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Memory Allocation: Mechanisms and Function

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Abstract

Memories for events are thought to be represented in sparse, distributed neuronal ensembles (or engrams). In this article, we review how neurons are chosen to become part of a particular engram, via a process of neuronal allocation. Experiments in rodents indicate that eligible neurons compete for allocation to a given engram, with more excitable neurons winning this competition. Moreover, fluctuations in neuronal excitability determine how engrams interact, promoting either memory integration (via coallocation to overlapping engrams) or separation (via disallocation to nonoverlapping engrams). In parallel with rodent studies, recent findings in humans verify the importance of this memory integration process for linking memories that occur close in time or share related content. A deeper understanding of allocation promises to provide insights into the logic underlying how knowledge is normally organized in the brain and the disorders in which this process has gone awry.

Keywords

memory; engram; allocation; neuronal excitability; fear; reward

INTRODUCTION

Memory may be defined as the retention over time of internal representations gained through experience and the capacity to reconstruct these representations at later times (Dudai 2007). These internal representations are thought to be encoded by long-lasting physical

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changes to the brain (memory traces, or engrams) (Josselyn et al. 2015, 2017; Schacter 2001; Tonegawa et al. 2015). The term engram was initially coined by Richard Semon, who defined it as "…the enduring though primarily latent modifications in the irritable substance produced by a stimulus…" (Semon 1921, p. 12). Memory recall results from the reactivation of the engram supporting that internal representation, thereby recapitulating the initial spatiotemporal pattern of neural activity that occurred during the experience. Semon called this process ecphory, "…influences which awaken the mnemic trace or engram out of its latent state into one of manifested activity…" (Semon 1921, p. 12). The prevailing view is that the formation of an engram involves strengthening of synaptic connections between populations of neurons (ensembles of neurons or cell assemblies) that are active during an event. This increases the likelihood that the same (or similar) activity pattern within this cell assembly can be recreated at a later time, resulting in the recall of that memory (Josselyn et al. 2015, 2017; Schacter 2001; Tonegawa et al. 2015).

It is generally agreed that different types of memory preferentially engage different brain regions (e.g., Scoville & Milner 1957, Squire 1992, White et al. 2013). Moreover, even within a given brain region, each engram supporting a memory preferentially engages only a subset of neurons. For instance, it has been well established that the amygdala, particularly the lateral nucleus of the amygdala (LA), is critical for auditory fear conditioning (Davis 1992, Fanselow & Gale 2003, Goosens & Maren 2001, LeDoux 2000, Pape & Pare 2010). In this Pavlovian conditioning paradigm, an initially motivationally neutral tone [the conditioning stimulus (CS)] is paired with an aversive foot shock [the unconditioned stimulus (US)]. Subsequent tone presentation elicits defensive responses, including freezing [a conditioned response (CR)] (see Figure 1). The LA is a critical site for the convergence of tone and foot shock information (LeDoux et al. 1990), and the majority of LA excitatory principal neurons (PNs) respond to both tones and foot shocks (Quirk et al. 1995, 1997; Repa et al. 2001). Therefore, most PNs in the LA are correctly wired and have the potential to become part of an engram supporting an auditory fear memory. However, converging evidence from multiple techniques, ranging from in vivo electrophysiology to labeling with neuronal activity markers, estimates that, although many are eligible, only roughly 10–30% of PNs become important for any one auditory fear memory (Bergstrom & Johnson 2014, Gouty-Colomer et al. 2015, Han et al. 2007, Quirk et al. 1997, Reijmers et al. 2007, Repa et al. 2001, Rumpel et al. 2005, Yang et al. 2016). A similar pattern emerges for the dorsal hippocampus, a region critical for encoding space, context, and episodic memories (Eichenbaum 2000, Lever et al. 2002, Milner et al. 1998, Morris et al. 1982). Again, although many PNs in the dorsal hippocampus (CA1) are eligible, only roughly 20–30% of PNs are engaged by a given experience (Cowansage et al. 2014, Garner et al. 2012, Guzowski et al. 1999, Leutgeb et al. 2004, Ramirez et al. 2013, Tayler et al. 2013, Thome et al. 2017, Vazdarjanova et al. 2006, Wilson & McNaughton 1993).

Devoting a relatively small population of neurons to any one memory is consistent with the concept of sparse population coding. Population coding that is sparse (i.e., minimizes the number of active neurons) and orthogonal (i.e., decreases the statistical correlation between codes) has been argued to maximize the number of patterns that can be stored within a neural network within biological constraints while minimizing interference (Amari 1989, McNaughton & Morris 1987, Rolls & Treves 1990, Wolfe et al. 2010). In this article, we

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review evidence from both experimental animal and human studies examining the factors that determine how neurons are allocated to a unique engram, and speculate about the function of allocation.

MECHANISMS OF ALLOCATION

That many neurons are eligible to become part of an engram, yet only a few end up being chosen, raises the question of what mechanisms mediate this selection process. Evidence indicates that eligible PNs in the LA compete against one another for allocation to an engram, with those neurons with relatively higher intrinsic excitability at the time of a training event winning this competition (Frankland & Josselyn 2015, Josselyn 2010, J.I. Kim et al. 2016, Rogerson et al. 2014, Silva et al. 2009).

Ca^{2+}/cAMP Response Element–Binding Protein Function Mediates Allocation in the Lateral Nucleus of the Amygdala

The first insights into the mechanisms underlying allocation originated with the somewhat perplexing observation that viral overexpression of the transcription factor Ca^{2+}/cAMP response element-binding protein (CREB) in a random, small (10–20%) population of PNs in the LA before auditory fear training enhanced memory of this event (Josselyn et al. 2001). To account for the observation that the manipulation of a small population of random neurons in one brain region was sufficient to enhance memory, Han et al. (2007) hypothesized that the virally infected neurons overexpressing CREB were preferentially recruited (or allocated) to the engram supporting that fear memory. To examine this possibility, they asked whether neurons overexpressing CREB were indeed overrepresented in this engram. As a proxy for visualizing the engram, they leveraged previous findings that one molecular signature of a recently (i.e., within the previous 5 min) active neuron is nuclear localization of mRNA for the activity-dependent gene *Arc* (activity-regulated cytoskeleton-associated protein) (Chawla et al. 2005, Guzowski et al. 1999). Mice were trained for auditory fear conditioning and, 24 h later, presented with the tone memory retrieval cue. Five min following this memory test, the overlap between CREB-overexpressing neurons and Arc^{+} neurons (components of the engram) was assessed.

