Seminars in Cell and Developmental Biology 125 (2022) 136–143

Contents lists available at ScienceDirect

Seminars in Cell and Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Neuronal ensembles in memory processes

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ARTICLE INFO

Keywords:
Neuronal ensembles
Memory engrams
Neurobiology of memory
Holographic optogenetics
Pattern completion
Pattern separation

ABSTRACT

A neuronal ensemble represents the concomitant activity of a specific group of neurons that could encompass a broad repertoire of brain functions such as motor, perceptual, memory or cognitive states. On the other hand, a memory engram portrays the physical manifestation of memory or the changes that enable learning and retrieval. Engram studies focused for many years on finding where memories are stored as in, which cells or brain regions represent a memory trace, and disregarded the investigation of how neuronal activity patterns give rise to such memories. Recent experiments suggest that the association and reactivation of specific neuronal groups could be the main mechanism underlying the brain's ability to remember past experiences and envision future actions. Thus, the growing consensus is that the interaction between neuronal ensembles could allow sequential activity patterns to become memories and recurrent memories to compose complex behaviors. The goal of this review is to propose how the neuronal ensemble framework could be translated and useful to understand memory processes.

1. Introduction

The study of neurophysiology was drastically influenced by Cajal and Sherrington that considered individual neurons and the linear flow of information as the axis to understand neuronal microcircuits [1,2]. On the other hand, the exploration of memory was strongly impacted by Semon and Lashley that pondered the loci of engrams as the guiding principle to comprehend learning processes [3,4]. Remarkably, both conjectures have evolved to converge in the idea proposed by Lorente de Nó [5] and developed by Hebb [6], that the interaction between recurrent groups of neurons defining ensembles could explain the mechanisms that support brain functions [7–13].

In the last decade, the knowledge about neuronal ensembles in different brain areas has been expanded by the refinement of optical techniques to simultaneously record and manipulate the activity of identified neuronal populations [14–18]. A neuronal ensemble is a group of neurons with coordinated and recurrent activity related to a particular function, experimental condition or feature of a mental state, and could be mathematically represented as a population vector [8]. In this way, groups of neurons related to several brain functions have been described all over the brain. It has been proposed that neuronal ensembles could work as distributed systems [19] where ensembles in different brain regions may support distinctive aspects of brain computations [20,21], provide general contextual information as an integrated index [22–24] or work as classification systems [25]. In parallel, the study of memory engrams has been catapulted by the development of engram tagging strategies that allow the visualization and manipulation of cells involved in learning paradigms [22,26–33]. For memory processes a permeating idea is that neuronal ensembles could represent specific attributes of engrams [9,10,12,34]. Despite the nuances in the working mechanisms of general brain functions and memories, engram's questions have revolved around which neurons are active instead of how population activity patterns define memory traces.

The relevance of recent studies linking population activity and interventional paradigms resides in the demonstration that the targeted activation of selected neuronal ensembles can enhance, disrupt or evoke learned behaviors [35–38] suggesting that a few neurons could engage a cascade of events across brain areas to control memory processes.

Extensive contemporary descriptions of what is a neuronal ensemble or what is a memory engram have been recently published [8,10]. Ergo, the focus of this short review is to propose how memory engrams could be interpreted from the neuronal ensemble framework with the purpose to move forward concepts and questions that could drive new experiments to understand the role of neuronal ensembles in the storage, retrieval and update of information.

2. Role of neuronal ensembles in memory processes

Understanding the role of different brain structures in learning requires the careful consideration of the type of memory studied [39]. The

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https://doi.org/10.1016/j.semcdb.2021.04.004
Received 14 January 2021; Received in revised form 30 March 2021; Accepted 1 April 2021
Available online 13 April 2021

ideal scenario is to use at first simple learning paradigms and then scale them to complex memories or behaviors [8,40]. Studies of engrams have focused on the identification of neurons associated with memory acquisition, consolidation and retrieval. In this way, it has been described that the enhancement of intrinsic excitability bias the inclusion of cells in engrams [26,41]. On the other hand, it has been demonstrated an increase in synaptic strength between engram cells [42,43]. But the cellular and circuit mechanisms at the mesoscale level underlying the formation and maintenance of memories remain unknown [44].

