Neuroscience Research xxx (2019) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience Research

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

Update Article

Dynamics of memory engrams

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ARTICLE INFO

Article history:
Received 21 February 2019
Received in revised form 18 March 2019
Accepted 27 March 2019
Available online xxx

Keywords:
Memory engram
Memory reconsolidation
Cell assembly
Engram cell
Multineuronal recording
Optogenetics
Multipotentiality

ABSTRACT

In this update article, we focus on "memory engrams", which are traces of long-term memory in the brain, and emphasizes that they are not static but dynamic. We first introduce the major findings in neuroscience and psychology reporting that memory engrams are sometimes diffuse and unstable, indicating that they are dynamically modified processes of consolidation and reconsolidation. Second, we introduce and discuss the concepts of cell assembly and engram cell, the former has been investigated by psychological experiments and behavioral electrophysiology and the latter is defined by recent combination of activity-dependent cell labelling with optogenetics to show causal relationships between cell population activity and behavioral changes. Third, we discuss the similarities and differences between the cell assembly and engram cell concepts to reveal the dynamics of memory engrams. We also discuss the advantages and problems of live-cell imaging, which has recently been developed to visualize multineuronal activities. The last section suggests the experimental strategy and background assumptions for future research of memory engrams. The former encourages recording of cell assemblies from different brain regions during memory consolidation–reconsolidation processes, while the latter emphasizes the multipotentiality of neurons and regions that contribute to dynamics of memory engrams in the working brain.

1. Introduction

"Memory engrams" are traces of long-term memory consolidated in the brain by experience. The search for engrams has a roughly 100-year long history in neuroscience. In the early stage, memory engrams were mainly investigated by dysfunction studies that used structural lesions to find specific regions containing engrams (localization studies). However, Karl Lashley, one of the pioneering researchers, found that memory engrams of mazes were not localized in any specific regions but were widely distributed in almost all neocortical regions (Lashley, 1921). He stated "Somehow, equivalent traces are established throughout the functional area. . .within a functional area the cells throughout the area acquire the capacity to react in certain definite patterns. . ." (Lashley, 1950, p.502). This "equipotentiality theory" might be too constrictive and specific to memory for mazes and many subsequent studies have reported that the varying parts of the brain are not completely homogeneous in their ability to perform memory consolidation (e.g., Squire, 1987; Krupa et al., 1993; Eichenbaum, 2002). Nevertheless, Lashley's notion that cells in many regions are able to acquire the ability to consolidate memory in certain definite patterns was the pioneering work emphasizing broad plasticity and dynamics of the brain for memory consolidation.

In cognitive psychology of memory, on the other hand, it was formerly believed that memory engrams transitioned from short-term to long-term via one consolidation process, thus making engrams intractable. However, many later psychological experiments have demonstrated that long-term memory is more dynamic than once believed and can be activated, modified, and reconsolidated in new forms (e.g., Schank, 1999). It is now obvious that long-term memory is not a simple process of one-time consolidation of experienced events, but dynamic and interactive processes of consolidation and reconsolidation (Alberini, 2013) (Fig. 1). These processes cause organizing, modifying, and relating the experienced events with stored and new information (McKenzie and Eichenbaum, 2011). Accordingly, several examples of behavioral data have shown that memory stores do not permanently remain in their original forms and that "false memory" can be created (Loftus, 1997). In other words, memory and information processing are inseparable, meaning that "Memory is determined by information processing" (Squire, 1987, p.124). This indicates that memory engrams are not completely static traces, but are dynamically changing and being processed.

