in these modalities and induces mutual synapse innervations among them. Visual cortical neurons that encode unitary signals in the image mutually innervate with auditory cortical neurons that encode words or phrases. For instance, the neurons encoding unitary signals in image lemon interconnect with the neurons that encode words "lemon", "yellow" and "oval", based on their coactivation in initial learning [7]. Numerous associations between unitary visual signals and auditory signals in social activities induce mutual synapse innervations between visual and auditory cortical neurons to form thousands and thousands of cell-pairs, i.e., the pairs of primary cross-modal associative memory cells that fulfill the integrative storage of these associated signals. Their active states grant memory retrieval. The accumulation of these associative memory cells that encode pairs of unitary signals confers the learning of complicated signals reorganized from these unitary signals as well as the recollection of these relevant signals. In postnatal development, the capabilities of axon growth and synapse formation are gradually attenuated [5]. The learning of complicated signals during aging may utilize another mechanism for their memories, i.e., the coactivity-dependent upregulation of associative memory cells in their excitability and mutually innervated synapses [7,33,18] as well as the activity-dependent conversion of inactive synapses into active synapses [205]. With repeated coactivations of these associative memory cells, their activity-dependent positive cycle in the recruitment and refinement elevates the number and function state of associative memory cells. As long as the upregulation of their number and function is maintained at a sufficiently high level, these complicated signals can be retrieved automatically and/or by cues [12].

Through the coactivation-induced mutual synapse innervation for recruiting associative memory cells and coactivation-induced functional upregulation among associative memory cells, individuals can gradually memorize associated signals from unitary to reorganized unitary, i.e., the transformation of simple to complicated information storage, in a topic-related manner [8]. Initially, the associations of simple images in the different intramodal features with words based on letters activate visual and auditory cortical neurons, respectively. With their mutual synapse innervation, intramodal and cross-modal associative memory cells are recruited including AMCs for pictures, letters as well as picture with words. The repeated activation of these associative memory cells by practices will induce their activity-dependent plasticity and recruit more associative memory cells, i.e., coactivity-dependent positive cycle in the recruitment and refinement of associative memory cells. The first grade of associative memory cells is formed [7]. With the accumulation of associative memory cells to store unitary signals, they become ready-recruited neurons to be associative memory cells that encode complicated associative signals. The complicated visual and auditory signals can be associatively learned by activating the first grade of associative memory cells in visual and auditory cortices. Their mutual synapse innervations and activity upregulation lead to the formation of the second grade of associative memory cells that encode complicated images and sentences reorganized from unitary signals. Thus, numerous groups of the first and second grades of associative memory cells are accumulatively recruited in lifespan learning. In advanced learning, multiple grades of associative memory cells are recruited to encode more complicated signals. When the different groups and grades of associative memory cells are accumulated, subsequent learning may be based on their activity-dependent function upregulation, which makes them to be easily activated for quick memory formation as well as quick transferring among the different modalities, such as visual images versus auditory signals, for their integrative memory. These mechanisms facilitate the memory of complicated signals in images and sentences quickly. Reading book or looking images induces intensive activities in certain groups of associative memory cells that encode these sentences and images, which leads to their activity-dependent function upregulation. The low threshold potential of these associative memory cells to fire spikes and active synapse inputs to drive these associative memory cells will permit the cues dominantly to reactivate them for the reciprocal recalls of images and sentences, as well as will confer their spontaneous activations to drive secondary associative memory cells for free associative thinking. The activities of associative memory cells lead to memory retrieval by behaviors if they successfully drive the activation of memory-output neurons in the motor cortex [7].

In addition to mutual synapse innervations among primary associative memory cells as well as advanced innervations among these multi-grades of associative memory cells, these is another mechanism for the cross-modal associative memory of unitary and complicated signals. Association cortices are thought to be able to integrate the signals from the different sensory modalities [235-238]. The coactivation of primary associative memory cells and multi-grade associative memory cells during repeated learning and memory retrievals will make their convergent and divergent innervations onto neurons in these association cortices [12] (Figure 2). The integrative storage of associated signals from different modalities in association cortices confer the translation among those associated signals from different modalities and the understanding of these signals through mutual translations among sensory modalities, such as the conversion between visual and auditory signals, as well as the mixed perceptions. The lesion of these association cortices will lead to memory deficits [239,240], such as the correlation of Wernicke's area lesion with understanding inability and cross-modal memory impairment [241-243].

Memories to olfactory signals or gustatory signals require their special association with words, phrases and sentences in the auditory system for the clear definition of these olfactory or gustatory sensations as well as for the integrative storage of these associated signals, in addition to the association to other sensory modalities. Otherwise, memories to these signals can only be presented by saying "tasted or smelled before". To fulfill these types of cross-modal associative memory, the mutual synapse innervations between auditory cortical neurons and piriform cortical neurons or between auditory cortical neurons and piriform cortical neurons should be formed to recruit associative memory cells, which remains to be experimentally tested [9,8]. Similar to the working principle of associative memory cells in other sensory cortices, the integrative storage of olfactory signals or gustatory signals with auditory signals can be completed in these correspondent sensory cortices for their future reciprocal retrievals. Furthermore, memories to olfactory and gustatory signals are often associated with emotion-relevant perceptions and reactions, so that various feelings and emotional reactions are expressed during the retrieval of odor and gustatory signals.

It is noteworthy that the complicated signals can also be dissected and memorized through the formation of associative memory cells that are able to encode multiple signals [9]. The complicated signals are composed of numerous unitary signals, which can be detected through the dissections by different sensory systems and intramodal sensory neurons. While learning these complicated signals, associative memory cells are recruited to integrate multiple simple signals, based

on the random association of these unitary signals to induce mutual synapse innervations among their correspondent recruitment-ready neurons. These associative memory cells with different integrative ability to associated signals are recruited and the activation of portions of these associative memory cells leads to the selective recall of these complicated signals [7].

There are three resources of synaptic inputs to drive and maintain the activities of associative memory cells, including new synaptic innervations from coactivated brain areas, innate synaptic inputs formed during development, and synaptic inputs from the arousal system. The latter two synapse-driving forces activate the neurons ready to be recruited as new associative memory cells. The ascending reticular activating pathway from the brain stem and the thalamus receives various sensory inputs and widely innervates the entire cerebral brain to permit the wakefulness and consciousness [212,244,245]. The ascending pathways from neuronal axons in the cholinergic nuclei, midbrain raphe nuclei and locus coeruleus innervate the forebrain to keep alertness and consciousness by releasing acetylcholine, serotonin and norepinephrine [214,215,217]. This arousal system maintains the basal activity of associative memory cells, and confers them to integrate innate and new synaptic inputs specifically and to memorize associated signals. This arousal system may also activate recruitment-ready neurons to influence the efficiencies of associative learning, of associative memory cells to facilitate memory retrievals as well as of primary and secondary associative memory cells to permit the association of memory with cognitive process and emotional reactions.

Learning efficiency is influenced by neuronal excitability, synapse responsiveness and neurons ready to be recruited [7]. Neurons ready to be recruited for storing new associated signals may be those cells that have been able to encode the storage of previous learnt signals from specific synapse innervations. These stored signals may be closely relevant to those associated signals that will be learned, and these ready recruited neurons can be activated by giving topic cues in the attention call. The number of the ready recruited neurons influences how the information is acquired and memorized easily as well as how the complicated signals can be efficiently learnt. That is a reason why the efficiency of associative learning is influenced by a fact whether individuals are knowledgeable in the topic to be learnt. In addition, the cortical neurons are diversified in their synapse inputs and intrinsic property [47], and the neurons with more synapse inputs and lower threshold potential are easily activated to fire spikes for high learning efficiency [5,188], which triggers the chain reaction of intensive spikes and microRNA expression changes for axon prolongation and synapse innervations [9,79]. Thus, activity-dependent upregulations in neuron excitability and synapse innervations facilitate the recruitment of associative memory cells to influence learning efficiency.

The efficiency of memory retrievals is influenced by the number and function state of associative memory cells as well as the coactivity-dependent positive cycle between recruitments and refinements of associative memory cells [7]. Under the conditions of normal consciousness and alertness, the recruited number of associative memory cells is positively proportional to the activated associative memory cells in memory retrieval, so that the efficiency of memory retrieval would be consistent to the efficiency of associative learning [5,188], the functional state of associative memory cells affects how they are easily activated in memory retrievals [18], and the coactivity-dependent positive cycle between the recruitment and refinement of associative memory cells will add more associative memory cells into memory traces. Therefore, the efficiency of memory retrieval would be high under the conditions of normal consciousness and alertness. Whether the stored information can be successfully retrieved also depends on the function state of memory-output cells, since the function downregulation of memory execution cells in the motor cortex leads to the inability of memory retrieval (i.e., memory extinction) though primary associative memory cells are well-maintained in the normal function [14,32]. Thus, the high number and the active intrinsic property of associative memory cells in memory traces as well as the coactivity-dependent positive cycle of their recruitment and refinement lead to automatic memory retrieval after repeated learning and thinking without the need of cues.

