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Manipulating memory in space and time

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Highlights:

- Identification and manipulations of memory engrams and engram cells
- Creating false memory by manipulating engram cells
- Countering depression-like behaviors by stimulating positive valence engram cells
- Restoring memory in early Alzheimer's mouse models by engineering engram cells

Abstract

One of the most fascinating aspects of an animal's brain is its ability to acquire new information from experience and retain this information over time as memory. The search for physical correlates of memory, the memory engram, has been a longstanding endeavor in modern neurobiology. Recent advances in transgenic and optogenetic tools have enabled the identification, visualization, and manipulations of natural, sensory-evoked, engram cells for a specific memory residing in specific brain regions. These studies are paving the way not only to understand memory mechanisms in unprecedented detail, but also to repair the abnormal state of mind associated with memory by engineering.

Introduction

Understanding the material basis of memory remains a central goal of modern neuroscience [1,2]. Descartes proposed that mental capacities, specifically memory, must be represented in the brain [3]. At the onset of the 20th century, Richard Semon theorized that learning induces enduring physical changes in specific brain cells that retain information of the experience and are subsequently reactivated by appropriate stimuli to induce recall. He termed these physical changes the engram [4,5]. Another term that is used by some contemporary neuroscientists is memory trace, which can be considered to be equivalent to Semon's engram. Even after Semon's engram theory, some leading scholars wondered whether memory is physically represented in the brain or psychically represented in the mind. It was Karl Lashley who advocated the physical theory of information storage in the central nervous system. In particular, Lashley adopted the concept of the engram and was among the first to attempt to localize memory engrams in the brain [6]. While Lashley's idea of Mass Action was later empirically disproved, some researchers after him continued to identify the location of memory representations in the brain [7]. In this review, we will discuss recent experimental studies demonstrating that memory is indeed stored in specific populations of brain cells and their associated circuits, with a focus on memory manipulation studies. More comprehensive reviews of recent memory engram studies, including early attempts, is available elsewhere [8••,9•,10].

Engram cell identification

Several groups found that cell populations active during the acquisition of a fear memory were preferentially reactivated during the recall of that memory in different areas of the mouse brain, such as the amygdala [11•], the hippocampus [12,13], layer II cortical areas including sensory cortex [14,15], and the prefrontal cortex [16]. Another approach that has been used to identify possible engram cell populations in the rodent brain employed the random overexpression of the transcription activator cAMP response element-binding protein (CREB) in a small population of neurons, making these cells more likely to be recruited to become a part of putative engram cell populations during subsequent learning [17]. By selectively manipulating these high-CREB cells via diphtheria toxin-based ablation [18•] or genetic-based inhibition [19•,20-23] memory recall was disrupted in mice. More recent studies showed that a shared neuronal ensemble is capable of linking distinct memories, only when two experiences occur close in time during periods of high excitability in hippocampal CA1 [24] and lateral amygdala [25]. Further, novel context exploration

during a narrow time window before or after weak object recognition training results in the formation of a long-term object recognition memory [26].

The most direct evidence of engram cells should come from gain-of-function manipulations, where a population of neurons activated by learning is artificially reactivated to mimic behavioral recall elicited by natural cues [27]. By combining the activity-dependent, doxycycline-dependent *c-fos-tTA* system and channelrhodopsin-2 (ChR2)-mediated optogenetics, researchers were able to tag a sparse population of dentate gyrus (DG) neurons activated by contextual fear conditioning with ChR2 in mice [28••]. Subsequently, when these cells were reactivated by blue light in a context different from the original one used for conditioning, the mouse subjects displayed freezing behavior as evidence of fear memory recall (Figure 1). Crucially, this optogenetic reactivation of a fear memory was not due to the activation of pre-wired neural circuits. This was demonstrated by disrupting the activity of the downstream CA1 region only during training, and finding that subsequent optogenetic DG engram activation did not elicit memory retrieval [29••]. Similarly, memory recall induced by the artificial reactivation of fear memory cells has been reported for multiple brain regions [14,30-32]. Along with these engram reactivation experiments, loss-of-function studies have also been performed [33-35].

Creating a false memory by manipulating engram cells

Memory recall is constructive in nature and the act of recalling a memory renders it labile and highly susceptible to modification [36]. In humans, memory distortions and illusions occur frequently, which often results from incorporation of misinformation from external sources [37]. In light of the fact that humans have a rich repertoire of mental representations generated internally [38], one possible reason for the formation of an episodic false memory is that the memory of a past experience becomes associated with a current external event of high valence.