In the case of the hippocampus, the dichotomy was also clear for many years where the neuronal ensemble framework was used to describe spatial navigation, whereas the engram approach was used to study memory. The convergence of these parallel worlds proposed that the neural algorithms underlying navigation and episodic memory were similar. In this way, the rhythms generated by the activity of neuronal ensembles could be translated to memory processes [45]. To support memory processes neuronal ensembles should be able to store information and use it to generate flexible sequential activity patterns [11,12,45]. Assuming that engrams are shaped by environmental features and internal states, then, neuronal ensembles related to retrieval signals must overlap with neuronal ensembles that represent encoding signals and ensembles related to diverse aspects of the memory [46]. How are neuronal ensembles organized in a memory trace? Calcium imaging and tagging techniques were used to identify engram (tagged) and non-engram cells (non-tagged but active). The experiments showed that sub-ensembles were active during learning, post-learning, sleep and retrieval and that such sub-ensembles could represent distinct pieces of information of the entire memory. The mentioned experiments concluded that engram cells signaled contextual indexing and non-engram cells represented place information [34]. In a different study it was shown that most place cells were non-tagged however most tagged cells were place cells. Non-tagged place cells were stable in the same context but remapped in a new context whereas tagged place cells fired in a context-specific manner with imprecise spatial information and did not remap in a new context [22]. Interestingly, just considering the tagging criteria, non-tagged cells that are presumably necessary for the orchestration of population patterns would be discarded from the engram. These examples suggest that in terms of neuronal ensembles there could be context specific ensembles, spatial ensembles and other ensembles related to a broad spectrum of brain functions related to memory processes [27,47–53] working in parallel [54]. Therefore, diverse sets of ensembles should be in constant interaction to create unique internal experiences separated in time that give rise to memory.

3. Interacting neuronal ensembles define memory engrams

How could the interaction between neuronal ensembles be related to memory processes? It has been proposed that in order to create a neuronal ensemble a group of neurons should fire together in a physiologically meaningful time window allowing the strengthening of the functional connections between such neurons [6]. Along these lines, the genesis of ensembles could begin with the acquisition of information followed by the creation of an internal model of the world. After that, it is necessary to bridge the internal model with the physical attributes of the external world allowing the generation of actions by contrasting external data with the internal model. In this way, the interaction between neuronal ensembles could define algorithms to solve general problems that in terms of memory processes could be understood as linked experiences from shared information to optimize preexisting knowledge. The interaction between neuronal ensembles related to learning has been shown to be supported by oscillations that replay sequential activity patterns [55–60] as a mechanism to consolidate and retrieve spatial and contextual memories [61,62].

The ability to create temporally structured activity patterns between neuronal ensembles emerges from the connectivity and diversity of the neurons that define brain microcircuits [60]. Cycles of activity could enhance the stability of memory representations increasing the probability that a core ensemble triggers the entire memory. The variability and overlapping of neurons that belong to different ensembles could endow neuronal microcircuits with compositional capabilities [63–65] and the flexibility required to create new memories [11,12] or store different memories in shared engrams [26,66–69]. Spontaneous activity patterns in the absence of sensory stimuli have been proposed as a neurobiological mechanism to maintain and compare information that could be used to create or modify ensembles related to memory processes [5,7]. Sequential activity patterns in the absence of structured inputs [70,71] could represent a replaying mechanism that resembles the activation of central pattern generators (CPGs) [72]. CPGs can produce robust sequential activity patterns even in the absence of sequential inputs suggesting that preexisting microcircuit properties produce an output that is relevant for the functionality of the circuit. In vitro and in vivo experiments have shown that a tonic excitatory drive could produce sequential patterns of activity between neuronal ensembles, indicating that the mechanisms for neuronal computations including memory processes share the ability to produce sequential activity patterns [72]. The link between CPGs and engrams could explain why chemical or optical bulk activation of tagged cells can recall a memory engram, since a non-patterned excitatory drive could engage the activation of sequential activity patterns that are most relevant for the internal dynamics of the ensembles affected by the manipulation [73]. In this way setting in action chunks of a stored pattern could be sufficient to reconstruct entire sequences even at different time scales. Recurrent neuronal ensemble sequences with variable intervals from seconds to tens of seconds could be explained by nested ensembles [65] and temporal associative learning mechanisms [32,58–60,74–76] that differ from constant and persisting activity [77].