Importantly, the number of Arc^{+} PNs in the LA was consistent with electrophysiological estimates of the size of the engram (Repa et al. 2001, Rumpel et al. 2005), validating this approach for identifying an engram. As hypothesized, PNs infected with the viral vector overexpressing CREB were more likely to be Arc^{+} than their noninfected neighbors, suggesting that CREB-overexpressing neurons were preferentially allocated to the engram (see Figure 2). Control studies showed that this colocalization was contingent on training, indicating that simply overexpressing CREB was not sufficient to induce nuclear localization of *Arc* mRNA in this protocol, consistent with previous reports (Barco et al. 2002). That increasing CREB function alone does not induce *Arc* expression may not be surprising as the critical *Arc* promoter contains CRE sites (which bind CREB) as well as binding sites for serum response factor and myocyte enhancer factor 2 (Kawashima et al. 2009). Additional control studies showed that PNs infected with a viral vector expressing green fluorescent protein (GFP) alone were equally likely to be Arc^{+} than their noninfected

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neighbors, suggesting that the allocation effect was not simply due to viral vector infection. Together these findings suggest a mechanism by which neurons with higher CREB function are preferentially recruited to the engram, supporting a conditioned fear memory. Although in this study the difference in CREB function between neurons is magnified (via viral overexpression) relative to the differences that occur naturally in nonmanipulated brains, we hypothesize that a similar process underlies normal allocation. Furthermore, we reason that the memory enhancement observed following CREB overexpression in a small population of neurons may be explained by findings indicating that increasing CREB function in PNs facilitates long-term potentiation (LTP) (Barco et al. 2002, Marie et al. 2005). In this way, overexpressing CREB in the study by Han et al. (2007) produced two outcomes, allocation and enhanced memory.

In contrast to the finding that increasing CREB in a small, random population of LA PNs enhanced memory, disrupting CREB function in a similar small, random population of LA PNs (by virally expressing a dominant-negative CREB construct, mCREB) did not disrupt memory. Critically, infected neurons expressing mCREB were far less likely than their noninfected neighbors to be Arc^{+} following the memory test. These results suggest that, first, neurons with decreased CREB function were actively excluded from the engram, and second, the remaining (noninfected) neurons with intact CREB function were sufficient to support normal auditory fear memory. In this case, memory was normal, as the engram supporting it was composed of noninfected neurons.

It is interesting to note that across these experiments (using viral vectors to express CREB, mCREB, or control GFP, and using different intensities of the foot shock US), the strength of the memory varied, but the size of the Arc^{+} engram in the LA remained constant. That is, the size of the engram did not increase in experiments in which memory was enhanced (by overexpressing CREB or increasing foot shock intensity). This finding suggests that neuronal allocation to an engram is a competitive, rather than cell-autonomous, process. Together these findings led to the novel hypothesis that eligible LA neurons compete for allocation to an engram supporting a fear memory and that neurons with relatively higher CREB function at the time of training win this competition.

The finding that overexpressing CREB in a small population of LA neurons enhances fear memory was replicated by several groups (Rexach et al. 2012, Sargin et al. 2013, Wallace et al. 2004) and extended to other types of aversive memory (Zhou et al. 2009). Overexpression of CREB in a small random population of LA neurons also enhances a cocaine-cue (rewarding) memory (Hsiang et al. 2014), indicating that in the LA, CREB-mediated allocation is not limited to aversively motivated memories. In contrast, increasing CREB function across PNs (rather than limiting overexpression to a small population of PNs) impairs memory formation (Barco et al. 2003, Viosca et al. 2009). Similar to a high tide lifting all boats, these findings highlight the importance of competition based on relative CREB function between eligible PNs in the allocation process.

Neuronal Excitability Mediates Allocation in the Lateral Nucleus of the Amygdala

CREB is a transcription factor implicated in a diverse array of cellular processes (Lonze & Ginty 2002). Which process, or combination of processes, mediates allocation? One of

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the first clues derived from the finding that CREB regulates neuronal intrinsic excitability (Benito & Barco 2010, Dong et al. 2006, Marie et al. 2005, Yiu et al. 2014, Zhou et al. 2009). Intrinsic excitability refers to the propensity of a neuron to fire action potentials in response to input signal. Increasing CREB function was shown to increase neuronal excitability. Conversely, decreasing CREB function decreased neuronal excitability (Dong et al. 2006). The excitability of a neuron is mediated by a complex interplay among ion channels along the plasma membrane (Catterall 1984). Although CREB-mediated processes regulate the expression of Na^+ channel subunits and K^+ channels (Dong et al. 2006, Wallace et al. 2009), the precise mechanisms by which overexpression of CREB increases neuronal excitability remain unknown. Interestingly, changes in intrinsic excitability were implicated in the formation of memory traces in invertebrates several decades ago (Alkon 1984a, Alkon et al. 1982, Scholz & Byrne 1987).