Another topic of memory dynamics is individual differences of brain functions for memory (Markowitsch, 1988), indicating that information processes of memory vary from individual to indi-

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https://doi.org/10.1016/j.neures.2019.03.005
0168-0102/

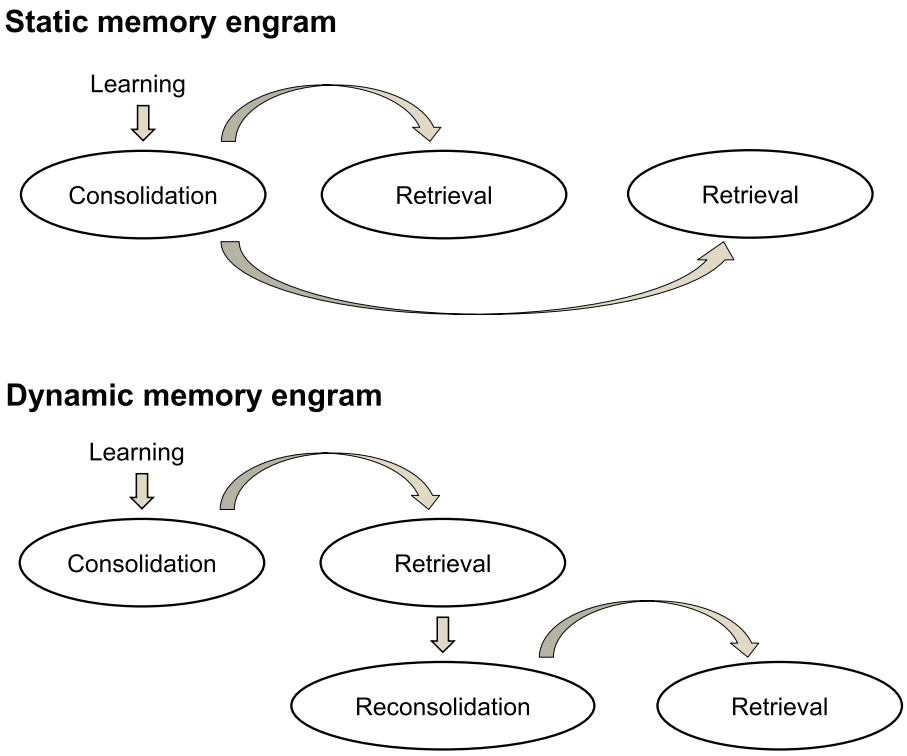

Fig. 1. The views of static (top) and dynamic (bottom) memory engram. The former is that memories are stored once and each time the memory is activated an engram of the original experience is retrieved. According to the latter view, memories are susceptible to change each time they are retrieved. The next time the memory is activated the version reconsolidated during the last retrieval is recalled and therefore gradually modified. Reconstructed and modified from Alberini and LeDoux (2013).

vidual. Although this individuality of memory functions has often been ignored or underestimated, some historical studies of psychology have emphasized its existence and validity (e.g., Carroll and Maxwell, 1979). For example, Geiselman et al. (1982) found individual differences in verbal list learning and suggested that the differences could be explained by memorized knowledge of specific cognitive processes already formed in the individuals by former experience. As Markowitsch (1985) suggests, this could explain why damage to various regions of the brain, including the limbic system and neocortices, sometimes disturbs mnemonic information processing to a different degree among individuals. It is not rare that patient and animal studies sometimes have conflicting reports on the sparing or loss of long-term memories after damage to specific regions, e.g., the temporal lobe and hippocampus (see Kim et al., 2001 for more discussion). There may be several regions that have the ability to process information for long-term memory. Based on these psychological and neuroscientific studies of long-term memory, it should be considered that memory engrams could be dynamically various and that consolidation of memories involves various information processes occurring in several brain regions.

2. Principal concepts of memory engrams

2.1. Cell assemblies

Besides the former and present localization studies, memory engrams of neuronal and circuitry levels have been investigated. The traditional and first established principle for neuronal networks underlying learning and memory is "**cell assembly**" (Hebb, 1949), which has led observation of correlation between dynamic activity of memory engrams and behavioral change. The cell assembly is a functional population of neurons encoding information in the brain. By activation of cell assemblies, it is possible that the perception of an entire image can be established by using fragmented stimuli only, and images and concepts can be formed from various pieces of information. These processes also involve memory, and Hebb stated "There may, then, be a memory trace that is wholly a function of a pattern of neural activity, independent of any structural change." (Hebb, 1949, p.61). Due to the flexible nature of cell assemblies generating such patterns of neural activity, information processing unique to memory, e.g., association, recollection, and reorganization, can be realized. Similar principles can be applied to explain the formation and transformation of memory engrams, which are closely connected with and mostly generated by perception and images (Hebb, 1949). The idea of cell assemblies is not a historical hypothesis, but one of the most reliable and established principles driving the field of neuroscience of memory at present (Buzsáki, 2010; Eichenbaum, 2018; Sakurai et al., 2018).