It has been theoretically proposed that a small fraction of neurons could be enough to store an item [78], this fact agrees with experimental data where the overlap of tagged neurons during training and testing is very low [29] and suggests that the temporal component and the non-tagged neurons are fundamental for the retrieval of sequences (Fig. 1). A possibility is that tagged neurons encode the content of a given engram while non-tagged neurons are related to the organization and internal representation of the memory that could involve different attributes of the memory [79,80]. This could explain the shifting in neuronal activity patterns observed with population recordings where animals are exposed to the same task for several trials. Therefore, neuronal population variability signals a shift in time suggesting that without variability time remains still.

4. Neuronal ensemble mechanisms related to engram reconfiguration

Experiments on engrams have shown that memories follow long-term potentiation (LTP) processes that can be measured as increased synapses or enhanced weights in the connectivity [81] between engram cells [43]. Accordingly, it has been shown that the shrinking of synapses is causally related to the deletion of memory traces in motor cortex [82]. Weak and strong memories label the same number of neurons suggesting that the strength of a memory is not dependent on the number of cells but on the properties of the connections. Interestingly, strong connectivity occluded further LTP indicating a limit in the number of memories that could be stored [41]. From such experiments it can be concluded that the synaptic connectivity from engram to engram cells is an important mechanism for the storage and retrieval of memories [83], but a remaining question would be how connectivity could be translated into flexible population activity patterns between neurons that belong to ensembles. In terms of neuronal ensembles in primary visual cortex, it has been shown that neurons that respond to the same visual stimulus have stronger connectivity than neurons that respond to different stimuli [84]. Correspondingly, electrophysiological studies combined