A series of findings converge to indicate that, as in invertebrates, intrinsic excitability mediates allocation and engram formation in rodents. First, the probability that an LA neuron is allocated to an engram supporting an auditory fear memory is increased by manipulations that increase excitability without directly targeting CREB (Yiu et al. 2014). Thus, expression of either a dominant-negative form of the voltage-gated K^+ channel [KCNQ2 (dnKCNQ2, hQ2-G279S) (Peters et al. 2005, Schroeder et al. 1998)] or the excitatory chemogenetic construct hM3Dq (Gq-mediated), in the presence of its ligand clozapine-*N*-oxide (CNO) (Armbruster et al. 2007), increases neuronal excitability and promotes allocation (Yiu et al. 2014). Second, the fear memory enhancement produced by CREB overexpression is phenocopied by increasing excitability in a similar small, random population of LA neurons. Thus, expression of dnKCNQ2 (Yiu et al. 2014) or excitatory chemogenetic (Yiu et al. 2014) or optogenetic (Rashid et al. 2016, Rogerson et al. 2016, Yiu et al. 2014) constructs enhances auditory fear memory. Third, the probability that an LA neuron is allocated to an engram is decreased by decreasing its excitability during training. Mirroring previous findings using the dominant-negative CREB construct (Han et al. 2007), neurons overexpressing the inwardly rectifying K^+ channel, Kir2.1 (Dong et al. 2006), were less likely than their noninfected neighbors to be allocated to the LA fear engram (Yiu et al. 2014). Fourth, the memory enhancement normally produced by CREB overexpression is prevented when the excitability of CREB-overexpressing neurons is decreased at the time of training (Yiu et al. 2014, Zhou et al. 2009). Finally, even in the absence of experimental manipulation of CREB or excitability, LA PNs with higher endogenous intrinsic excitability at the time of training are biased toward allocation (Gouty-Colomer et al. 2015). This finding suggests that at any given time a limited number of PNs exist in a primed state, which biases their allocation to an engram, and that endogenous, stochastic fluctuations in PN excitability dictate how (and where) information is encoded in the LA.

The experimental findings that LA PNs with relatively higher excitability before training are preferentially allocated to an engram supporting a conditioned fear memory are also predicted by computational studies. Kim et al. (2013) used a 1,000-cell conductance-based model that incorporated the known composition of PNs and interneurons in the LA. Importantly, all PNs received the same types and numbers of inputs. The excitability of a random, small subset of in silico PNs was increased (by changing K^+ currents) just prior to network training (corresponding to auditory fear conditioning). The resulting engram

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(corresponding to PNs showing plasticity to the tone) was composed of a greater number of these more excitable PNs than would be predicted by chance alone. Together these data show that relatively higher levels of intrinsic neuronal excitability constitute a determining factor in neuronal allocation both in vivo and in silico.

Allocation Beyond the Amygdala

The LA may be a unique brain region in terms of allocation, as this region lacks defined layers and the distribution of PNs and interneurons shows no obvious anatomical organization. However, allocation is also observed in laminated structures such as the hippocampus and cortex (see Figure 3). For example, increasing excitability in a small, random population of PNs in the dorsal hippocampus (including the dentate gyrus and CA1 regions) enhances spatial or contextual memory (Brightwell et al. 2007; Park et al. 2016; Sekeres et al. 2010, 2012), suggesting that a similar process of allocation could underlie engram formation in this region.

More direct evidence for this idea has emerged from studies of the development of place cells in the CA1 region of the hippocampus. Place cells (i.e., cells exhibiting location-modulated firing) (O'Keefe & Dostrovsky 1971) form rapidly as rodents explore a novel environment (Wilson & McNaughton 1993). Only a subset of CA1 PNs become place cells in a given environment, with the majority remaining relatively silent (Wilson & McNaughton 1993). By intracellularly recording hippocampal CA1 PNs while rats explore a novel environment, Lee and colleagues (Cohen et al. 2017, Epsztein et al. 2011, Rich et al. 2014) showed that PNs with relatively higher excitability immediately before novel environment exploration were more likely to become place cells for that environment. This observational study was complemented by an experiment in which this team artificially excited an initially silent neuron and biased that cell toward becoming a place cell. That is, a random, silent neuron showed place fields after injection of current into its soma (Lee et al. 2012). A similar result was obtained from an all-optical experiment in which a randomly chosen silent cell showed place fields following optogenetic stimulation (Rickgauer et al. 2014). Together the findings from these observational and causal studies mirror those of memory engram studies in the LA and hippocampus. They show that increasing excitability before, and excitation during, a training event biases a CA1 PN toward becoming a place cell.

In addition to the LA and hippocampus, there is also evidence of allocation in the cortex. For instance, in the piriform cortex, neurons experimentally made more excitable became key components of an engram supporting an olfactory memory (Choi et al. 2011). Similarly, allocation is also found in the insular cortex underlying a conditioned taste aversion memory (Sano et al. 2014) and in the retrosplenial cortex underlying a spatial memory (Czajkowski et al. 2014).

Allocated Neurons Are Both Necessary and Sufficient for Memory Recall

Allocated neurons become critical components of an engram. Their activation is both necessary and sufficient for subsequent memory expression. For instance, Han et al. (2009) first allocated neurons by using a viral vector to overexpress CREB prior to auditory fear

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conditioning and then used a genetic ablation strategy to kill only those infected neurons after fear conditioning. Posttraining permanent ablation of allocated neurons disrupted recall of a conditioned fear memory (Han et al. 2009). This disruption was observed for the trained memory only, as mice showed no deficit in the recall of other memories. Mice also showed normal memory following retraining on the same fear conditioning task but showed no sign of behavioral savings, suggesting that memory loss was profound. Memory recall was not impacted by ablating a similar number of nonallocated neurons expressing GFP alone (Han et al. 2009). Similar results were obtained by exploiting chemogenetics (Czajkowski et al. 2014, Hsiang et al. 2014, Park et al. 2016, Rashid et al. 2016, Sano et al. 2014) or optogenetics (Park et al. 2016, Rashid et al. 2016) to reversibly inhibit the activity of allocated neurons immediately prior to a memory test. Therefore, once allocated, neurons become necessary for subsequent expression of that specific memory.

In terms of sufficiency, artificial reactivation of neurons allocated to an engram induces memory expression in the absence of an external retrieval cue (Rogerson et al. 2016, Yiu et al. 2014). That is, chemogenetic or optogenetic reactivation of allocated neurons alone, without presentation of the tone or the context in which the mouse received the foot shock during training, induced freezing behavior (the CR in the conditioned fear paradigm).