Using a method that permits optogenetic labeling and manipulation of memory engram cells [28••], a study tested this possibility in mice [39••]. The authors labeled contextual engram cells in the DG with ChR2 by exposing mice to context A (Figure 2), thereby activating c-Fos in the engram. On the next day, as the labeling window was shut down by switching mice from regular to doxycycline-containing food, mice received foot shocks in a distinct context B as their context A engram cells were artificially reactivated with pulses of blue light. On the third day, when the animals were reintroduced to context A to test the context A-shock association memory, animals displayed freezing behavior despite never having received foot shocks in context A. The freezing behavior was not due to generalization because the mice did not freeze above background levels in another distinct context C. Of course, these mice also froze when tested in context B, indicating that they also formed a genuine context B-shock association memory. Importantly, freezing levels in context B were significantly lower than in a group of mice that did not receive blue light delivery on day 2 while foot shocks were delivered. This observation suggests that formation of the false and genuine memory representations on day 2 were in competition. Moreover, using the same cFos-driven ChR2 labeling strategy, a recent study demonstrated that, in addition to optogenetically driving a hippocampal contextual engram, basolateral amygdala cells responding to a stimulus of high valence can be simultaneously activated to form an association with the hippocampal-driven contextual memory [40•]. Such findings indicate that at least some form of false memory is

generated by an association of internal brain activity representing recall of a past experience with the current external or internal experience of high valence [39••,40•,41].

Countering depression by positive valence engram activation

The conceptual framework of the interaction between the neural circuits governing memory valence and those encoding neutral components of an episode is that the engrams for the latter, like the one in the hippocampus, are free to associate with either positive or negative valence engrams in the amygdala [42••]. The development of new technologies that permit engineering of these engrams opens up the possibility of adding a novel approach to the classical approaches for the treatment of psychopathologies. For example, depression is characterized by a pervasive and persistent blunted mood that is accompanied by motivational impairments and a loss of interest or pleasure in normally enjoyable activities. How positive episodes interact with psychiatric disease-related impairments at the neural circuit level has remained unknown.

In a recent study, the researchers demonstrated that optogenetic reactivation of engram cells formed in the DG by a naturally rewarding experience was sufficient to acutely suppress depression-related behavior [43••]. This study further demonstrated that glutamatergic transmission from the amygdala's axonal terminals to the nucleus accumbens (NAcc) shell is necessary for the real-time antidepressant-like effects of the reactivated DG engram cells. Notably, the NAcc has recently been identified as a potential therapeutic node for deep brain stimulation to alleviate anhedonia in humans [44], and previous reports also identified amygdala axonal terminals onto NAcc as being sufficient to support self-stimulation and reward-seeking behavior in a dopamine D1 receptor-mediated manner [45]. It is important to note here that directly reactivating cells associated with a positive memory is qualitatively different from exposing depressed subjects to naturally rewarding experiences, which would normally activate these corresponding brain areas in the healthy brain. In the psychiatric diseased-related state, acute administration of naturally rewarding external cues may not have access to, or sufficiently activate, the positive valence engram cells' representations associated with the positive experience. Direct optogenetic stimulation of these cells may be able to overcome this obstacle. These studies provide causal evidence that engram cells can be directly manipulated to modulate a specific behavioral program associated with psychiatric disease-related states.

Restoring memory engrams in mouse models of early Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of brain degeneration, and typically begins with impairments in cognitive functions [46]. Most research has focused on understanding the relationship between memory impairments and the formation of pathological hallmarks seen in late stages of AD. Early phases of AD have received relatively less attention, although synaptic phenotypes have been identified as major correlates of cognitive impairments in both human patients and mouse models [47]. Several studies have suggested that the episodic memory deficit of AD patients is due to ineffective encoding of new information [48]. However, since cognitive measures used in these studies rely on memory retrieval, it has not been possible to rigorously discriminate between impairments in information storage and disrupted retrieval of stored

information. This issue has an important clinical implication: if the amnesia is due to retrieval impairments, memory could be restored by technologies involving targeted brain stimulation.

Focusing on memory engrams, a recent study examined long-term memory impairments in mouse models of early AD [49••]. Using APP/PS1 AD mice, the authors observed that amyloid plaque deposition started in 9-month old mice, however memory deficits were clearly visible several months before plaque deposition. In a contextual fear-conditioning paradigm, 7-month old AD mice exhibited normal short-term memory but performed poorly 24 hr later in long-term memory tests. This behavioral impairment correlated with a decreased number of c-Fos-positive cells in the DG as well as decreased engram cell-specific dendritic spine density in AD mice. However, preferential functional connectivity between engram cells was maintained in the early AD mice. Next, in order to examine whether functional DG engram cells persisted in early AD mice, despite these animals being amnesic at the behavioral level, the authors developed a novel strategy using a double adeno-associated virus system to label engrams [49••]. As expected, engram-labeled early AD mice were amnesic a day after fear conditioning; but remarkably, these mice exhibited memory recall as robustly as equivalently treated control mice in response to blue light stimulation of engram cells. Following early findings [50] that long-term potentiation (LTP) induction results in a spine density increase, Roy et al. [49••] applied repeated optogenetic LTP induction specifically to entorhinal cortex engram cell inputs into DG engrams. This procedure reversed the spine density deficit in early AD mice. Crucially, this spine restoration led to the rescue of a long-term fear memory recall in AD mice. The authors also demonstrated that an ablation of DG engram cells containing restored spine density prevents the rescue of long-term memory recall in early AD mice [49••,51,52•]. Together, it is clear that genetic manipulations of specific neuronal populations can have profound effects on cognitive impairments of AD.