In the transformation from exogenous signals to endogenous signals and their integrative memories [193,11,32,33,7], the efficiency to correlate associative memory with cognitive processes and emotional reactions is a critical issue. In this process, the interactions between primary and secondary associative memory cells by their mutual synapse innervations (Figure 1) as well as the number and functional state of these associative memory cells should be taken into account during logical reasoning and associative thinking [7]. Thus, cellular processes involved in the efficiency for the learning, storage and retrieval of exogenous associated signals may similarly work for the transformation of exogenous-to-endogenous signals.

In terms of the relationships between associative memory cells and memory patterns, such as declarative or explicit memory versus nondeclarative or implicit memory, episodic memory versus semantic memory as well as the transformation between these patterns, our interpretations are below. In spite of these psychological classifications, there is no clear border line to separate them. Declarative memory is an intentional remember with clear state under consciousness, while nondeclarative memory is an effortless remember with no conscious awareness [34,6]. In fact, implicit memory is formed in individuals by paying attention when they initially learn these processes and operations. With long-term practice to be skilled, the expression of such processes and operations are not necessarily to be fulfilled with conscious effort. Based on coactivity-dependent positive cycle in the recruitment and refinement of associative memory cells, the repeated coactivations of primary and secondary associative memory cells can recruit more associative memory cells and upregulate their function state [19372,5,7,18], as well as strengthen synapse connections from associative memory cells to memory-output cells in the motor cortex [14,32], so that explicit memory can be converted into implicit memory. In other words, there may be the reverse relationship between the number and upregulation of associative memory cells and the requirement of consciousness, a homeostasis for memory retrieval. Implicit memory based on more associative memory cells that are easily activated is supported by phenomena that it can usually be expressed spontaneously. In explicit memory, episodic memory in individual events can be converted into semantic memory after the repeated associative thinking and logical reasoning strengthen associative memory cells that have stored a common signal of the events through central synapse innervations or place associative memory cells that have stored those events with similar topics together to reorganize them into a group of memory cells for the general concepts and to convergently innervate on another grade of associative memory cells in an abstraction manner [7].

Consciousness is the combinational state of wakefulness and memory for individuals to aware and identify themselves and objects in the environment [246]. The normal consciousness may be based on the basal activation of associative memory cells by the arousal system and the specific activation of associative memory cells from their associated inputs triggered by sensory cues [7]. Thus, the number and functional state of associative memory cells are proportional to the state of consciousness. The combination of consciousness and a specific alert constitutes the attention, in which a specific group of associative memory cells is activated for memory retrieval as well as the

alert-relevant recruitment-ready neurons are coactivated for learning alert-relevant signals. Once individuals are under consciousness, they have two forms of logical reasoning and associative thinking, i.e., critical versus creative. The critical thinking activates more recruited secondary associative memory cells for the evaluation, while creative thinking may generate newer secondary associative memory cells for inspiration [7].

The awareness state can be classified into consciousness and unconsciousness. The sleeping can be fell into unconsciousness (slow wave sleeping) and incomplete consciousness (fast wave sleeping) [246]. How do different groups of associative memory cells work together during fast wave sleeping or dreaming? Dreams are often accompanied by highly activities in electronic encephalograph and behaviors, such as rapid eye movement, muscle twitch and active respiration/heat beat, indicating high activity in the forebrain. In the meantime, associative memory cells for specific events, which have been frequently thought in daytime, are activated. Associative memory cells that are intensively activated in daytime lead to the coactivity-dependent positive cycle of their recruitment and upregulation. So, these events are playbacks. As the reverse relationship between the upregulation of associative memory cells and the requirement of consciousness, associative memory cells with large population and upregulated function due to repeated learning and thinking can be activated under incomplete consciousness condition, such that playback events are incompletely identical to realistic ones [7]. As the playbacks can be recalled and stated, associative thinking and logical reasoning (the integration of endogenous signals) based on primary and secondary associative memory cells can be fulfilled under incomplete consciousness [8]. This viewpoint is granted by an observation that temporal sequences of place cell activities in a novel spatial experience are detected during the resting or sleeping period preceding the experience. This replay occurs in the disjunction to sequences of replay in a familiar experience. These results suggest that internal neuronal dynamics during resting or sleep organize cellular assemblies into temporal sequences that contribute to encode a relevant novel experience in the future [247].

Furthermore, images, odors, tastes and events are presented by word-based language in associative thinking and logical reasoning. In initial learning, the sensations, perceptions and events are associated to their correspondent word descriptions, such that associative memory cells for encoding these processes and word descriptions have been recruited. Once these processes are recalled in the sequential playbacks, their word descriptions in these associative memory cells are initiated to substitute the complicated images and events, which is the requirement of speeding up memory retrieval and cognition. The substitution of words to images and events is realized based on the recruitment of more associative memory cells and their upregulations in coactivity-dependent positive cycle manner by repeated practices. However, if words and these processes are associated improperly, the corrections of these associations are difficult because of the presences of these recruited synapse innervations, associative memory cells and their circuits [7].

Associative memory cells in pathology

The integrative storage and the reciprocal retrieval of the associated signals are critical for the bidirectional alertness and prediction in the life. Based on primary and secondary associative memory cells as well as their multi-grade integrations [7], one signal will induce the recall of its associated signals, or the other way around, as well as the signals learned from one modality are recalled through the conversion into another modality. Individuals are able to fulfill logical reasoning and associative thinking as well as to predict future events in forward and backward manners. Furthermore, associative memory cells in each of the coactivated brain regions encode the associated innate signal and newly learned signal, as well as each of the associated signals is stored in multiple brain areas, which largely reduces the chance of memory loss [5,8]. The storage of multiple signals in an associative memory cell strengthens the efficiency of memory retrieval [9]. The storage of multiple signals in a cortical area and the recall of one signal triggered by multiple signals will enable these individuals to strengthen their abilities in memory retrieval and well-organized cognitions. In these regards, the deficit of associative memory cells in their morphology, functions and local environment declines memory retrievals and cognitions as well, which are usually associated with neurological diseases and psychiatric disorders.

It is widely accepted that the normal consciousness and well attention are important for memory formation [248,249,34], which can be explained by associative memory cells and their features [7]. With the arousal system to maintain wakefulness and the activation of ready-recruited neurons by topic cues in the attention call, their activation and activity make them to encode the associated signals. These associative memory cells under the wakefulness condition grant individuals to identify themselves and environmental objects, which constitute consciousness. On the other hand, the consciousness based on wakefulness and memory supports the activation and activity of associative memory cells to execute activity-dependent positive cycle in their refinement and recruitment, such that more associative memory cells are recruited and impressive memory is formed in the mind. Thus, the deficit of associative memory cells makes consciousness to be obscure.

Psychological disorders, such as anxiety, depression and even schizophrenia, are accompanied by unusual memory [250,144]. For instance, fear memory induced by acute stress is often associated with anxiety [251,252. Stimulations to engram cells through optogenetic approach in the hippocampus activate fear memory recall and anxiety [23]. Memory to the outcomes of chronic mild stresses are associated with depression-like behaviors [253,254]. On the other hand, the activation of positive memory traces by optogenetic method in the amygdala suppresses depression-like behaviors [152]. These data indicate that the formation of associative memory cells induced by different patterns of abnormal stimulations can lead to psychological disorders, i.e., acute severe stresses recruit associative memory cells relevant to fear memory and anxiety, and chronic mild stresses recruit associative memory cells related to negative memory and depression [253,251].

The proper coactivation of active neurons makes them to be recruited as associative memory cells [5,7], and the activity-dependent upregulation of associative memory cells facilitates the integrative storage of associated signals [13,187,7,18,188]. These processes constitute the coactivity-dependent positive cycle in the recruitment and refinement of associative memory cells, such that more associative memory cells will be recruited. However, the further upregulation of associative memory cells, such as the dysfunction of GABAergic neurons in schizophrenia and epilepsy [255,256], allows associative memory cells to be overly and widely activated. The overly upregulation of associative memory cells in sensory cortices will lead to hallucination. The overly upregulation of associative memory cells in cognition- and emotion-related brain areas leads to illusion [7].

The efficiency of learning and memory decays in age-relevant manner [257,258]. There is a bell-shaped pattern in the efficiency of associative learning and memory [5]. In terms of cell mechanisms, synaptic potentiation matures during postnatal development [205], and neuronal excitability in cortical neurons is upregulated until a plateau level at postnatal weeks 3~4 [180], which matches dynamical changes

in associative memory well [5]. Neural plasticity and associative memory cell recruitment in postnatal development constitute the coactivity-dependent positive cycle in the recruitment and refinement of associative memory cells, such that more associative memory cells are recruited to raise the efficiency of learning and memory [187,188], which may constitute neuronal substrates for eidetic memory in young age [259]. In the aged mammalians, the accumulations of insoluble β-amyloid and phosphorylated tau-proteins in the brain influence axon prolongations and synapse formations [9,79] to suppress the recruitment and upregulation of the associative memory cells, to silence active associative memory cells and/or to deteriorate those recruited associative memory cells for the memory deficit [260,7,8](Roy et al., 2017; Wang and Cui, 2017, 2018). On the other hand, the activity of associative memory cells can strengthen coactivity-dependent positive cycle in the recruitment and refinement of associative memory cells, which prevents the conversion of soluble β-amyloid into its insoluble form and promotes the clearance of β-amyloids by associative memory astrocytes [5,7]. A current report supports this point in that light and sound stimulations coordinately reduce the accumulation of β-amyloid [261].