These findings parallel those of related studies in which allocated neurons are tagged at the time of training by strategies exploiting the use of activity-dependent gene promoters (Reijmers et al. 2007). As observed in allocation studies, disrupting the activity of tagged (allocated) neurons specifically impairs memory retrieval. This was shown using various techniques to disrupt neuronal activity across several brain regions and for a variety of memory tasks (Bossert et al. 2011, Denny et al. 2014, Koya et al. 2009, Tanaka et al. 2014). Conversely, artificial activation of allocated neurons induces behaviors that mimic natural memory expression (Cowansage et al. 2014, Kim et al. 2014, Liu et al. 2012, Redondo et al. 2014). Although studies point to an equivalency between an artificially retrieved and a naturally retrieved memory (Cowansage et al. 2014, Kim et al. 2014), it is an open question whether subtle differences exist in behavioral outcome between these methods of inducing memory recall. Although the neurons that are experimentally manipulated likely do not represent the entire engram, which may be composed of much more broadly distributed ensembles of neurons, the finding that disrupting the neurons' activity impairs memory expression supports the conclusion that these neurons are a critical node or entryway into the engram.

Allocation and Valence-Agnostic Neurons

Most studies of allocation use aversively motivated tasks, but allocation has also been observed in appetitively motivated tasks (Choi et al. 2011, Hsiang et al. 2014). Moreover, in some brain regions, individual neurons can be allocated to either an aversive or a rewarding memory. For instance, Choi et al. (2011) excited a small, random population of PNs in the primary olfactory piriform cortex and allocated these neurons to either an aversive or an appetitive odor-related engram (see Figure 4). In one experiment, optogenetic activation of PNs was paired with foot shock. Subsequent optogenetic activation of these PNs alone was sufficient to induce active avoidance behavior, suggesting that the engram supporting the

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aversive memory was reactivated. In another experiment, optogenetic activation of a random population of PNs was paired with a water reward. Again, subsequent optogenetic activation of these PNs alone induced licking behavior in a go/no-go task, suggesting that artificial activation of this engram brought to mind the rewarding memory. Moreover, in the same experiment, piriform PNs initially paired with a water reward (and therefore allocated to a rewarding engram) could be reassigned and allocated to become part of an aversive engram. Activating this previously allocated population of neurons in the presence of an aversive stimulus was sufficient to flip their valence such that subsequent optogenetic activation induced active avoidance behavior. These data indicate that PNs in the piriform cortex are neither hardwired nor genetically predetermined to become part of an aversive or appetitive engram; instead, their valence is shaped by experience.

It is interesting to note that a similar process also occurs outside the sensory cortex, in the LA. Increasing excitability in a small, arbitrarily chosen population of neurons allocates these neurons to an engram underlying either an aversively motivated (Han et al. 2007, Zhou et al. 2009) or an appetitively motivated (Hsiang et al. 2014) memory, depending on the training experience. Together these findings suggest that PNs in the piriform cortex and LA are valence agnostic. In contrast, PNs in other brain regions, such as the more ventral basal amygdala, may have a valence preference that is governed by genetic identity (J. Kim et al. 2016, 2017) or projection pattern (Beyeler et al. 2016, Namburi et al. 2015). These findings raise the possibility that precise PN cell type or anatomical connectivity influences valence-agnostic versus valence-committed allocation in other nonperceptual brain regions.

FUNCTION OF ALLOCATION

Some experiences are best remembered as distinct, specific episodes. Indeed, many studies show that the hippocampus encodes episodes as discrete events, thereby facilitating the recall of an unambiguous memory, rich in detail (Kirwan & Stark 2007, Leutgeb et al. 2007, Norman & O'Reilly 2003). However, it may be advantageous to link related episodes to facilitate the extraction of generalized principles (Eichenbaum 2000, Schlichting & Frankland 2017). Such memory linking or integration may serve as the foundation for the construction of schemas (or, more broadly, knowledge) (Gilboa & Marlatte 2017, McKenzie & Eichenbaum 2011, Schlichting & Preston 2015, Tse et al. 2007, Zeithamova et al. 2012). Several lines of evidence in both experimental animals and humans suggest that one of the key functions of allocation is to direct engrams underlying different experiences related by temporal or contextual variables to become linked (or integrated) and unrelated memories to become disambiguated (or separated) (Eichenbaum 2000, Schlichting & Frankland 2017).

Linking Temporally Related Memories During Encoding

Although the general concept that memories acquired near in time may be linked such that they are often remembered together is not new (see Estes 1955, Howard & Eichenbaum 2013, Kahana et al. 2002), the mechanisms underlying this integration were unknown until recently (see Figure 5).

Experiments in rodents.—Learning itself may increase neuronal excitability (for reviews, see Mozzachiodi & Byrne 2010, Song et al. 2012, Titley et al. 2017, Zhang

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& Linden 2003). Learning-induced increases in excitability are observed across many behavioral paradigms and in both vertebrate and invertebrate species (Alkon 1974, 1984b; Alkon et al. 1985; Disterhoft et al. 1986; Moyer et al. 1996; Oh et al. 2003; Thompson et al. 1996; Woody & Black-Cleworth 1973). Consistent with these observations, more recent studies show that allocated neurons have higher CREB function and remain more excitable than their nonallocated neighbor neurons for a limited time after a training event (Cai et al. 2016, Gouty-Colomer et al. 2015, Rashid et al. 2016). Therefore, if a second, related event occurs within this time window, these more excitable (previously allocated to event 1) neurons may also become allocated to an engram supporting the memory for the second event. Following this period of heightened excitability, though, homeostatic processes (e.g., Turrigiano 2011) that decrease the excitability of neurons allocated to event 1 are thought to be invoked (Frankland & Josselyn 2015, Rashid et al. 2016, Rogerson et al. 2014, Silva et al. 2009). This would bias these previously allocated neurons from being allocated to a new engram underlying an event occurring outside the window of heightened excitability. This situation may parallel the findings from experiments in which neurons expressing the dominant-negative form of CREB (with decreased excitability) were excluded from an engram (see Figure 1b) (Han et al. 2007).