Conclusions and perspectives

Many lines of evidence for the long-sought memory engram and engram-containing cells have recently been reported. Such evidence has been obtained by combining multiple technologies, each addressing a specific level of complexity [8••,9•,10]. Despite the fact that the memory engram has clearly come of age, a number of issues remain to be investigated. A central issue is the nature of the enduring changes that occur in the engram cells and their connections. A first study addressing this issue [29••] demonstrated the validity of the long-held hypothesis that synaptic strengthening and structural plasticity occurred specifically in engram-positive cells as opposed to engram-negative cells in the same brain region. The demonstration of learning-induced changes strongly argues that they are indeed cells that carry an engram component, rather than cells necessary just for performance. However, this study did not determine the *in vivo* firing patterns of the engram cells (e.g., are they place cells? What firing pattern would be observed before and after recall cues are delivered, etc.?). A recent study [53•] using similar technology as [29••] reported that CA1 engram cells exhibit place-specific firing in an environment, thereby adding to the understanding of cFos-positive engram cells.

Memory, however, appears in many different types (e.g., emotional, procedural, working, semantic, perceptual), each supported by one or more distinct brain regions. The basic technology used to identify memory engram cells for classical conditioning may, in principle, be applicable to other types of memories. For instance, procedural or habit memories develop slowly with multiple rounds

of training. Can one identify the putative habit engram cells and their circuits, and elucidate how they may change as training is repeated and learning advances? An additional example includes the memory for a temporal sequence of events – a crucial component of episodic memory. Are there engram cell ensemble(s) that hold the sequence information identifiable by the current engram cell technology? These studies are expected to reveal both common and memory type-specific features of engram cells.

One of the great advantages of the gain-of-function demonstration of memory engrams compared to the loss-of-function demonstration is the availability of specific engram cells not only for basic research but also for their engineering by optogenetic and other technologies. This permitted manipulations of memory-associated cognitions and behaviors both in health (e.g., false memory inception) and neurological (e.g., early AD) or psychiatric (e.g., depression) diseases. These studies conducted with animal models are providing proof of concept evidence for the potential future development of therapies based on direct manipulation of patients.

Conflict of interest statement

Nothing declared.

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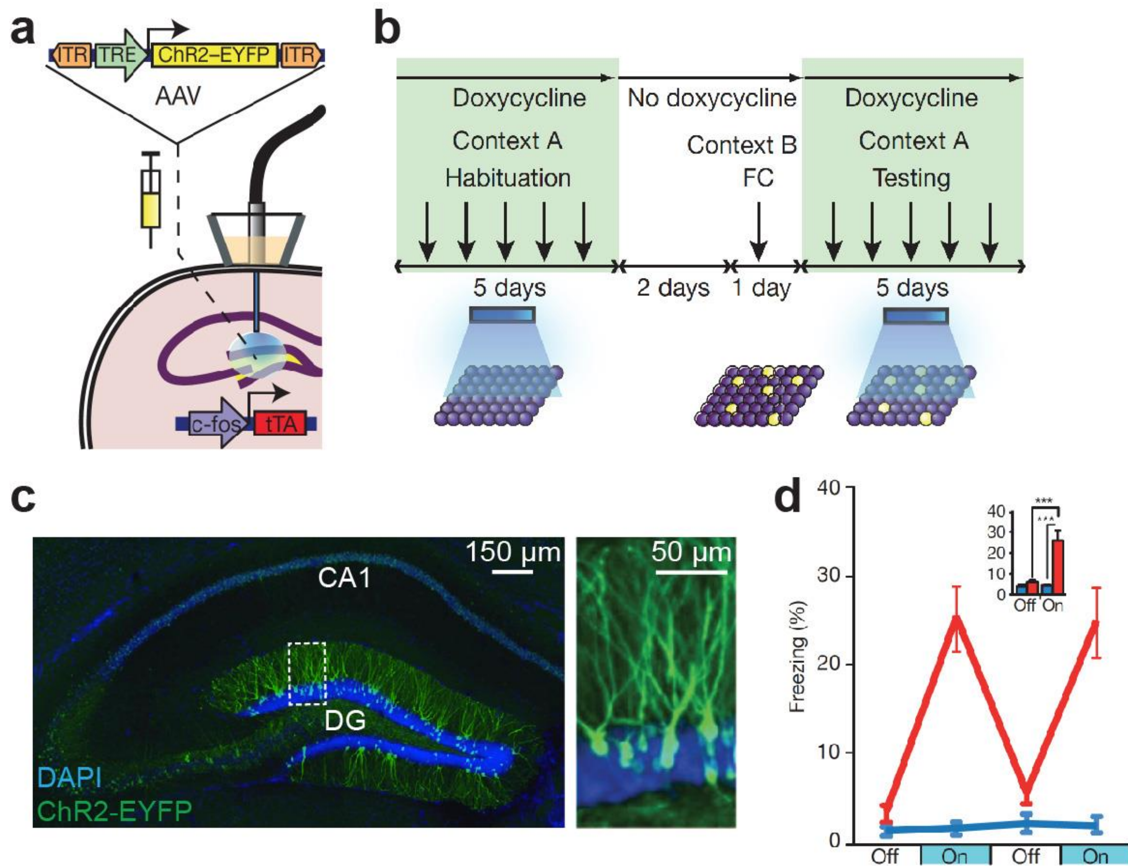