In age-related neurodegeneration, such as Alzheimer's disease, insoluble β-amyloid may be accumulated differently in various brain areas. For instance, the optogenetic activation of engram cells, which have a lack of increased synaptic strength and dendritic spines under protein synthesis inhibition-induced amnesia leads to memory retrievals [154]. The optogenetic activation of hippocampal engram cells leads to memory retrievals in mice, though they show the amnesia under the condition of using natural recall cues in the transgenic mouse model of early Alzheimer's disease [153]. In addition to the indication about the wide distribution of memory traces for signal storage and retrieval, these results suggest that areas involved in natural memory retrieval are dominantly impaired by the deposition of β-amyloid, rather than memory trace cells, as well as that regions for memory retrievals are not specific for a given memory. In this regard, synapse connections from associative memory cells to memory-output cells should be strengthened in the early stage of Alzheimer's disease [14,32,7].

In terms of memory maintenance versus extinction, the recruitment and refinement of associative memory cells are not significantly declined, but the activity of memory-output neurons in the motor cortex is lowered [14,32]. The sustained presence of associative memory cells as well as the recruitment of more associative memory cells in repeated brain activities confer memorized signals to be retrieved in lifespan, in which the information can be retrieved as long as their innervations onto memory-output neurons successfully drive the latter to be functionally active. It is noteworthy that memory retrievals show different patterns in spontaneous, cue-induced and realistic object-triggered manner with the ages. For instance, spontaneous retrievals often occur in child stage or brain excitation, the cue-induced retrievals usually occur in young and adult, the real object-induced retrievals occur in senior individuals. In addition, when the brain is highly excited in many areas, such as euphoria perception, extreme fear and strong stimulations, more associative memory cells are recruited through their mutual innervations, so that impressive memory and spontaneous recalls to these experiences are generated in lifespan [14,32]. It is difficult to remove the newly formed synapse innervation and the recruited associative memory cells to relieve fear memory. Alternative approaches are the avoidance of fear stimulations and the induction of happiness in order to rebalance these two states and weaken fear memory, since the lack of uses in neural circuits related to fear memory, especially from associative memory cells to memory-output neurons, may drive them to be functional silence. In the brains of individuals with history of substance abuse or addiction, primary and secondary associative memory cells relevant to these events are recruited in large amount and in extensive areas under euphoria condition, leading to potential relapses in their lifetime [8]. Similarly to electrical shock to activate whole brain, addiction drugs can widely activate numerous areas based on the distribution of their receptors, such as opioid receptors, monoamine receptors and glutamate receptors. Based on activity together, wire together and strengthening together, mutual synapse innervations and their strengthening are widely distributed in the brain in response to drug cue. There are no confident ways to erase synapse innervations and associative memory cells newly formed in drug abuse, as well as to relieve memories to drug-relevant cues that lead to psychological and physical dependence and addiction to the drugs [262]. The strategies to weaken addiction-relevant memory in the individuals include the avoidance of environment cues associated with substance abuse to reduce the activation of the relevant associative memory cells, as well as the establishment of alternative happiness to recruit associative memory cells that innervate memory-output cells through competition with innervations from addiction memory cells, so that the rebalance of these two states strengthens memory-output cells away from addiction-related associative memory cells [7].

Conclusion remarks

Associative memory cells are those nerve cells that encode the integrative storage of associated signals in objects and environments, receive synapse innervations from coactivated brain areas and innervate their downstream associative memory cells. Mutual synapse innervations among coactivated neurons in a group of primary associative memory cells and their convergent innervations onto secondary associative memory cells constitute the basic neural circuits for the reciprocal retrieval of associated signals, the automatic conversion retrieval of associated signals as well as the processes of cognition and emotional reactions. Coactivity-dependent positive cycle in the recruitment and upregulated refinement of associative memory cells determines the memory specificity as well as the efficiency of learning and memorizing associated signals. The cue-induced or spontaneous activations and persistent activities of associative memory cells lead to the recall of associated signals, as well as the presentation of associated signals by behaviors if they successfully activate memory-output cells. Thus, associative memory cells in neural circuits are basic units in engrams. Morphological basis for associative memory cells to encode multi-associated signals is their receptions of innate input and new synapse innervations from coactivated brain areas. Based on localizations in the cerebral brain, associative memory cells are classified into the primary group that integrates exogenous signals in sensory cortices and innervate neurons in cognition- and emotion-relevant brain areas as well as the secondary group that integrate endogenous signals from the primary group during cognitive processes and emotional reactions. Based on the complication of integrating associated signals, associative memory cells are classified into grade one, grade two, grade three and so on, whose activity-dependent upregulation works for the integrative storage and reciprocal retrieval of complicated associative signals. Associative memory cells plus their upregulation make them being more active, recruit more ready-recruited neurons to be associative memory cells, and cause coactivity-dependent positive cycle in the recruitment and refinement of associative memory cells for impressive memory in repetitive learnings. Primary associative memory cells are basic unit for the storage of exogenous associated signals that can influence the specific contents of cognitions and emotion reactions. The consequences and processes of cognition and emotion recruit more associative memory cells for them to be stored. The recycle in memory and cognition allows individual capabilities, skills and experiences to be strengthened. In addition, the functional state of associative

memory cells is modulated by the arousal system from midbrain raphe nuclei, cholinergic nuclei, locus coeruleus and substantial nigra, which regulate the efficiency of learning and memory. The impairment of associative memory cells through neurodegeneration themselves and abnormal internal environment lead to memory deficits in various neurological diseases and psychological disorders.

Acknowledgement

This study is funded by National Key R&D Program of China (2016YFC1307100) and Natural Science Foundation China (81671071) to JHW. Numerous papers related to learning and memory are published, and author apologizes for not being able to list all references in the review of associative memory cells. Author thanks to Ms. Shan Cui for drawing partial diagrams.

Competing interests: Author declares no competing interests.