Cai et al. (2016) directly observed coallocation of two events occurring within a short temporal window. The authors exploited implantable miniature endoscopes to image GCaMP6 calcium transients (as a proxy for neuronal activity) in dorsal hippocampal CA1 PNs in freely moving mice. Mice were exposed serially to three distinct contexts (contexts A, B, and C) separated by either long or short intervals. Specifically, mice were exposed to context A, then, 7 days later, to context B, and, 5 h after that, to context C. The time interval between context exposures impacted both the degree of overlap in the neural representations of each context and the degree of behavioral generalization between the contexts. When the interval between context exposures was short (i.e., 5 h), the contexts engaged largely overlapping engrams. Importantly, slice physiology recordings showed that neurons activated by context exploration remained more excitable than their neighbors for 5 h. This difference suggests that the neurons excited by exposure to context B remained more excitable than their neighbors and were also allocated to context C. In contrast, when the interval between context exposures was long (i.e., 7 days), the contexts engaged largely nonoverlapping engrams. Moreover, mice generalized between the two temporally proximal contexts (i.e., contexts B and C) but not between the two temporally distal contexts (i.e., contexts A and C). Together these findings indicate that contextual memories acquired near in time became functionally linked via coallocation.

Analogous findings were observed in the LA. Rashid et al. (2016) observed coallocation and memory linking in nonmanipulated mice only when two training events (auditory fear conditioning using two distinct tones) occurred near in time. That is, there was marked overlap between two LA engrams if the intervening time between training was short (between 30 min and 6 h) but not long (over 18 h). Importantly, this mirrored the time-course of CREB activation following a single training session (high CREB activation 6 h, but not 18 h, following training), thereby directly linking posttraining increases in CREB function (and, by extension, excitability) with coallocation. Moreover, the second memory was potentiated only if acquired shortly after the first, similar to the findings of enhanced

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memory produced by artificially overexpressing CREB in a small population of neurons (e.g., Han et al. 2007). To verify that the two tone fear memories for events occurring close in time became functionally linked, this team experimentally extinguished the memory of tone 2 and examined the impact on the memory of tone 1. Even though the memory for tone 1 was not explicitly experimentally extinguished, mice showed decreased freezing in response to tone 1 if the two training events occurred close in time (6 h apart, but not 24 h apart), as would be expected if the two memories were functionally linked. This linking phenomenon was not limited to conditioned fear events using two different auditory stimuli as CSs: Memory linking was also observed in conditioned fear events using CSs of different modality (light and tone) or two contextual CSs.

Rashid et al. (2016) went on to establish a causal role for neuronal excitability in coallocation and memory linking. The authors reasoned that if neuronal excitability is critical to coallocation and memory linking, it should be possible to artificially link the normally discrete memories for two events occurring 24 h apart by increasing neuronal excitability to promote coallocation. When they optogenetically increased the excitability of the same small population of random LA neurons before each training event, the two normally discrete memories became artificially linked (see Figure 6).

The finding that two memories become linked based on close temporal context is generally consistent with results from behavioral tagging experiments. In a typical behavioral tagging study, memory for an event is potentiated if an experience, even one that is not sufficiently strong to result in memory formation, occurs in the hours before training (Moncada & Viola 2007, Parsons & Davis 2012, Viola et al. 2014). For instance, brief exposure to a novel environment potentiates inhibitory avoidance memory if that exposure occurs shortly before inhibitory avoidance training (Moncada & Viola 2007). Interestingly, CREB activation is implicated in this behavioral tagging phenomenon, as novel context exposure activates CREB (Moncada & Viola 2006). The allocation data discussed above suggest that the enhanced inhibitory avoidance memory in this example may be attributed to novel context exposure increasing CREB in a population of neurons that then goes on to be allocated to the inhibitory avoidance memory. The allocation process is also consistent with, and provides further cellular, network, and functional insights into, the phenomenon of metaplasticity, in which past experience influences future learning (learning to learn) via changes in intrinsic excitability (Abraham & Bear 1996, Sehgal et al. 2013).

Experiments in human subjects.—Human studies examining memory integration benefit from applying sophisticated functional MRI (fMRI) tools (e.g., Kriegeskorte et al. 2008) to brain images acquired during specific behavioral memory tasks (Schlichting & Frankland 2017). The conclusions from these human studies are remarkably consistent with those from rodent studies: The representations of memories for events related in time or content overlap, thereby facilitating generalization or flexible use of this shared information (e.g., Levy & Wagner 2013, Mack et al. 2017, Schlichting & Preston 2015, Schlichting et al. 2014, Zeithamova et al. 2012).

For example, Zeithamova & Preston (2017) directly assessed the role of temporal proximity between training events on memory integration using an associative inference task. Subjects

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learned an A–B association and, either 30 min or 24 h later, a B–C association. Memory integration was assessed using two measures: behavioral and neural. For the behavioral measure, subjects were tested on the indirect association (A–C). If the representations for the A–B and B–C associations became linked, then subjects would respond faster and more accurately on the indirect association than if the representations were separate. Neural signatures of memory integration were obtained by decoding fMRI data obtained during single trials in the training and testing sessions. Subjects were faster and more accurate on the indirect association test if the training events occurred 30 min, rather than 24 h, apart, suggesting that the A–B and B–C representations became linked. In addition to this behavioral evidence for memory integration, the neural evidence for integration during encoding was stronger with temporally proximal events. That is, the fMRI data suggest that B–C information became integrated with A–B information if learning events occurred 30 min apart. Although the resolution of human imaging has not yet reached the cellular resolution offered by rodent studies, these data are entirely consistent with the general concepts from rodent studies. Moreover, that the time-course of memory integration in this human fMRI study, in which participants were trained on object-face associations, mirrors that obtained by Rashid et al. (2016), in which mice were trained on two fear conditioning tasks, suggests that this time-course is neither task nor species dependent.

Linking Temporally Related Memories via Retrieval and Encoding

Engrams are reactivated by memory retrieval (e.g., Liu et al. 2012). Thus, memory retrieval may open an additional temporal window for coallocation.

Experiments in rodents.—Rashid et al. (2016) tested the prediction that a new memory can be linked to a retrieved, older memory by training mice to fear two different tones. First, tone 1 was paired with a foot shock. To reactivate this engram, tone 1 was presented in a different context 24 h later. If a second auditory fear conditioning event (tone 2) occurred 6 h, but not 24 h, later, the reactivated tone 1 memory became linked to tone 2 memory and memory for tone 2 was enhanced. That the second memory is enhanced may reflect increased CREB activation in the overlapping engram, resulting in enhanced LTP-related processes (see above). Therefore, two memories may become integrated by explicit retrieval of an older memory close in time to acquisition of a new, related memory. This general mechanism may explain how new information becomes integrated with preexisting knowledge.