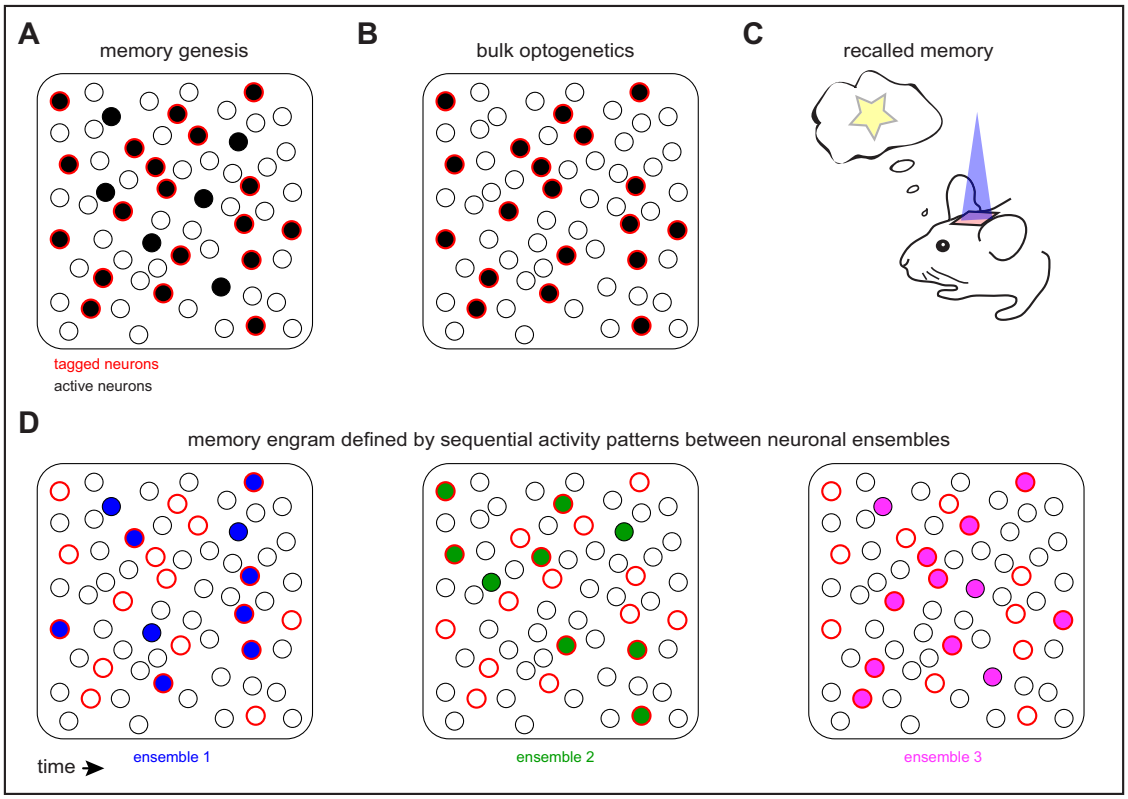

Fig. 1. Interacting neuronal ensembles underly memory engrams (A) Schematic representation of all active neurons during the learning process (black). Red contours depict tagged cells. (B) Bulk optogenetics is used to activate tagged cells. (C) Optogenetic activation of tagged cells in an undefined volume can retrieve the memory. (D) Schematic representation of the same engram shown in (A) but from the neuronal ensemble perspective (colorful). Note that sequential activity patterns between neuronal ensembles (including tagged and non-tagged cells) define the memory engram.

with calcium imaging recordings demonstrated that neurons that belong to the same neuronal ensemble have strong synaptic connections between them, whereas neurons that belong to different neuronal ensembles firing sequentially have weak synaptic connections [85]. These results suggest that short term synaptic depression between engram neurons generates synchronous activity, whereas short term synaptic facilitation between neurons that belong to different ensembles generates sequential activity patterns. According to the mentioned experiments, changes in synaptic connectivity elicited by the creation of new memories [86] should be reflected as modified neuronal ensemble dynamics in learning related brain areas.

On the other hand, it has been shown that interneurons could control the number of cells that belong to engrams [31,87]. However, some interneurons preferentially target the somatic region of a neuron, indicating that their role could be to define the identity and accuracy of ensembles, whereas other interneurons that target preferentially distal dendrites could dictate the generation of sequential activity patterns between ensembles or the recalling order of temporally linked ensembles [88–90]. Supporting this idea, it has been proposed that enhanced feedforward inhibition makes memories more reliable [91,92], presumably by reducing the variability of neuronal ensembles that represent a memory trace at different time points. In the same line of thought, it could be concluded that if ensembles belonging to engrams lack variability then learned memories will remain stable, but the creation of new memories will be compromised [93,94].

It has been shown that sequential activity patterns between neuronal ensembles are also liable to neuromodulation. In this way, the changes in intrinsic excitability and synaptic weights caused by neuromodulators should be able to reconfigure neuronal ensemble dynamics. Supporting this hypothesis it was found that dopaminergic modulation reduced the variability of neuronal ensembles favoring precision and recurrence, due to a reduction in variability of the neurons that participate in a given ensemble at different times and an increment in the repetition of the same sequence between ensembles [95]. On the other hand, it has been shown that cholinergic modulation favored the flexibility between sequential ensembles by increasing the synchronization and variability of neuronal population vectors [65,96]. Related results comprising engrams have been described in hippocampal dependent memories where dopaminergic modulation was necessary for the formation of novel contextual memories [97,98] and cholinergic modulation played a role in the creation of new associative memories [93].

5. Pattern completion and pattern separation of neuronal ensembles to understand memory processes

So far, the mechanisms described for neuronal ensemble formation and reconfiguration highlighted the importance of characterizing population activity patterns to understand memory engrams. Hence, the next question should focus on how neuronal ensemble dynamics could be related to pattern completion and pattern separation, that are the hallmarks of memory storage and retrieval. Using simultaneous two-photon imaging and two-photon optogenetics the property of pattern completion was demonstrated experimentally at the level of neuronal ensembles [14]. It was shown that a group of neurons that never fired together could be imprinted into an artificial neuronal ensemble by the recurrent activation of such randomly chosen neurons. After the neuronal ensemble was formed the activation of one neuron was able to recall the entire group. Interestingly, the imprinted ensemble continued firing in a coordinated way spontaneously for several days without any further photoactivation opening the possibility to artificially storage information with high spatial resolution.