References

1. Albright TD (2012) On the perception of probable things: neural substrates of associative memory, imagery, and perception. *Neuron* 74: 227-245.
2. Byrne JH (1987) Cellular analysis of associative learning. *Physiol Rev* 67: 329-439.
3. Kandel ER, Pittenger C (1999) The past, the future and the biology of memory storage. *Philos Trans R Soc Lond B Biol Sci* 354: 2027-2052.
4. Suzuki WA (2008) Associative learning signals in the brain. *Prog Brain Res* 169: 305-320.
5. Wang D, Zhao J, Gao Z, Chen N, Wen B, et al. (2015) Neurons in the barrel cortex turn into processing whisker and odor signals: a cellular mechanism for the storage and retrieval of associative signals. *Front Cell Neurosci* 9: 320.
6. Wasserman EA, Miller RR (1997) What's elementary about associative learning? *Annu Rev Psychol* 48: 573-607.
7. Wang JH, Cui S (2018) Associative memory cells and their working principle in the brain. *F1000Res* 7: 108.
8. Wang JH, Cui S (2017) Associative memory cells: Formation, function and perspective. *F1000Res* 6: 283.
9. Feng J, Lu W, Wang D, Ma K, Song Z, et al. (2017) Barrel Cortical Neuron Integrates Triple Associated Signals for Their Memory Through Receiving Epigenetic-Mediated New Synapse Innervations. *Cereb Cortex* 27: 5858-5871.
10. Wang JH, Chen N, Gao Z, Bo W (2014) Upregulation of Glutamatergic Receptor-Channels is Associated with Cross-Modal Reflexes Encoded in Barrel Cortex and Piriform Cortex. *Biophysical Journal* 106: 191a.
11. Wang JH, Feng J, Xiao H, Lu W (2018) Prefrontal Cortical Neurons are Recruited as Secondary Associative Memory Cells for Associative Memory and Cognition. *Biophysical Journal* 114: 155a.
12. Wang JH (2019) Searching basic units of memory traces: associative memory cells. *F1000Research* 8: 1-28.
13. Gao Z, Chen L, Fan R, Lu W, Wang D, et al. (2016) Associations of Unilateral Whisker and Olfactory Signals Induce Synapse Formation and Memory Cell Recruitment in Bilateral Barrel Cortices: Cellular Mechanism for Unilateral Training Toward Bilateral Memory. *Front Cell Neurosci* 10: 285.
14. Guo R, Ge R, Zhao S, Liu Y, Zhao X, et al. (2017) Associative Memory Extinction Is Accompanied by Decayed Plasticity at Motor Cortical Neurons and Persistent Plasticity at Sensory Cortical Neurons. *Front Cell Neurosci* 11: 168.
15. Liu Y, Gao Z, Chen C, Wen B, Huang L, et al. (2017) Piriform cortical glutamatergic and GABAergic neurons express coordinated plasticity for whisker-induced odor recall. *Oncotarget* 8: 95719-95740.
16. Wang JH, Wang D, Gao Z, Chen N, Lei Z, et al. (2016a) Both Glutamatergic and Gabaergic Neurons are Recruited to be Associative Memory Cells. *Biophysical Journal* 110: 481a.
17. Wang JH, Chen N, Gao ZL, Wen B, Chen CF, et al. (2014) Upregulation of glutamatergic receptor-channels is associated with cross-modal reflexes encoded in barrel cortex and piriform cortex. *Biophysical Journal* 106: 191a.
18. Yan F, Gao Z, Chen P, Huang L, Wang D, et al. (2016) Coordinated Plasticity between Barrel Cortical Glutamatergic and GABAergic Neurons during Associative Memory. *Neural Plasticity*.
19. Cai DJ, Aharoni D, Shuman T, Shobe J, Biane J, et al. (2016) A shared neural ensemble links distinct contextual memories encoded close in time. *Nature* 534: 115-118.
20. Ehrlich I, Humeau Y, Grenier F, Ciocchi S, Herry C, et al. (2009) Amygdala inhibitory circuits and the control of fear memory. *Neuron* 62: 757-771.
21. Kitamura T, Ogawa SK, Roy DS, Okuyama T, Morrissey MD, et al. (2017) Engrams and circuits crucial for systems consolidation of a memory. *Science* 356: 73-78.
22. Li H, Penzo MA, Taniguchi H, Kopec CD, Huang ZJ, et al. (2013) Experience-dependent modification of a central amygdala fear circuit. *Nat Neurosci* 16: 332-339.
23. Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, et al. (2012) Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature* 484: 381-385.
24. Naya Y, Yoshida M, Miyashita Y (2003) Forward processing of long-term associative memory in monkey inferotemporal cortex. *J Neurosci* 23: 2861-2871.
25. Okuyama T, Kitamura T, Roy DS, Itohara S, Tonegawa S (2016) Ventral CA1 neurons store social memory. *Science* 353: 1536-1541.
26. Otis JM, Namboodiri VM, Matan AM, Voets ES, Mohorn EP, et al. (2017) Prefrontal cortex output circuits guide reward seeking through divergent cue encoding. *Nature* 543: 103-107.
27. Pape HC, Pare D (2010) Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. *Physiol Rev* 90: 419-463.
28. Takehara-Nishiuchi K, McNaughton BL (2008) Spontaneous changes of neocortical code for associative memory during consolidation. *Science* 322: 960-963.
29. Viskontas IV (2008) Advances in memory research: single-neuron recordings from the human medial temporal lobe aid our understanding of declarative memory. *Curr Opin Neurol* 21: 662-668.
30. Xu W, Südhof TC (2013) A Neural Circuit for Memory Specificity and Generalization. *Science* 339: 1290-1295.

31. Yokose J, Okubo-Suzuki R, Nomoto M, Ohkawa N, Nishizono H, et al. (2017) Overlapping memory trace indispensable for linking, but not recalling, individual memories. *Science* 355: 398-403.

32. Wang JH, Guo R, Wei Z (2017) Associative memory extinction is accompanied by decays of associative memory cells and their plasticity at motor cortex but not sensory cortex. *Society for Neuroscience* 81: 10385.

33. Wang JH, Feng J, Xiao H, Xu Y (2019) Secondary Associative Memory Cells and their Plasticity in the Prefrontal Cortex. *Biophysical Journal* 116: 427a.

34. Reder LM, Park H, Kieffaber PD (2009) Memory systems do not divide on consciousness: Reinterpreting memory in terms of activation and binding. *Psychol Bull* 135: 23-49.

35. Kandel ER, Dudai Y, Mayford MR (2014) The molecular and systems biology of memory. *Cell* 157: 163-186.

36. Poo MM, Pignatelli M, Ryan TJ, Tonegawa S, Bonhoeffer T, et al. (2016) What is memory? The present state of the engram. *BMC Biol* 14: 40.

37. Tonegawa S, Pignatelli M, Roy DS, Ryan TJ (2015) Memory engram storage and retrieval. *Curr Opin Neurobiol* 35: 101-109.

38. Black J, Greenough W (1991) Developmental approaches to the memory process, in Learning and Memory. Martinez J, Kesner R, Editors. Academic Press, Inc: San Diego, LA, USA 61-91.

39. Brown M, Keynes R, Lumsden A (2001) Development of cerebral cortex and cerebellar cortex. The development of brain, edn. M.e.a. Brown. New York: Oxford University Press Inc. UK, 169-193.

40. Chang H, Hoshina N, Zhang C, Ma Y, Cao H, et al. (2018) The protocadherin 17 gene affects cognition, personality, amygdala structure and function, synapse development and risk of major mood disorders. *Mol Psychiatry* 23: 400-412.

41. Dajani DR, Uddin LQ (2015) Demystifying cognitive flexibility: Implications for clinical and developmental neuroscience. *Trends Neurosci* 38: 571-578.

42. Dumas TC (2005) Developmental regulation of cognitive abilities: modified composition of a molecular switch turns on associative learning. *Prog Neurobiol* 76: 189-211.

43. Kadosh RC, Walsh V (2006) Cognitive Neuroscience: Rewired or Crosswired Brains? *Curr Biol* 16: R962-R963.

44. Chen N, Chen SL, Wu YL, Wang JH (2006a) The refractory periods and threshold potentials of sequential spikes measured by whole-cell recordings. *Biochemical and Biophysical Research Communications* 340: 151-157.

45. Chen N, Chen X, Wang JH (2008) Homeostasis established by coordination of subcellular compartment plasticity improves spike encoding. *J Cell Sci* 121: 2961-2971.

46. Chen N, Zhu Y, Gao X, Guan S, Wang JH (2006b) Sodium channel-mediated intrinsic mechanisms underlying the differences of spike programming among GABAergic neurons. *Biochemical and Biophysical Research Communications* 346: 281-287.

47. Wang JH, Wei J, Chen X, Yu J, Chen N, et al. (2008) Gain and fidelity of transmission patterns at cortical excitatory unitary synapses improve spike encoding. *J Cell Sci* 121: 2951-2960.

48. Thompson RF (2005) In search of memory traces. *Annu Rev Psychol* 56: 1-23.

49. Thompson RF (2013) An essential memory trace found. *Behav Neurosci* 127: 669-675.

50. Reijmers LG, Perkins BL, Matsuo N, Mayford M (2007) Localization of a stable neural correlate of associative memory. *Science* 317: 1230-1233.

51. Tayler KK, Tanaka KZ, Reijmers LG, Wiltgen BJ (2013) Reactivation of neural ensembles during the retrieval of recent and remote memory. *Curr Biol* 23: 99-106.

52. Link W, Konietzko U, Kauselmann G, Krug M, Schwanke B, et al. (1995) Somatodendritic expression of an immediate early gene is regulated by synaptic activity. *Proc Natl Acad Sci USA* 92: 5734-5738.

53. Morgan JI, Curran T (1989) Stimulus-transcription coupling in neurons: role of cellular immediate-early genes. *Trends Neurosci* 12: 459-462.

54. Blough DS, Millward RB (1965) Learning: Operant Conditioning and Verbal Learning. *Annu Rev Psychol* 16: 63-94.

55. Bracha V, Zbarska S, Parker K, Carrel A, Zenitsky G, et al. (2009) The cerebellum and eyeblink conditioning: learning vs. network performance hypotheses. *Neuroscience* 162: 787.

56. Burhans LB, Smith-Bell C, Schreurs BG (2008) Conditioning-specific reflex modification of the rabbit's nictitating membrane response and heart rate: behavioral rules, neural substrates, and potential applications to posttraumatic stress disorder. *Behav Neurosci* 122: 1191-1206.

57. Davis M, Falls WA, Campeau S, Kim M (1993) Fear-potentiated startle: a neural and pharmacological analysis. *Behav Brain Res* 58: 175-198.

58. Glanzman DL (1995) The cellular basis of classical conditioning in Aplysia californica--it's less simple than you think. *Trends Neurosci* 18: 30-36.

59. Hawkins RD (1984) A cellular mechanism of classical conditioning in Aplysia. *J Exp Biol* 112: 113-128.

60. Lansink CS, Goltstein PM, Lankelma JV, McNaughton BL, Pennartz CM (2009) Hippocampus leads ventral striatum in replay of place-reward information. *PLoS Biol* 7: e1000173.

61. Lechner HA, Baxter DA, Byrne JH (2000) Classical conditioning of feeding in Aplysia: I. Behavioral analysis. *J Neurosci* 20: 3369-3376.

62. Maren S (2008) Pavlovian fear conditioning as a behavioral assay for hippocampus and amygdala function: cautions and caveats. *Eur J Neurosci* 28: 1661-1666.