Figure 1. Tagging and manipulating memory engram cells

(a) Using the activity-dependent labeling technology developed by [28••], c-fos-tTA mice were injected with the AAV_9-TRE-ChR2-EYFP virus and implanted with an optic fiber targeting the hippocampal dentate gyrus (DG). (b) Behavioral schedule. Mice were habituated to context A with light stimulation, then taken off doxycycline-containing food for 2 days and fear conditioned (FC) I context B. Mice were put back on doxycycline-containing food and tested in context A with light stimulation. (c) Representative image showing the expression of ChR2-EYFP in memory engram cells of the DG for a contextual fear memory (left). Boxed DG region is magnified (right). (d) Following fear conditioning, blue light stimulation of DG engram cells induces memory recall (freezing behavior) in neutral context A.

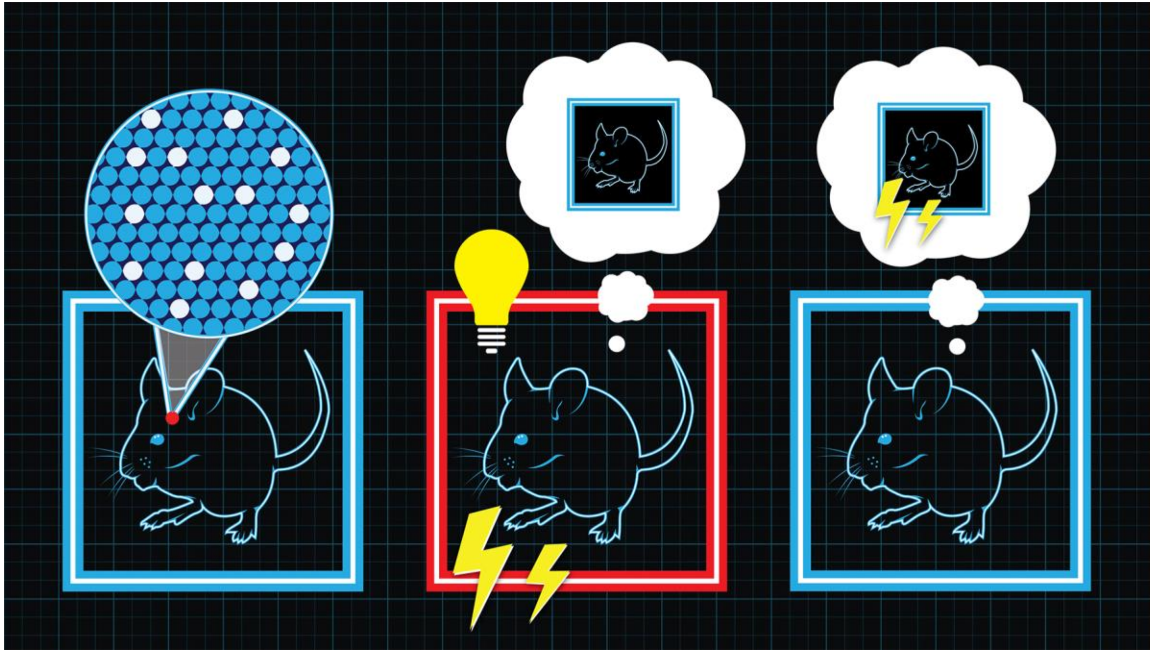

Figure 2. Creating a false memory by manipulating engram cells
Tagging memory engram cells in the hippocampus encoding the blue, neutral context information with ChR2 (left). The next day, mice received mild electric footshocks in the red context with simultaneous light activation of the blue context memory engram cells (middle). On day 3, mice were returned to the blue context and displayed fear memory recall (right).