Several functions have been proposed for pattern completion and

pattern separation including the formation, generalization, internal recalling and disambiguation of memories [33,69,78,93,94,99–107]. In terms of engrams composed by neuronal ensembles, pattern completion neurons should have synaptic connections that create attractor states as a product of learning [108], whereas pattern separation neurons should have synaptic connections that delimit the boundaries between attractors [99,106]. A neuronal ensemble should comprise pattern completion neurons to recall a given aspect of the memory from only a few neurons but should also have pattern separation neurons that constrain the activation of neurons that jeopardize the identity of the ensemble. Thus, pattern completion and pattern separation neurons could define the generation of sequential activity patterns. According to this idea it has been shown in experiments of immediate free recall that context retrieved by recalled items serves as a cue for subsequent recall [109]. Moreover, pattern completion neurons should represent specific attributes of an engram recalling the closest set of population vectors related to the original memory whereas pattern separation neurons should represent feature differences limiting the overlapping between population vectors. Thus, even though ensembles are constantly changing and prone to error, a general representation of the initial engram could remain accessible for retrieval. As a matter of interest, it has been shown that engram cells that link different memories are not necessary to recall individual memories [69], suggesting that each ensemble preserves its own pattern completion and pattern separation neurons and that when different ensembles are associated a new set of pattern completion and pattern separation neurons is incorporated into the ensemble [110]. Accordingly, it has been proposed that the overlap of neurons from different engrams could link experiences, whereas the removal of shared neurons from different engrams could disambiguate experiences. In this way, linking mechanisms could enable generalization of shared information by the use of past and present information [10]. Future experiments to functionally link neuronal ensembles and memory engrams using holographic optogenetics should consider the intrinsic dynamics of targeted neurons before and after manipulation, the short- and long-term changes produced by learning and the molecular identity of the neurons. For this purpose, chronic recordings of the same neurons should be performed throughout the learning process to demonstrate if the targeted and recurrent activation of a set of neurons that belong to different ensembles is enough to link such ensembles adding new attributes to an engram (Fig. 2).

6. Neuronal ensembles and memory processes in pathological conditions

Neurodegenerative disorders are an increasing health problem due to higher life expectancy worldwide. It has been broadly demonstrated that brain disorders are related to pathological neuronal synchronization [111]; however, how sequential activity patterns between neuronal ensembles are related to neurodegenerative disorders [112,113] and how optogenetics could be used to restore loss functions in memory impaired animal models are emergent fields in neuroscience [114].

It has been shown that the coordinated activity of neuronal ensembles is engaged into a dominant network state in animal models of Parkinson's disease, indicating that the identity of neuronal ensembles and their characteristic sequential activity patterns are disrupted [112,113]. Additionally, in epileptic animals the transitions between neuronal ensembles are abolished generating pathological synchronization and producing overlapping ensembles [115] that could interrupt the storage, consolidation and retrieval of information. Moreover, in animal models of schizophrenia the specificity of neuronal ensembles to different sensory stimuli is lost [116] indicating aberrant information processing. Furthermore, models of early Alzheimer's disease have shown increased activity of hippocampal neurons [117–121]. Promisingly, the optogenetic activation of engram cells [30] has shown potential to rescue memory loss.