63. Pennypacker HS, King FA, Achenbach KE, Roberts L (1966) An apparatus and procedure for conditioning the eye-blink reflex in the squirrel monkey. *J Exp Anal Behav* 9: 601-604.

64. Perkowski JJ, Murphy GG (2011) Deletion of the mouse homolog of KCNAB2, a gene linked to monosomy 1p36, results in associative memory impairments and amygdala hyperexcitability. *J Neurosci* 31: 46-54.

65. Sears RJ, Baker JS, Frey PW (1979) The eye blink as a time-locked response: implications for serial and second-order conditioning. *J Exp Psychol Anim Behav Process* 5: 43-64.

66. Staddon JE, Cerutti DT (2003) Operant conditioning. *Annu Rev Psychol* 54: 115-144.

67. Theios J, Brelsford JW Jr. (1966) A Markov model for classical conditioning: Application to eye-blink conditioning in rabbits. *Psychol Rev* 73: 393-408.

68. Woodruff-Pak DS, Disterhoft JF (2008) Where is the trace in trace conditioning? *Trends Neurosci* 31: 105-112.

69. Martinez M, Calvo-Torrent A, Pico-Alfonso MA (1998) Social defeat and subordination as models of social stress in laboratory rodents: A review. *Aggressive Behavior* 24: 241-256.

70. Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, et al. (2006) Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat Neurosci* 9: 519-525.

71. Vasconcelos M, Stein DJ, de Almeida RM (2015) Social defeat protocol and relevant biomarkers, implications for stress response physiology, drug abuse, mood disorders and individual stress vulnerability: a systematic review of the last decade. *Trends Psychiatry Psychother* 37: 51-66.

72. Liu Y, Gao Z, Chen C, Wen B, Huang L, et al. (2017a) Piriform cortical glutamatergic and GABAergic neurons express coordinated plasticity for whisker-induced odor recall. *Oncotarget* 8: 95719-95740.

73. Wang JH (2013) Neurons in barrel cortex turn into processing whisker and odor signals: A novel form of associative learning. *Society for Neuroscience* 14: 653.

74. Asok A, Leroy F, Rayman JB, Kandel ER (2019) Molecular Mechanisms of the Memory Trace. *Trendsin Neurosciences* 42: 14-22.

75. Dubnau J, Chiang AS, Tully T (2003) Neural substrates of memory: from synapse to system. *J Neurobiol* 54: 238-253.

76. Josselyn SA, Köhler S, Frankland PW (2015) Finding the engram. *Nat Rev Neurosci* 16: 521-534.

77. Josselyn SA, Kohler S, Frankland PW (2017) Heroes of the Engram. *J Neurosci* 37: 4647-4657.

78. Lisman J, Cooper K, Sehgal M, Silva AJ (2018) Memory formation depends on both synapse-specific modifications of synaptic strength and cell-specific increases in excitability. *Nature Neuroscience* 21: 309–314.

79. Lei Z, Wang D, Chen N, Ma K, Lu W, et al. (2017) Synapse Innervation and Associative Memory Cell Are Recruited for Integrative Storage of Whisker and Odor Signals in the Barrel Cortex through miRNA-Mediated Processes. *Front Cell Neurosci* 11: 316.

80. Simon RW (1923) Mnemic psychology. London: Allen Unwin, edn. Semin RW London: Allen, Unwin.

81. McGaugh JL (1972) The search for the memory trace. *Ann N Y Acad Sci* 193: 112-123.

82. McClelland JL, McNaughton BL, O'Reilly RC (1995) Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol Rev* 102: 419-457.

83. Hebb DO (1947) Spontaneous neurosis in chimpanzees; theoretical relations with clinical and experimental phenomena. *Psychosom Med* 9: 3-19.

84. Penfield W (1948) Bilateral frontal gyrectomy and postoperative intelligence. *Res Publ Assoc Res Nerv Ment Dis* 27 : 519-534.

85. Lashley KS (1931) Mass Action in Cerebral Function. *Science* 73: 245-254.

86. Lashley KS (1947) Structural variation in the nervous system in relation to behavior. *Psychol Rev* 54: 325-334.

87. Hebb DO (1949) The organization of behavior, a neuropsychological theory. New York, NY: Wiley.

88. Hebb DO (1950) Animal and physiological psychology. *Annu Rev Psychol* 1: 173-188.

89. Bliss TVP Lynch MA (1988) Long-term potentiation of synaptic transmission in the hippocampus: properties and mechanisms, in Long-term Potentiation: From Biophysics to Behavior, Landfield PW, Deadwyler SA, Editors. Alan R. Liss, Inc.: New York,NY. 3-72.

90. Buzsaki G (1991) Network properties of memory trace formation in the hippocampus. *Boll Soc Ital Biol Sper* 67: 817-835.

91. Jahans-Price T, Gorochowski TE, Wilson MA, Jones MW1, Bogacz R (2014) Computational modeling and analysis of hippocampal-prefrontal information coding during a spatial decision-making task. *Front Behav Neurosci* 8: 62.

92. Katkov M, Romani S, Tsodyks M (2017) Memory Retrieval from First Principles. *Neuron* 94: 1027-1032.

93. Lansner A (2009) Associative memory models: from the cell-assembly theory to biophysically detailed cortex simulations. *Trends Neurosci* 32: 178-186.

94. McClelland JL, McNaughton BL, O'Reilly RC (1995) Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol Rev* 102: 419-457.

95. Schwindel CD McNaughton BL (2011) Hippocampal-cortical interactions and the dynamics of memory trace reactivation. *Prog Brain Res* 193: 163-177.

96. McNaughton BL, Barnes CA, O'Keefe J (1983) The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Exp Brain Res* 52: 41-49.

97. Zhao J, Wang D, Wang JH (2012) Barrel cortical neurons and astrocytes coordinately respond to an increased whisker stimulus frequency. *Mol Brain* 5: 12.

98. Carr MF, Jadhav SP, Frank LM (2011) Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. *Nat Neurosci* 14: 147-153.

99. Harris KD, Csicsvari J, Hirase H, Dragoi G, Buzsáki G (2003) Organization of cell assemblies in the hippocampus. *Nature* 424: 552-556.

100. Jadhav SP, Kemere C, German PW, Frank LM (2012) Awake hippocampal sharp-wave ripples support spatial memory. *Science* 336: 1454-1458.

101. Ji D, Wilson MA (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat Neurosci* 10: 100-107.

102. Kay K, Sosa M, Chung JE, Karlsson MP, Larkin MC, et al. (2016) A hippocampal network for spatial coding during immobility and sleep. *Nature* 531: 185-190.

103. Kudrimoti HS, Barnes CA, McNaughton BL (1999) Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. *J Neurosci* 19: 4090-4101.

104. McNaughton BL, Barnes CA, O'Keefe J (1983) The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Exp Brain Res* 52: 41-49.

105. Penfield W, Perot P (1963) The Brain's Record of Auditory and Visual Experience. A Final Summary AND Discussion. *Brain* 86: 595-696.

106. Sirota A, Csicsvari J, Buhl D, Buzsáki G (2003) Communication between neocortex and hippocampus during sleep in rodents. *Proc Natl Acad Sci USA* 100: 2065-2069.

107. Skaggs WE, McNaughton BL (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. Science 271: 1870-1873.

108. Wilson MA, McNaughton BL (1993) Dynamics of the hippocampal ensemble code for space. *Science* 261: 1055-1058.

109. Wilson MA, McNaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. *Science* 265: 676-679.

110. Wirth S, Yanike M, Frank LM, Smith AC, Brown EN, et al. (2003) Single neurons in the monkey hippocampus and learning of new associations. *Science* 300: 1578-1581.

111. Yokose J, Okubo-Suzuki R, Nomoto M, Ohkawa N, Nishizono H, et al. (2017) Overlapping memory trace indispensable for linking, but not recalling, individual memories. *Science* 355: 398-403.

112. Yu JY, Liu DF, Loback A, Grossrubatscher I, Frank LM (2018) Specific hippocampal representations are linked to generalized cortical representations in memory. *Nat Commun* 9: 2209.

113. Jones MW, Wilson MA (2005) Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol* 3: e402.

114. Khodagholy D, Gelinas JN, Buzsáki G (2017) Learning-enhanced coupling between ripple oscillations in association cortices and hippocampus. *Science* 358: 369-372.

115. Rothschild G, Eban E, Frank LM (2017) A cortical-hippocampal-cortical loop of information processing during memory consolidation. *Nat Neurosci* 20: 251-259.

116. Lansink CS, Goltstein PM, Lankelma JV, McNaughton BL, Pennartz CM (2009) Hippocampus leads ventral striatum in replay of place-reward information. *PLoS Biol* 7: e1000173.

117. Takehara-Nishiuchi K, McNaughton BL (2008) Spontaneous changes of neocortical code for associative memory during consolidation. *Science* 322: 960-963.

118. Girardeau G, Inema I, Buzsáki G (2017) Reactivations of emotional memory in the hippocampus–amygdala system during sleep. *Nat Neurosci* 20: 1634-1642.