The detailed features of a cell assembly are described below (Palm, 1993; Sakurai, 1999). The cell assembly can be formed at any time according to the information to be encoded and processed, and neurons constituting the assembly exhibit synchronous firing. Individual neurons participate in different cell assemblies and therefore each neuron exhibits multiple functions. Moreover, the neurons show changes of synchronous firing within an assembly or among assemblies, which reflect connection dynamics among the neurons, to encode different memory engrams and occasionally form both large and small cell assemblies according to the type of engram being processed. These characteristics can be detected by recording multineuronal activity in a brain that is encoding and processing multiple memory engrams, such as in an animal performing complicated or multiple memory tasks. Several such experiments and some modeling studies (e.g., Sakurai, 1996; Sakurai and Takahashi, 2006; Roudi et al., 2015) suggest the existence of cell assemblies by detecting the functional overlap of individual neurons and the functional connection dynamics among the neurons between different memory tasks.

Please cite this article in press as: Takamiya, S., et al., Dynamics of memory engrams. Neurosci. Res. (2019), https://doi.org/10.1016/j.neures.2019.03.005

The key techniques for those experiments are stable and long-term multineuronal recordings from behaving animals along with statistical analysis tools that can detect significant and temporary synchrony among neurons. Long-term multineuronal recordings are the only method that can measure spiking synchrony of neurons in real time and are constantly under development (e.g., Xie et al., 2016). On the other hand, analysis methods to detect functional connectivity among many neurons, have been controversial and many methods have been proposed (e.g., Lopes-dos-Santos et al., 2013; Tatsuno, 2015). However, the traditional cross-correlation analysis (e.g., Aertsen et al., 1989) which is used to observe synchronous firing between two neurons, may be the useful method, even at present, because a neuron-pair correlation could be regarded as a reflection of synchronous firing of a large number of surrounding neurons (see Roudi et al., 2015 and Sakurai et al., 2018 for more discussion).

2.2. Engram cells

The newer principle for memory formation, the "**engram cell,**" describes the causal relationship of memory-engram activity and behavioral change. Engram cells are defined as neurons that are activated during learning to encode a specific experience and can subsequently be selectively reactivated to produce the memory of that experience (retrieval) or inhibited to prevent the memory (retrieval failure) (Tonegawa et al., 2015). Engram cells were discovered by combining activity-dependent cell labelling with optogenetics (Tonegawa et al., 2018). Liu et al. (2012), one of the pioneering studies, conducted a contextual fear conditioning using c-fos-promotor driven tetracycline transactivator (tTA) transgenic mice with the AAV9-TRE-ChR2-EYFP virus. They explains that their approach directly couples the promoter of c-fos, an immediate early gene often used as a marker of recent neuronal activity, to tTA, a key component of the doxycycline (Dox) system for inducible expression of a gene of interest. The presence of Dox inhibits c-fos-promoter driven tTA from binding to its target tetracycline-responsive element (TRE) site, which prevents it from driving ChR2–EYFP (enhanced yellow fluorescent protein) expression. In the absence of Dox, training-induced neuronal activity selectively labels active c-Fos-expressing hippocampal neurons with ChR2–EYFP, which can be reactivated by light stimulation during testing (Liu et al., 2012). In the day after conditioning, the mice showed a freezing response only when in the same environment as during conditioning. However, when light stimulation was applied to the hippocampus of mice, the neurons that were active during the fear conditioning were activated again and the mice showed a fear response, even when placed in a different environment. The authors stated that the activated neurons are the engram cells in which memory of fear was previously consolidated and was subsequently recalled via light stimulation.