These studies show that the spatial and temporal activation of

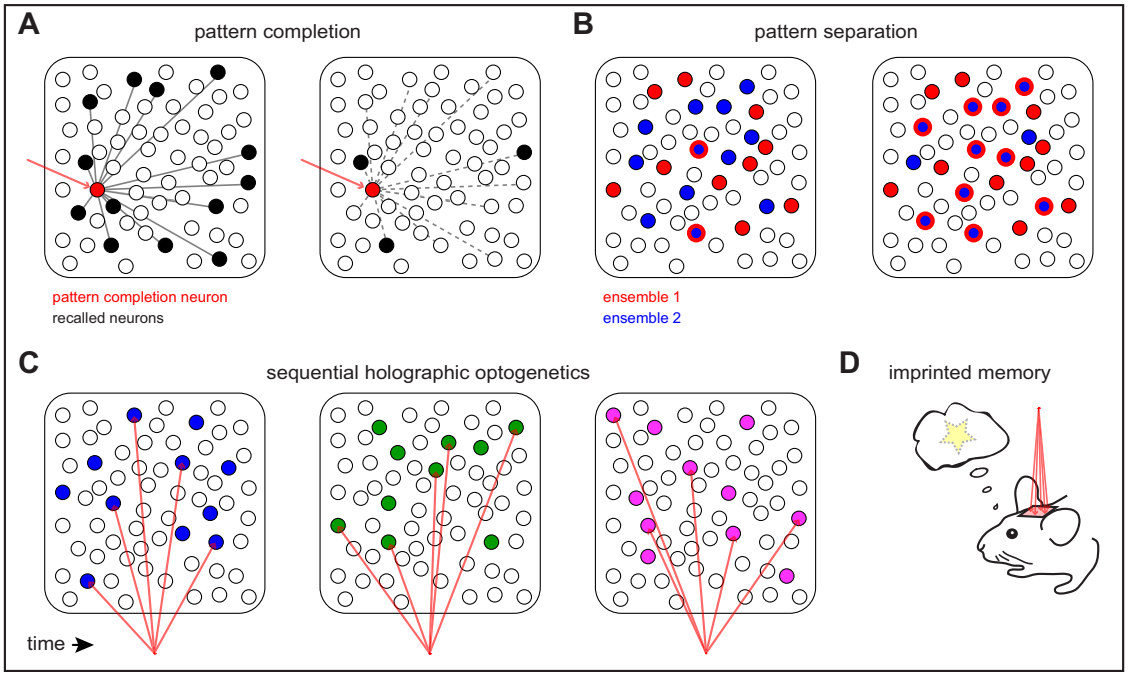

Fig. 2. Interventional approaches to reprogram memory processes. (A) Schematic representation of neuronal ensembles with disrupted pattern completion properties. Left: In normal conditions the activation pattern completion neurons can recall a whole ensemble. Right: in pathological conditions the activation of pattern completion neurons fails to recall an ensemble. (B) Schematic representation of neuronal ensembles with impaired pattern separation properties. Left: In normal conditions overlapped ensembles can be separated from each other. Right: in pathological conditions overlapped ensembles are indistinguishable. (C) Schematic representation of holographic optogenetic manipulation in sequential order of identified pattern completion neurons and pattern separation neurons that belong to ensembles composing a memory engram. (D) Brain circuits could be reprogramed by the precise control of identified neurons. Pattern completion neurons could be targeted to recall ensembles and pattern separation neurons could be targeted to disambiguate overlapped ensembles.

ensembles are key components to understand pathological activity patterns that derive in behavioral deficits and impaired pattern completion and pattern separation processes. The systematic characterization of the changes in neuronal ensemble dynamics at different stages of a neurological disease could define biomarkers and result in the development of personalized intervention strategies. Understanding neuronal ensembles as the basic building blocks of engrams could guide novel hypotheses that go beyond active or inactive cells to decipher how awry ensembles generate memory impairments in pathological states.

7. Computational approach to study neuronal ensembles related to memory

Once accepted that neuronal ensembles could work as basic building blocks [5,13], the last question would be how to define a neuronal ensemble in a way that can be generalized to brain computations related to memory processes. One of many solutions is to define neuronal ensembles as multidimensional population vectors where the dimensionality of the vectors is given by the total number of recorded cells instead of the temporal changes of individual cells [8,40,88,122]. Multidimensional population vectors can be compared at different times rigorously and the similarity between neuronal ensembles can be measured [123]. The implementation of dimensionality reduction methods could be used to visualize the dynamical changes of neuronal ensembles and depict features of interest even if neuronal ensembles fluctuate at different trials [124,125]. The right choice of a dimensional reduction method could be used to generate data driven hypothesis and render the population response structure under different experimental conditions [126]. Moreover, it has been shown that the projection of neuronal ensembles in a low dimensional space can be used to characterize sequential activity patterns and study compositional properties [65,70,85,95]. Therefore, the proposed framework to understand the formation and temporal interaction between neuronal ensembles could be applied intuitively to memory processes where an engram that represents a series of external and internal states could be decomposed as nested neuronal ensembles interacting in time and space [10,11,20,34].