119. Varela C, Kumar S, Yang JY, Wilson MA (2014) Anatomical substrates for direct interactions between hippocampus, medial prefrontal cortex, and the thalamic nucleus reuniens. *Brain Struct Funct* 219: 911-929.

120. Nikolenko V, Poskanzer KE, Yuste R (2007) Two-photon photostimulation and imaging of neural circuits. *Nat Methods* 4: 943-950.

121. Stosiek C, Garaschuk O, Holthoff K, Konnerth A (2003) In vivo two-photon calcium imaging of neuronal networks. *Proc Natl Acad Sci USA* 100: 7319-7324.

122. Wang KH, Majewska A, Schummers J, Farley B, Hu C, et al. (2006) In vivo two-photon imaging reveals a role of arc in enhancing orientation specificity in visual cortex. *Cell* 126: 389-402.

123. Mao D, Neumann AR, Sun J, Bonin V, Mohajerani MH, et al. (2018) Hippocampus-dependent emergence of spatial sequence coding in retrosplenial cortex. *Proc Natl Acad Sci USA* 115: 8015-8018.

124. Fu M, Yu X, Lu J, Zuo Y (2012) Repetitive motor learning induces coordinated formation of clustered dendritic spines in vivo. *Nature* 483: 92-95.

125. Sugiura H, Tanaka H, Yasuda S, Takemiya T, Yamagata K (2009) Transducing neuronal activity into dendritic spine morphology: new roles for p38 MAP kinase and N-cadherin. *Neuroscientist* 15: 90-104.

126. Thiagarajan TC, Piedras-Renteria ES, Tsien RW (2002) alpha- and betaCaMKII. Inverse regulation by neuronal activity and opposing effects on synaptic strength. *Neuron* 36: 1103-1114.

127. Wong-Riley MT (1989) Cytochrome oxidase: an endogenous metabolic marker for neuronal activity. *Trends Neurosci* 12: 94-101.

128. Link W, Konietzko U, Kauselmann G, Krug M, Schwanke B, Frey U, et al. (1995) Somatodendritic expression of an immediate early gene is regulated by synaptic activity. *Proc Natl Acad Sci USA* 92: 5734-5738.

129. Guzowski JF, McNaughton BL, Barnes CA, Worley PF (1999) Environment-specific expression of the immediate-early gene Arc in hippocampal neuronal ensembles. *Nat Neurosci* 2: 1120-1124.

130. Bissiere S, Zelikowsky M, Ponnusamy R, Jacobs NS, Blair HT, et al. (2011) Electrical synapses control hippocampal contributions to fear learning and memory. *Science* 331: 87-91.

131. Gründemann J, Lüthi A (2015) Ensemble coding in amygdala circuits for associative learning. *Curr Opin Neurobiol* 35: 200-206.

132. Tanaka KZ, McHugh TJ (2018) The Hippocampal Engram as a Memory Index. *J Exp Neurosci* 12: 1179069518815942.

133. Tonegawa S, Liu X, Ramirez S, Redondo R (2015) Memory Engram Cells Have Come of Age. *Neuron* 87: 918-931.

134. Wang KH, Majewska A, Schummers J, Farley B, Hu C, et al. (2006) In vivo two-photon imaging reveals a role of arc in enhancing orientation specificity in visual cortex. *Cell* 126: 389-402.

135. Kiessling M, Gass P (1993) Immediate early gene expression in experimental epilepsy. *Brain Pathol* 3: 381-393.

136. Meldrum BS (2002) Concept of activity-induced cell death in epilepsy: historical and contemporary perspectives. *Prog Brain Res* 135: 3-11.

137. Simonato M, Hosford DA, Labiner DM, Shin C, Mansbach HH, et al. (1991) Differential expression of immediate early genes in the hippocampus in the kindling model of epilepsy. *Brain Res Mol Brain Res* 11: 115-124.

138. Wang X, Song X, Wu L, Nadler JV, Zhan RZ (2016b) Persistent Hyperactivity of Hippocampal Dentate Interneurons After a Silent Period in the Rat Pilocarpine Model of Epilepsy. *Front Cell Neurosci* 10: 94.

139. Abe H, Nowak TS Jr (2004) Induced hippocampal neuron protection in an optimized gerbil ischemia model: insult thresholds for tolerance induction and altered gene expression defined by ischemic depolarization. *J Cereb Blood Flow Metab* 24: 84-97.

140. Bokesch PM, Marchand JE, Connelly CS, Wurm WH, Kream RM (1994) Dextromethorphan inhibits ischemia-induced c-fos expression and delayed neuronal death in hippocampal neurons. *Anesthesiology* 81: 470-477.

141. Kiessling M, Stumm G, Xie Y, Herdegen T, Aguzzi A, et al. (1993) Differential transcription and translation of immediate early genes in the gerbil hippocampus after transient global ischemia. *J Cereb Blood Flow Metab* 13: 914-924.

142. Sossin WS (2008) Molecular memory traces. *Prog Brain Res* 169: 3-25.

143. Milo R (2013) What is the total number of protein molecules per cell volume? A call to rethink some published values. *Bioessays* 35: 1050-1055.

144. Penfield W (1958) Some Mechanisms of Consciousness Discovered During Electrical Stimulation of the Brain. *Proc Natl Acad Sci USA* 44: 51-66.

145. Penfield W, Welch K (1949) Instability of response to stimulation of the sensorimotor cortex of man. *J Physiol* 109: 358-365.

146. Rasmussen T, Penfield W (1947) The human sensorimotor cortex as studied by electrical stimulation. *Fed Proc* 6: 184.

147. Ferry B, Roozendaal B, McGaugh JL (1999) Role of norepinephrine in mediating stress hormone regulation of long-term memory storage: a critical involvement of the amygdala. *Biol Psychiatry* 46: 1140-1152.

148. Meneses A, Liy-Salmeron G (2012) Serotonin and emotion, learning and memory. *Rev Neurosci* 23: 543-553.

149. Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, et al. (2012) Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature* 484: 381-385.

150. Liu X, Ramirez S, Tonegawa S (2014b) Inception of a false memory by optogenetic manipulation of a hippocampal memory engram. *Philos Trans R Soc Lond B Biol Sci* 369: 20130142.

151. Ramirez S, Liu X, Lin PA, Suh J, Pignatelli M, et al. (2013) Creating a false memory in the hippocampus. *Science* 341: 387-391.

152. Ramirez S, Liu X, MacDonald CJ, Moffa A, Zhou J, et al. (2015) Activating positive memory engrams suppresses depression-like behavior. *Nature* 522: 335-339.

153. Roy DS, Arons A, Mitchell TI, Pignatelli M, Ryan TJ, et al. (2016) Memory retrieval by activating engram cells in mouse models of early Alzheimer's disease. *Nature* 531: 508-512.

154. Ryan TJ, Roy DS, Pignatelli M, Arons A, Tonegawa S (2015) Engram cells retain memory under retrograde amnesia. *Science* 348: 1007-1013.

155. Lashley KS (1931) Mass Action in Cerebral Function. *Science* 73: 245-254.

156. Lashley KS (1947) Structural variation in the nervous system in relation to behavior. *Psychol Rev* 54: 325-334.

157. Lashley KS (1958) Cerebral organization and behavior. *Res Publ Assoc Res Nerv Ment Dis* 36: 1-4.

158. Milner B, Penfield W (1955) The effect of hippocampal lesions on recent memory. *Trans Am Neurol Assoc* 42-48.

159. Penfield W (1948) Bilateral frontal gyrectomy and postoperative intelligence. *Res Publ Assoc Res Nerv Ment Dis* 27: 519-534.

160. Penfield W (1968) Engrams in the human brain. Mechanisms of memory. Proc R Soc Med 61: 831-840.

161. Penfield W, Milner B (1958) Memory deficit produced by bilateral lesions in the hippocampal zone. *AMA Arch Neurol Psychiatry* 79: 475-497.

162. Flexner JB, Flexner LB, Stellar E (1963) Memory in mice as affected by intracerebral puromycin. *Science* 141: 57-59.

163. Flexner JB, Glexner LB (1969) Studies on memory: evidence for a widespread memory trace in the neocortex after the suppression of recent memory by puromycin. *Proc Natl Acad Sci USA* 62: 729-732.

164. Flexner LB, Flexner JB, Roberts RB (1967) Memory in mice analyzed with antibiotics. Antibiotics are useful to study stages of memory and to indicate molecular events which sustain memory. *Science* 155: 1377-1383.

165. Silva AJ, Paylor R, Wehner JM, Tonegawa S (1992) Impaired spatial learning in alpha-calcium-calmodulin kinase II mutant mice. *Science* 257: 206-211.

166. Liu X, Ramirez S, Redondo RL, Tonegawa S (2014a) Identification and Manipulation of Memory Engram Cells. *Cold Spring Harb Symp Quant Biol* 79: 59-65.

167. Ramirez S, Tonegawa S, Liu X (2013b) Identification and optogenetic manipulation of memory engrams in the hippocampus. *Front Behav Neurosci* 7: 226.