Experiments in human subjects.—Human studies provide further evidence that a reinstated memory and a related new experience may be encoded in a shared representation and thus linked. For instance, Shohamy & Wagner (2008) used an acquired equivalence task in which subjects learned temporally intermixed sets of partially overlapping associations (A–X, B–X, A–Y). Because both A and B predict X, A and B acquire functional equivalency. That is, subjects may later generalize that because both A and B predicted X, and A predicted Y (a direct association), B also predicts Y (an indirect association). As would be expected by the direct retrieval of an encoded association, when later tested, all subjects recalled the direct associations (A–X, B–X, A–Y) quickly and accurately. However, subjects fell into two groups on the basis of their performance on indirect associations (B–

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Y). Good indirect association performers were as fast and accurate on the test for indirect associations as on that for direct associations, suggesting that performance on both the direct and indirect associations resulted for the direct retrieval of an encoded association. Consistent with this, the learning phase fMRI data on these good indirect performers showed evidence for integrative encoding. In contrast, the poor indirect association performers showed poorer accuracy and slower reaction times on the indirect association trials than on the direct association trials, suggesting that performance on the indirect test did not simply involve the direct retrieval of an encoded association. These poor performers also showed no neural fMRI evidence for integrative encoding. Together these results provide both behavioral and neural evidence for integration of a retrieved memory and new memory in humans. Although the temporal dimensions of the mouse and human studies of this form of memory integration may differ, the parallels between the findings of these disparate studies remain remarkable.

Linking Memories by Coretrieval

Finally, it may be possible to link two distinct memories by simple coretrieval. Yokose et al. (2017) trained mice for two aversively motivated events, auditory fear conditioning (see Figure 1) and conditioned taste aversion (in which mice trained to associate saccharin consumption with a malaise-inducing agent show decreased consumption of saccharin upon subsequent presentation). The memories for the two events were acquired 4 days apart. Each engram was marked by retrieval-induced expression of a unique immediate early gene. As expected from this training schedule (in which the two tasks were acquired at relatively distal times), there was little overlap between the populations of neurons composing the two engrams in the basolateral complex of the amygdala (roughly 2% of total cells, not different from chance). However, repeated synchronous presentation of the CSs for both memories (tone and saccharin; i.e., coretrieval) produced a profound change in behavior. Following coretrieval, saccharin (the CS from the conditioned taste aversion memory) gained the ability to elicit freezing (the CR from the conditioned fear memory). Saccharin failed to elicit freezing in no-coretrieval control experiments. Moreover, following coretrieval the overlap between the neuronal components of the engrams supporting the conditioned fear and conditioned taste aversion memories increased (roughly 5% of total cells, above chance levels). These findings suggest that some components of the original memories became linked by coretrieval. Silencing this small population of overlapping neurons disrupted the ability of saccharin to induce freezing but did not impact recall of the original memories. These intriguing findings suggest that coretrieval supported the development of a new engram that was not (or no longer) an essential component of either original engram but instead was critical for linking these two engrams.

Although a directly analogous experiment has not yet been conducted in humans, this overall finding is reminiscent of human studies examining the processes engaged by memory retrieval. For instance, the retrieval of a particular memory is thought to inhibit the retrieval of competing memories (a phenomenon called retrieval-induced forgetting) (Anderson 2003, Storm & Jobe 2012). Wimber et al. (2015) provide neural evidence for the long-held hypothesis that retrieving one memory engages inhibitory control mechanisms that suppress competing memories (see also Anderson 2003, Storm & Jobe 2012). Therefore, given the

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findings from these human studies that retrieval of one memory suppressed the retrieval of another memory, one might not expect coretrieval to link memories as in Yokose et al.'s (2017) study. It is important to point out, though, that in Yokose et al.'s (2017) study, the retrieved memories were similar in valence, a situation that may not engage the inhibitory processes identified in human studies. Alternatively, the repeated coretrieval used in Yokose et al.'s (2017) study may have overcome these inhibitory processes such that the two retrieved memories became linked. The answers to these intriguing questions await further experimentation.

Artificially Separating Temporally Related Memories During Encoding: Insights into Memory Separation

Optimal knowledge structuring in the brain may derive from linking related events and separating unrelated events. The above studies provide convergent evidence regarding the mechanisms underlying memory linking. The basic principle emerging from findings in humans and experimental animals suggests that events connected in time or content become physically connected or linked via enhanced excitability and coallocation to a shared neural representation. How does memory separation occur?

It has long been hypothesized that discrete nonrelated events are differentiated via pattern separation (Leutgeb et al. 2007, Marr 1971, Rolls & Treves 1994, Yassa & Stark 2011). Pattern separation refers to the hypothesized process of reducing interference among similar inputs by assigning them to nonoverlapping orthogonal representations. Accordingly, one strategy to separate patterns and minimize interference between memories would be to engage nonoverlapping orthogonal engrams. Although there are theoretical and computational data on the phenomenon of pattern separation (Gilbert et al. 1998, Hunsaker & Kesner 2013, McNaughton & Morris 1987, Rolls & Treves 1994), the neural mechanisms mediating pattern separation remain largely unknown.

Rashid et al. (2016) examined the process of memory separation in terms of allocation and neuronal excitability. Above, we discuss evidence that the memories for two events acquired near in time become linked via coallocation to overlapping engrams, a process mediated by neuronal excitability. This team artificially increased neuronal excitability in previously allocated neurons and artificially linked the memories of two events that would normally be remembered separately (trained 24 h apart) by facilitating the overlap of the two engrams. Is the reverse possible? That is, is it possible to artificially unlink normally linked memories (two events occurring 6 h apart) by experimentally encouraging the orthogonalization and nonoverlap of engrams by manipulating neuronal excitability?

To examine this question, Rashid et al. (2016) used a unique viral vector that allowed the same small population of initially random LA PNs to be optogenetically excited or inhibited simply with different wavelengths of light. Three key findings emerged from these studies. First, winning PNs transiently inhibit nonwinning (loser) PNs (consistent with the neuronal competition hypothesis of allocation). Second, this inhibition is transient (lasting approximately 6 h) and mediated by GABAergic interneurons. Third, blocking this inhibition allows two temporally proximal memories to be encoded in nonoverlapping

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neuronal populations. This pattern of observations suggested a winners-take-all mechanism for memory allocation.