As a hypothetical example, in the case of a movement dependent memory, several neuronal ensembles should interact for the successful execution of a learned sequential pattern: from ensembles that execute motor commands to feed-back ensembles that adjust the internal and external representation of the body. Using the proposed approach (or any other method for ensemble identification), the different ensembles that are part of the motor sequence could be tested to characterize which ensembles satisfy the engram criteria [9,10,46,127]. The identification of ensembles considered as part of the engram would be useful to dissect the neuronal population mechanisms that define how engrams are composed. Up to now a general framework for population analysis is still missing in neuroscience studies, so to study an define neuroscience concepts analytical tools that allow the explanation of circuit mechanisms and the definition of biologically based models should be necessary to understand how neuronal ensembles create and organize in an internal model the content and relevance of the physical world.

8. Conclusions and perspectives

The methods to characterize neuronal ensembles and their functional connectivity properties could be useful to depict different attributes of an engram allowing the understanding of the role of specific neurons in the consolidation and retrieval of a whole memory trace. The conjoint use of the engram and ensemble frameworks could reveal the circuit mechanisms of generalized brain functions, including memory processes, bridging both fields.

Studying the temporal and spatial properties of neuronal ensembles could be used to characterize the mechanisms of pattern completion and pattern separation and their relation to normal and pathological states.

Most engram studies have described fear conditioning memories where usually one trial is enough to produce a memory, so engram tools could be biased to such strong behavioral events. Other types of memories such as working memory or motor memories will require the further refinement of tagging techniques or the molecular identification of neurons that participate in different features of a memory trace. It has been recently shown using single cell technologies that the molecular identity of neurons could dictate their physiological function [128]. Therefore the development of techniques to molecularly define the identity of all the neurons that belong to a given ensemble could shed light into the mechanisms that make neurons belong to a neuronal ensemble and reveal why some neurons have pattern completion or pattern separation properties.

The further refinement of all-optical techniques and analytical tools to record, identify and manipulate the activity of multiple neurons with single cell precision [15–17,40,129] could be a valuable method to explore more subtle memory processes that require more trials and evolve in longer time scales. The targeted activation of spatially selected neurons could be used to reprogram neuronal activity patterns and therefore could be used to add or remove engram cells from a given memory trace and study the repercussion in the network dynamics [130] and behavioral performance [35,37,38,129].

An open question remains: can all brain activity that is recurrent and evokes the same behavior be considered as part of an engram? A possible answer could arise from the avalanche of studies that will come using several learning paradigms and single cell resolution techniques to selectively target members of ensembles that can recall whole learned behaviors. Visualizing the changes in the functional connectivity of neuronal ensembles that belong to engrams is fundamental to understand learning processes and the rules that allow recurrent sequential activity patterns to become memories. The further development of techniques to manipulate targeted neurons across brain areas will answer where memories are stored and how the patterns of activity between neurons in different brain areas interact to give sense of the environment and act upon it based on previous information. Understanding how ensembles are formed, how they interact, and the causal relation of activating selected members of ensembles that are part of memory engrams will eventually be useful to restore loss functions observed in pathological conditions or to imprint procedures, memories or cognitive abilities into the brain, reprogramming and reconfiguring synchronous and sequential activity patterns in short and long time scales.

Funding source

Dirección General de Asuntos del Personal Académico de la Universidad Nacional Autónoma de México PAPIIT (IA201421). CONACyT (CF6653, CF154039).

Declaration of competing interest

The author declares no competing financial interests.

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