168. Cabeza R, Ciaramelli E, Olson IR, Moscovitch M (2008) Parietal Cortex and Episodic Memory: An Attentional Account. *Nat Rev Neurosci* 9: 613-625.

169. Dubnau J, Chiang AS, Tully T (2003) Neural substrates of memory: from synapse to system. *J Neurobiol* 54: 238-253.

170. Josselyn SA, Kohler S, Frankland PW (2015) Finding the engram. *Nat Rev Neurosci* 16: 521-534.

171. Josselyn SA, Kohler S, Frankland PW (2017) Heroes of the Engram. *J Neurosci* 37: 4647-4657.

172. Poo MM, Pignatelli M, Ryan TJ, Tonegawa S, Bonhoeffer T, et al. (2016) What is memory? The present state of the engram. *BMC Biol* 14: 40.

173. Bliss TV, Lomo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol* 232: 331-356.

174. Debanne D, Poo MM (2010) Spike-Timing Dependent Plasticity Beyond Synapse – Pre- and Post-Synaptic Plasticity of Intrinsic Neuronal Excitability. *Front Synaptic Neurosci* 2: 21.

175. Stanton PK, Sejnowski TJ (1989) Associative long-term depression in the hippocampus induced by hebbian covariance. *Nature* 339: 215-218.

176. Aizenmann C, Linden DJ (2000) Rapid, synaptically driven increases in the intrinsic excitability of cerebellar nuclear neurons. *Nature Neuroscience* 3: 109-111.

177. Campanac E, Debanne D (2007) Plasticity of neuronal excitability: Hebbian rules beyond the synapse. *Arch Ital Biol* 145: 277-287.

178. Daoudal D, Debanne D (2003) Long-term plasticity of intrinsic excitability: learning rules and mechanisms. *Learning & Memory* 10: 456-465.

179. Sourdet V, Russier M, Daoudal G, Ankri N, Debanne D (2003) Long-term enhancement of neuronal excitability and temporal fidelity mediated by metabotropic glutamate receptor subtype 5. *J Neurosci* 23: 10238-10248.

180. Zhang M, Hung FS, Zhu Y, Xie Z, Wang JH (2004) Calcium signal-dependent plasticity of neuronal excitability developed postnatally. *J Neurobiol* 61: 277-287.

181. Banerjee SB, Gutzeit VA, Baman J, Aoued HS, Doshi NK, et al. (2017) Perineuronal Nets in the Adult Sensory Cortex Are Necessary for Fear Learning. *Neuron* 95: 169-179.e3

182. Doucette W, Gire DH, Whitesell J, Carmean V, Lucero MT, et al. (2011) Associative cortex features in the first olfactory brain relay station. *Neuron* 69: 1176-1187.

183. Raymond JL, Lisberger SG, Mauk MD (1996) The cerebellum: a neuronal learning machine? *Science* 272: 1126-1131.

184. Timmann D, Drepper J, Frings M, Maschke M, Richter S, et al. (2010) The human cerebellum contributes to motor, emotional and cognitive associative learning. A review. *Cortex* 46: 845-857.

185. Wang JH, Lu W (2018) Molecular profiles in the brain are involved in fear memory induced by physical and psychological stress. *Society for Neuroscience* 425: III61.

186. Weinberger NM (2004) Specific long-term memory traces in primary auditory cortex. *Nat Rev Neurosci* 5: 279-290.

187. Liu Y, Ge R, Zhao X, Guo R, Huang L, Zhao S, et al. (2017b) Activity strengths of cortical glutamatergic and GABAergic neurons are correlated with transgenerational inheritance of learning ability. *Oncotarget* 8: 112401-112416.

188. Zhao X, Huang L, Guo R, Liu Y, Zhao S, Guan S, et al. (2017) Coordinated plasticity among glutamatergic and GABAergic neurons and synapses in the barrel cortex is correlated to learning efficiency. *Frontiers in Cellular Neuroscience* 11: 1-12.

189. Yang Z, Chen N, Ge R, Qian H, Wang JH (2017b) Functional compatibility between Purkinje cell axon branches and their target neurons in the cerebellum. *Oncotarget* 8: 72424–72437.

190. Yu J, Qian H, ChenN, Wang JH (2011) Quantal Glutamate Release Is Essential for Reliable Neuronal Encodings in Cerebral Networks. *PLoS One* 6: e25219.

191. Yu J1, Qian H, Wang JH (2012) Upregulation of transmitter release probability improves a conversion of synaptic analogue signals into neuronal digital spikes. *Mol Brain* 5: 26.

192. Cai DJ, Aharoni D, Shuman T, Shobe J, Biane J, Song W, et al. (2016) A shared neural ensemble links distinct contextual memories encoded close in time. *Nature* 534: 115-118.

193. Feng J, Lu W, Wang GY, Zhu ZM, Sun Y, et al. (2018) Cell-specific plasticity associated with integrative memory of triple sensory signals in the barrel cortex. *Oncotarget* 9: 30962-30978.

194. Grewe BF, Gründemann J, Kitch LJ, Lecoq JA, Parker JG, et al. (2017) Neural ensemble dynamics underlying a long-term associative memory. *Nature* 543: 670-675.

195. Xu C, Krabbe S, Gründemann J, Botta P, Fadok JP, et al. (2016) Distinct Hippocampal Pathways Mediate Dissociable Roles of Context in Memory Retrieval. *Cell* 167: 961-972.e16.

196. Baldi E, Bucherelli C (2015) Brain sites involved in fear memory reconsolidation and extinction of rodents. *Neurosci Biobehav Rev* 53: 160-190.

197. Hübner C, Bosch D, Gall A, Lüthi A, Ehrlich I (2014) Ex vivo dissection of optogenetically activated mPFC and hippocampal inputs to neurons in the basolateral amygdala: implications for fear and emotional memory. *Front Behav Neurosci* 8: 64.

198. Bailey CH, Kandel ER, Harris KM (2015) Structural Components of Synaptic Plasticity and Memory Consolidation. *Cold Spring Harb Perspect Biol* 7: a021758.

199. Bliss TV, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361: 31-39.

200. Malenka RC, Nicoll RA (1999) Long-term potentiation--a decade of progress? *Science* 285: 1870-1874.

201. Liao D, Zhang X, O'Brien R, Ehlers MD, Huganir RL (1999) Regulation of morphological postsynaptic silent synapses in developing hippocampal neurons. *Nat Neurosci* 2: 37-43.

202. Petralia RS, Esteban JA, Wang YX, Partridge JG, Zhao HM, Wenthold RJ, et al. (1999) Selective acquisition of AMPA receptors over postnatal development suggests a molecular basis for silent synapses. *Nat Neurosci* 2: 31-36.

203. Takumi Y, Ramirez-Leon V, Laake P, Rinvik E, Ottersen O (1999) Different modes of expression of AMPA and NMDA receptors in hippocampal synapses. *Nat Neurosci* 2: 618-624.

204. Liao D, Hessler NA, Malinow R (1995) Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. *Nature* 375: 400-404.

205. Wang JH, Kelly P (2001) Calcium-calmodulin signalling pathway up-regulates glutamatergic synaptic function in non-pyramidal, fast spiking rat hippocampal CA1 neurons. *J Physiol* 533: 407-422.

206. Malinow R, Schulman H, Tsien RW (1989) Inhibition of postsynaptic PKC or CaMKII blocks induction but not expression of LTP. *Science* 245: 862-866.

207. Wang JH, Kelly PT (1996) Balance between postsynaptic Ca2+-dependent protein kinase and phosphatase activities controlling synaptic strength. *Learning & Memory* 3: 170-181.

208. Grienberger C, Milstein AD, Bittner KC, Romani S, Magee JC (2017) Inhibitory suppression of heterogeneously tuned excitation enhances spatial coding in CA1 place cells. *Nat Neurosci* 20: 417-426.

209. Titley HK, Brunel N, Hansel C (2017) Toward a Neurocentric View of Learning. *Neuron* 95: 19-32.

210. Mozzachiodi R, Lorenzetti FD, Baxter DA, Byrne JH (2008) Changes in neuronal excitability serve as a mechanism of long-term memory for operant conditioning. *Nat Neurosci* 11: 1146-1148.

211. Yang Z, Chen N, Ge R, Qian H, Wang JH (2017a) Functional compatibility between Purkinje cell axon branches and their target neurons in the cerebellum. *Oncotarget* 8: 72424-72437.

212. Kayama Y, Ito S, Koyama Y, Jodo E (1991) Tonic and phasic components of the ascending reticular activating system. *Fukushima J Med Sci* 37: 59-74.

213. Neylan TC (1995) Physiology of arousal: Moruzzi and Magoun's ascending reticular activating system. J *Neuropsychiatry Clin Neurosci* 7: 250.

214. Adell A, Celada P, Abellán MT, Artigas F (2002) Origin and functional role of the extracellular serotonin in the midbrain raphe nuclei. *Brain Res Brain Res Rev* 39: 154-180.