Interestingly, a winners-take-all mechanism has been hypothesized to sparsify coding in neural networks (Rumelhart & Zipser 1985), and recent studies identify important roles for inhibitory interneurons and local inhibitory circuits in maintaining the sparsity of an engram (Burghardt et al. 2012, Drew et al. 2016, Feng et al. 2016, D. Kim et al. 2016, Lucas et al. 2016, Morrison et al. 2016, Stefanelli et al. 2016). For example, silencing parvalbumin-containing interneurons in the LA and basal amygdala increased the size of an engram underlying a conditioned fear memory (Morrison et al. 2016). Similarly, silencing somatostatin-containing interneurons in the dentate gyrus of the dorsal hippocampus increased the size of an engram underlying a context memory (Stefanelli et al. 2016). Finally, computational modeling studies show that highly excitable PNs inhibit their neighbors (and exclude them from becoming part of an engram) through a disynaptic mechanism involving inhibitory interneurons (Feng et al. 2016, D. Kim et al. 2016). The study by Rashid et al. (2016) suggests that this same winners-take-all process may govern not only engram size but also how engrams (and the memories they support) interact (i.e., whether they are linked or separated).

Inhibitory neurons are also thought to play an important role in the formation of inhibitory engrams or negative images (Barron et al. 2016, 2017; Hennequin et al. 2017). Engram formation in excitatory PNs is hypothesized to invoke homeostatic processes that rebalance and stabilize circuit function (Turrigiano 2011). One such homeostatic process may involve the potentiation of inhibition onto active postsynaptic PNs in the engram, resulting in the formation of a corresponding inhibitory engram (Barron et al. 2016, 2017; Hennequin et al. 2017). According to this hypothesis, for every engram composed of excitatory neurons, an equal and opposite inhibitory engram would be formed. Such a compensatory process would prevent runaway excitation and may explain some aspects of behavioral habituation (Barron et al. 2017). Human fMRI studies provide compelling evidence for the existence of inhibitory engrams (Barron et al. 2016). Following the association of two stimuli, researchers observed overlap in the cortical ensembles representing the two associated stimuli (similar to an excitatory engram). Interestingly, when subjects were tested 24 h later, there was no evidence for increased activity in the cortical ensemble (akin to the excitatory engram entering a latent phase). However, the excitatory cortical ensemble was revealed by locally disrupting cortical GABA transmission via transcranial direct current stimulation. An integrated overall understanding of the role of inhibitory neurons in allocation and memory linking remains to be determined.

CONCLUSIONS

In this article, we review the findings from many studies showing that allocation determines how engrams form and interact. Allocation has been observed across multiple brain regions and implicated in a range of different learning tasks. Parallels have emerged between results from human and laboratory animal studies, and these parallels highlight the general nature of the neural mechanisms mediating memory linking and separating. Together these studies show that allocation is a winners-take-all competitive process that serves as a

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means of connecting the past with present experience. Moreover, the allocation process allows information to be highly structured in the brain and may facilitate the adaptive transformation of memories for individual events into organized conceptual knowledge. Therefore, allocation may represent a general organizing principle for structuring memories and mnemonic information in the brain.

More broadly, the findings from these allocation studies may reveal a neural mechanism underlying memory distortion (Schacter et al. 2011). One example of this phenomenon is postevent misinformation, in which erroneous information encountered after an original event is incorporated into the original memory (e.g., Edelson et al. 2011, Loftus 2005). Importantly, reactivation of the original memory is thought to be a necessary condition for this phenomenon. In this way, misinformation errors may reflect a bug (or feature) of a dynamic memory system that uses allocation to structure memory representations (see Buonomano 2011).

Deficient allocation may also contribute to disorders, such as schizophrenia, that are characterized by loose associations (i.e., derailment or tangentiality) and disordered thought. For instance, patients with schizophrenia show deficits in the memory linking required by associative inference tasks (Armstrong et al. 2012), as well as impairments in a pattern separation task (Das et al. 2014), a phenomenon that may also be interpreted as stemming from a disruption in memory allocation. Intriguingly, deficits in inhibitory neuronal function, particularly parvalbumin-containing interneurons, have also been described in patients with schizophrenia (Enwright et al. 2016, Lewis et al. 2012), suggesting a potential mechanistic link between impairments in allocation-based processes and information-processing deficits in these patients. Therefore, insights into the basic mechanisms of allocation may provide a platform for the development of the next generation of more effective and targeted treatments for conditions associated with a breakdown in the optimal structuring of information.

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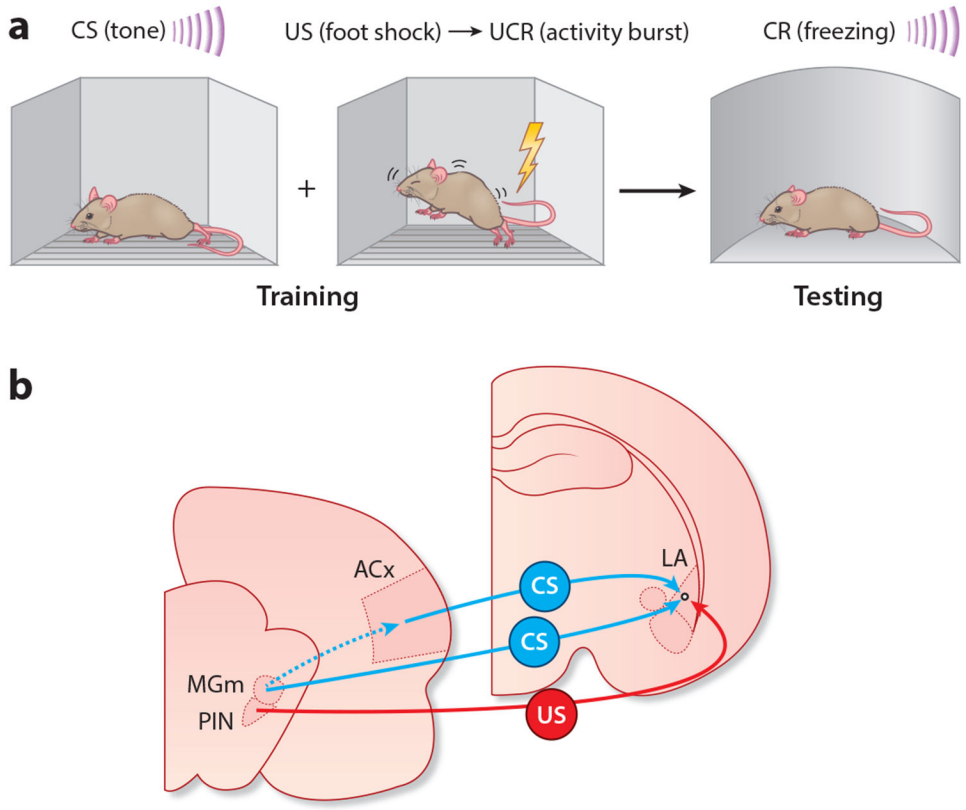