In another pioneering study, Ohkawa et al. (2015), expressed ChR2 in neuronal populations in the hippocampus and the amygdala, some of which were active when the mouse was placed in a cylindrical box, and the others were active when the mouse was placed in a cubic box where it experienced an electric shock. On the following day when the mouse was in the home cage, light stimulation was given to activate all neuronal populations simultaneously. Thereafter, the mouse showed a fear response, even in the safe cylindrical box, indicating that the simultaneous activation of different engram-cell populations generated a new engram-cell population that associates those memories.

Some engram cells, in particular cells in prefrontal cortex (PFC), are referred to as "silent engram cells" (Kitamura et al., 2017). These cells are not reactivated by natural cues in the early period of post-training days, but can be reactivated artificially even in such a period by optogenetic stimulation to recall their encoded memory. In addition, the silent engram cells became active 10 days after the learning. Tonegawa et al. (2018) hypothesizes that reduced synaptic potentiation occurs in the PFC engram cells in the early period after learning. Therefore, memory is not retrievable from these cells by natural cues, but optogenetic stimulation bypasses synapses and causes memory retrieval. They also suggest that the relationship between silent and active engram cells is bidirectional and conversion of engram cells from a silent to an active state and vice versa is possible (Tonegawa et al., 2018). Actually, the PFC engram cells changed from silent to active in several days after the learning (Kitamura et al., 2017). The silent engram cells were also found in the hippocampus of amnesia model mice and Alzheimer's disease model mice (Ryan et al., 2015; Roy et al., 2016). The similarities and differences of the hippocampal and PFC engram cells could provide models of memory consolidation and retrieval (see Tonegawa et al., 2018 for more discussion).

3. Detection of memory engrams

3.1. Relation of engram cells and cell assemblies

Populations of engram cells could be considered as cell assemblies encoding memory engrams. From that point of view, the findings of Ohkawa et al. (2015) are meaningful because they are consistent with Hebb's original theory, which states that a new larger cell assembly is created by associating different smaller cell assemblies via synchronous firing and thus a "concept" is formed (Hebb, 1949) (Fig. 2). However, the concept of engram cell has not necessarily prerequisite of synchronous firing of neurons to encode a memory, despite cells consisting of a cell assembly being defined as functionally connected neurons via synchronous firing. In other words, engram cells are not thought of as a unit necessary to form an engram, but a collection of neurons that is activated to recall a memory. Therefore, the present studies of engram cells might result not in revealing neuronal mechanisms but in finding macroscopic circuits and finally demonstrate the functional differences and interactions of memory-related brain regions (e.g., Tonegawa et al., 2018). Even though the engram cells were detected by the new innovating methods of neuroscience, this macroscopic investigation might become a type of traditional localization studies, which present us only static pictures of memory-related regions and circuits. In order to observe and reveal dynamic, not static, features of neuronal activities and their functional connections actually occur during memory encoding, consolidation and reconsolidation, recording studies are also needed in addition to the studies of engram cells.

In addition, a few considerations are needed to accurately interpret the results of optogenetic stimulation studies describing engram cells. Differences between behaviorally-triggered or natural stimulus-triggered patterns of neuronal ensemble activity and activity induced by optogenetic stimulation should be carefully examined, although some differences in relation to the assumption of active and silent engram cells have already been discussed as described above. A recent study using multineuronal recording combined with Cre-LoxP neurogenetics and optogenetics reported that localized optogenetic manipulation disrupted network oscillations and caused changes in neuronal firing patterns in many areas of the brain (Xie et al., 2016). This result raises the possibility that optogenetically elicited behaviors are caused not by reactivation of the previously activated neurons but by newly excited activity patterns that cause the same behaviors as those that appeared during the training. Besides, most studies of engram cells have used behavioral tasks that can be learned in one experience, e.g., contextual fear conditioning, to instantaneously express ChR2 in a specific neuronal population. In contrast with this, most