215. Aston-Jones G, Cohen JD (2005) An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci* 28: 403-450.

216. Chandler DJ, Gao WJ, Waterhouse BD (2014) Heterogeneous organization of the locus coeruleus projections to prefrontal and motor cortices. *Proc Natl Acad Sci USA* 111: 6816-6821.

217. Steriade M, Datta S, Paré D, Oakson G, Curró Dossi RC (1990) Neuronal activities in brain-stem cholinergic nuclei related to tonic activation processes in thalamocortical systems. *J Neurosci* 10: 2541-2559.

218. Hasselmo ME (2006) The Role of Acetylcholine in Learning and Memory. *Curr Opin Neurobiol* 16: 710-715.

219. Levey AI (1996) Muscarinic acetylcholine receptor expression in memory circuits: implications for treatment of Alzheimer disease. *Proc Natl Acad Sci USA* 93: 13541-13546.

220. Roberts RB, Flexner JB, Flexner LB (1970) Some evidence for the involvement of adrenergic sites in the memory trace. *Proc Natl Acad Sci USA* 66: 310-313.

221. Tully K, Bolshakov VY (2010) Emotional enhancement of memory: how norepinephrine enables synaptic plasticity. *Mol Brain* 3: 15.

222. Yi F, Ball J, Stoll KE, Satpute VC, Mitchell SM, et al. (2014) Direct excitation of parvalbumin-positive interneurons by M1 muscarinic acetylcholine receptors: roles in cellular excitability, inhibitory transmission and cognition. *J Physiol* 592: 3463-3494.

223. Ferry B, Roozendaal B, McGaugh JL (1999) Role of norepinephrine in mediating stress hormone regulation of long-term memory storage: a critical involvement of the amygdala. *Biol Psychiatry* 46: 1140-1152.

224. Wagatsuma A, Okuyama T, Sun C, Smith LM, Abe K, et al. (2018) Locus coeruleus input to hippocampal CA3 drives single-trial learning of a novel context. *Proc Natl Acad Sci USA* 115: E310-E316.

225. Xu S, Das G, Hueske E, Tonegawa S (2017) Dorsal Raphe Serotonergic Neurons Control Intertemporal Choice under Trade-off. *Curr Biol* 27: 3111-3119.e3

226. Kempadoo KA, Mosharov EV, Choi SJ, Sulzer D, Kandel ER (2016) Dopamine release from the locus coeruleus to the dorsal hippocampus promotes spatial learning and memory. *Proc Natl Acad Sci USA* 113: 14835-14840.

227. Sariñana J, Tonegawa S (2016) Differentiation of forebrain and hippocampal dopamine 1-class receptors, D1R and D5R, in spatial learning and memory. *Hippocampus* 26: 76-86.

228. Achee N, Zoran M (1997) Serotonin-induced modulation of excitability in an identified Helisoma trivolvis neuron. *J Exp Biol* 200: 1537-1548.

229. Malyshev AY, Bravarenko NI, Pivovarov AS, Balaban PM (1998) Effects of serotonin levels on postsynaptically induced potentiation of snail neuron responses. *Neurosci Behav Physiol* 28: 556-563.

230. Mastwal S, Ye Y, Ren M, Jimenez DV, Martinowich K, et al. (2014) Phasic dopamine neuron activity elicits unique mesofrontal plasticity in adolescence. *J Neurosci* 34: 9484-9496.

231. Guyton AC, Hall JE (2006) The Nervous System: B.The Special Senses. 11th edn. Textbook of Medical Physiology, edn. Guyton AC, Hall AC. Elsevier Inc. China.

232. Zhang F, Liu B, Lei Z, Wang JH (2012) mGluR1,5 activation improves network asynchrony and GABAergic synapse attenuation in the amygdala: implication for anxiety-like behavior in DBA/2 mice. *Mol Brain* 5: 20.

233. Van Hoesen GW (1993) The modern concept of association cortex. *Curr Opin Neurobiol* 3: 150-154.

234. Zeki S (1993) The visual association cortex. *Curr Opin Neurobiol* 3: 155-159.

235. Rosen ML, Sheridan MA, Sambrook KA, Peverill MR, Meltzoff AN, et al. (2018) The Role of Visual Association Cortex in Associative Memory Formation across Development. *J Cogn Neurosci* 30: 365-380.

236. Goldman-Rakic PS (1988) Topography of cognition: parallel distributed networks in primate association cortex. *Annu Rev Neurosci* 11: 137-156.

237. Masterton RB, Berkley MA (1974) Brain function: changing ideas on the role of sensory, motor, and association cortex in behavior. *Annu Rev Psychol* 25: 277-312.

238. Torrealba F, Valdes JL (2008) The parietal association cortex of the rat. *Biol Res* 41: 369-377.

239. Colombo M, D'Amato MR, Rodman HR, Gross CG (1990) Auditory association cortex lesions impair auditory short-term memory in monkeys. *Science* 247: 336-338.

240. Goldman-Rakic PS (1987) Circuitry of the frontal association cortex and its relevance to dementia. *Arch Gerontol Geriatr* 6: 299-309.

241. Ardila A, Bernal B, Rosselli M (2016) How Extended Is Wernicke's Area? Meta-Analytic Connectivity Study of BA20 and Integrative Proposal. *Neurosci J* 4962562.

242. Binder JR (2017) Current Controversies on Wernicke's Area and its Role in Language. *Curr Neurol Neurosci Rep* 17: 58.

243. DeWitt I, Rauschecker JP (2013) Wernicke's area revisited: parallel streams and word processing. *Brain Lang* 127: 181-191.

244. Neylan TC (1995) Physiology of arousal: Moruzzi and Magoun's ascending reticular activating system. *J Neuropsychiatry Clin Neurosci* 7: 250.

245. Yeo SS, Chang PH, Jang SH (2013) The ascending reticular activating system from pontine reticular formation to the thalamus in the human brain. *Front Hum Neurosci* 7: 416.

246. Hobson JA, Pace-Schott EF (2002) The cognitive neuroscience of sleep: neuronal systems, consciousness and learning. *Nat Rev Neurosci* 3: 679-693.

247. Dragoi G, Tonegawa S (2010) Preplay of future place cell sequences by hippocampal cellular assemblies. *Nature* 469: 397-401.

248. Henke K (2010) A model for memory systems based on processing modes rather than consciousness. *Nat Rev Neurosci* 11: 523-532.

249. Raffone A, Srinivasan N, LeeuwenCV (2014) The interplay of attention and consciousness in visual search, attentional blink and working memory consolidation. *Philos Trans R Soc Lond B Biol Sci* 369: 20130215.

250. Elizalde N, Gil-Bea FJ, Ramírez MJ, Aisa B, Lasheras B, et al. (2008) Long-lasting behavioral effects and recognition memory deficit induced by chronic mild stress in mice: effect of antidepressant treatment. *Psychopharmacology (Berl)* 199: 1-14.

251. Sun X, Song Z, Si Y, Wang JH (2018) microRNA and mRNA profiles in ventral tegmental area relevant to stress-induced depression and resilience. *Prog Neuropsychopharmacol Biol Psychiatry* 86: 150-165.

252. Wang JH, Lu W (2018) Molecular profiles in the brain are involved in fear memory induced by physical and psychological stress. *Society for Neuroscience* 425.19: III61.

253. Si Y, Song Z, Sun X, Wang JH (2018) microRNA and mRNA profiles in nucleus accumbens underlying depression versus resilience in response to chronic stress. *Am J Med Genet B Neuropsychiatr Genet* 177: 563-579.

254. Xu A, Cui S, Wang JH (2016) Incoordination among Subcellular Compartments Is Associated with Depression-Like Behavior Induced by Chronic Mild Stress. *Int J Neuropsychopharmacol* 19: pyv122.

255. Benes FM, Berretta S (2001) GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. *Neuropsychopharmacology* 25: 1-27.

256. Galanopoulou AS (2010) Mutations affecting GABAergic signaling in seizures and epilepsy. *Pflugers Arch* 460: 505-523.

257. Blank T, Nijholt I, Spiess J (2007) Treatment strategies of age-related memory dysfunction by modulation of neuronal plasticity. *Mini Rev Med Chem* 7: 55-64.

258. Maillet D, Rajah MN (2014) Age-related differences in brain activity in the subsequent memory paradigm: a meta-analysis. *Neurosci Biobehav Rev* 45: 246-257.

259. Wasinger K, Zelhart PF, Markley RP (1982) Memory for random shapes and eidetic ability. *Percept Mot Skills* 55: 1076-1078.

260. Roy DS, Muralidhar S, Smith LM, Tonegawa S (2017) Silent memory engrams as the basis for retrograde amnesia. 114: E9972-E9979.

261. Martorell AJ, Paulson AL, Suk HJ, Abdurrob F, Drummond GT, et al. (2019) Multi-sensory Gamma Stimulation Ameliorates Alzheimer's-Associated Pathology and Improves Cognition. *Cell* 176: 1-16.

262. Nestler EJ (2013) Cellular basis of memory for addiction. *Dialogues Clin Neurosci* 15: 431-443.