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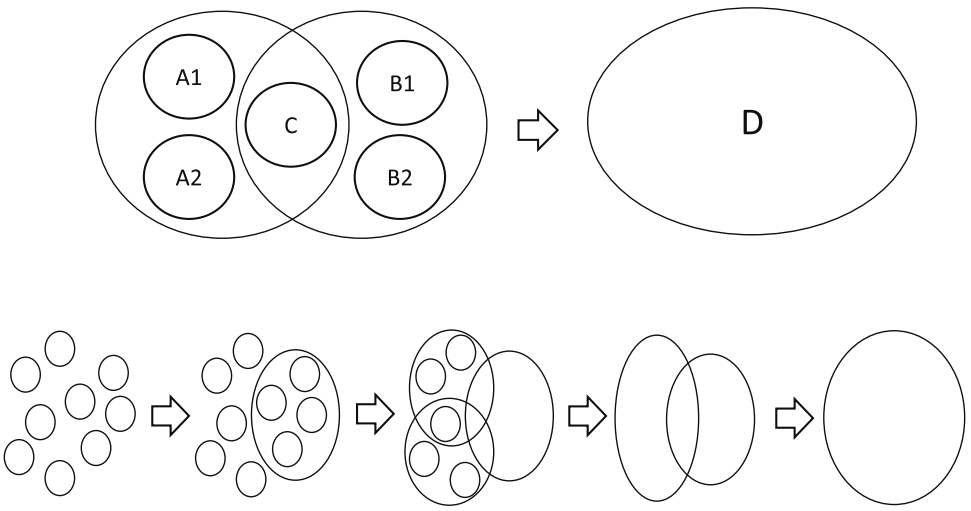

Fig. 2. Top panel: Schematic based on Hebb's hypothesis postulating association of cell assemblies. The circles represent cell assemblies. One concept is encoded by small assemblies A1, A2, and C, and the other concept is encoded by small assemblies B1, B2, and C. The two large assemblies have a common small assembly C that acts as a basis of prompt association to generate a larger assembly encoding a new concept D. Reconstructed and modified from Hebb (1949). Bottom panel: Schematic of dynamic association processes among small and large cell assemblies constructed by the association described in the top panel. Transition of these associations finally generate the largest assembly (the right end) and makes it possible to encode the highest concept as a memory engram.

of higher-order and positive memories are formed by learning over longer time periods with rewards. There is currently no evidence that reward-seeking learning and punishment-avoidance learning have common mechanisms of memory consolidation and, actually, learned behaviors and underlying neural mechanisms of these types of learning are different to some degree (Whishaw and Kolb, 2005).

3.2. A developing method for the detection

Multineuronal recordings can detect neuronal spikes in real time but cannot detect activities of entire neuron populations or full pictures of engram cells or cell assemblies. Live-cell imaging methods have been developed recently to compensate for such weaknesses of multineuronal recordings. This method can visualize individual neuron activity as a function of changes in Ca^{2+} levels (e.g., Grienberger and Konnerth, 2012) and has been applied to measure the activity of hundreds of neurons or more in real time from awake rodents (e.g., Dombeck et al., 2010).

This method is still in development and currently has a weakness in the time resolution (sampling rate of imaging), which is ~60 Hz when hundreds of neurons are measured simultaneously. Thus it cannot precisely detect timings of single-neuron spikes. As such, synchronization at the submillisecond level between adjacent neurons, as seen in the PFC and hippocampus (Sakurai and Takahashi, 2006; Takahashi and Sakurai, 2009; Diba et al., 2014), which might reflect the activity of cell assemblies, cannot be detected. In addition, it is necessary to remove most of the overlying cortex to enable direct imaging from the hippocampus and other subcortical structures by two-photon microscopy (e.g., Denk and Svoboda, 1997). The effects of such large cortical lesions on the cellular activity of the subcortical structures are unknown. Despite these limitations, the ability to monitor the activity of a large population of neurons in awake and behaving animals is important for further research on cell assemblies and memory engrams. Even with a low sampling rate, particularly if the imaging is of calcium, this method can allow for burst detection via high calcium influx to cells (e.g., Vogelstein et al., 2009). This means that the synchronous burst firing of many cells constituting a cell assembly can be monitored, even though single-neuron spikes cannot be accurately monitored in real time.

4. Conclusions and future directions of research

The future directions of research of memory engrams should focus on their dynamic consolidation/reconsolidation processes as well as on multiple memory systems (Kim and Baxter, 2001; Eichenbaum, 2002). Some pioneering studies (John, 1972; Olds, 1975) have already indicated that many neurons distributed across multiple regions have the capacity to change their activity during processes of memory consolidation. Although these findings have been followed by many more recent studies, multiple memory systems have been investigated mainly by dysfunction or inactivation studies (e.g., Eichenbaum, 2002; Matsuo, 2015). Some recent recording studies have examined consolidation/reconsolidation (recall) processes for either a single or two regions (e.g., Igarashi et al., 2014; Rothschild et al., 2017; Grewe et al., 2017), but few have analyzed neuronal population activity in three or more regions. Therefore, it is recommended that future studies apply multineuronal recording and/or live-cell imaging to monitor spikes and their synchrony in neuronal populations in multiple regions (hippocampus, PFC, temporal cortex, amygdala, etc.) throughout the entire process of memory consolidation and reconsolidation (recall) in unique behavioral tasks. This will allow for detection of activities of cell assemblies and their interactions for dynamics of memory engrams.

In addition to the new experimental strategy with highly developed behavioral and recording techniques, new background assumptions are needed to detect real dynamic features of memory engrams. Recent studies have reported that memory can be formed even by the activation of random populations of cortical neurons (Huber et al., 2008; Choi et al., 2011). Choi et al. (2011) conducted an experiment using optogenetics to induce ChR2 expression in a random population of piriform cortical neurons, allowing for firing of action potentials in response to light stimulation. The mouse exhibited an escape response when it received a foot shock along with light stimulation. After the initial experience, the light stimulation alone elicited escape response. This result indicates that activation of a random population of cortical neurons (~500), not a population activated by the environment or the foot shock, can be used as a conditioned stimulus (CS) and elicit a conditioned escape response. They also showed that light stimulation of random ChR2-expressing neurons effectively elicited a discriminative

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response for a reward. These results showed that our brain can use artificial activation of random neuronal populations as cues for learning. It suggests that our brains have plasticity in their information processing. In the dynamic memory engram model (Fig. 1), the brain must be capable of reading out information correctly from dynamic engrams, even if the organization of engram cells has changed through repeated reconsolidation processes. This plasticity may be the background mechanism which underlies memory engram dynamics.

These experiments could also be interpreted to support the hypothesis that the cortical area is a random network whose connectivity is sculpted by individual experience, similar to the individual differences of memory systems described in the Introduction. Huber et al. (2008) have shown that the ability of a random population of neurons to act as cues in an association task was not restricted to the piriform cortex, but also present in the barrel cortex, and that the effectiveness of light stimulation depended on the number of ChR2-expressing neurons. These examples highlight the nervous system's remarkable dynamics for memory consolidation and that the activity of random populations of neurons in different brain regions could serve as memory engrams.

These recent findings lead us back to the notion by Lashley (1950), discussed in the Introduction, that cells in many regions are able to acquire the ability to consolidate memory in certain definite patterns. They also direct a spotlight on the idea by John (1972) suggesting that the brain employs plastic and statistical processing for memory consolidation in distributed regions, rather than switchboard-like processing in one or a few specific regions, and that any neuron and region may contribute to mediating a diversity of functions ("multipotentiality": John, 1980). These old and new notions may provide us with significant background assumptions to understand the dynamics of memory engrams in the working brain.

Acknowledgments

This work was supported by JSPS KAKENHI Grant Numbers 16H02061 and 18H05088 to YS.

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