Figure 1.

Using Pavlovian fear conditioning to study memory. (*a*) An initially motivationally neutral conditioned stimulus (CS), such as a tone, is paired with an aversive unconditioned stimulus (US), such as a foot shock. The US elicits an unconditioned response (UCR), an activity burst. Upon subsequent presentation of the tone CS in a novel context, rodents exhibit a conditioned response (CR), such as freezing. (*b*) Circuit diagram depicting converging sensory inputs to the lateral nucleus of the amygdala (LA) critical for auditory fear conditioning. Auditory information (CS pathway) travels from the auditory thalamus [medial geniculate nucleus, medial portion (MGm) and adjacent posterior intralaminar nucleus (PIN)], as well as from secondary auditory cortical regions (ACx), to the LA (see LeDoux et al. 1985, Linke et al. 2000). Information about the foot shock (US pathway) is relayed to the LA through the somatosensory thalamic nuclei (including the PIN) (see Lanuza et al. 2008, LeDoux et al. 1990, McDonald 1998, Shi & Davis 1999).

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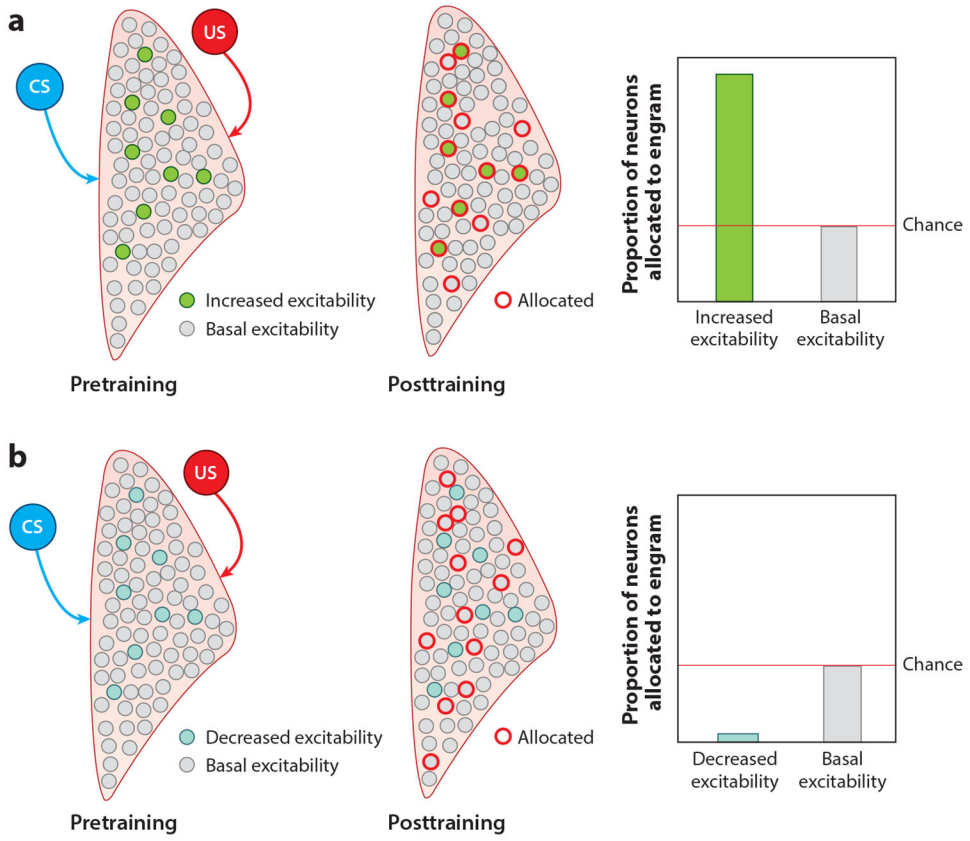

Figure 2.

Schematic depicting allocation process in the lateral nucleus of the amygdala. (*a*) Although the majority of excitatory principal neurons (PNs) respond to both tone [conditioned stimulus (CS)] and shock [unconditioned stimulus (US)] inputs, only a small subset of these eligible neurons become allocated to a given auditory fear memory. Eligible PNs compete against one another for allocation, and neurons with increased excitability (*filled green circles*) at the time of training are more likely to win this competition and become allocated to that engram (*circles outlined in red*, also depicted in the graph on right). This has been shown using several different methods of increasing excitability, including overexpressing the transcription factor Ca^{2+}/cAMP response element–binding protein (CREB), manipulating potassium channels, and using excitatory chemogenetic or optogenetic constructs. (*b*) In contrast, neurons with decreased excitability during training (*filled teal circles*) are less likely than their neighboring PNs with basal excitability to be allocated to an engram (*circles outlined in red*, also depicted in the graph on right). This has been shown by expressing a dominant-negative form of CREB and an inward-rectifying potassium channel (Kir2.1) (see Gouty-Colomer et al. 2015, Han et al. 2007, Kim et al. 2013, Rashid et al. 2016, Rogerson et al. 2016, Yiu et al. 2014, Zhou et al. 2009).

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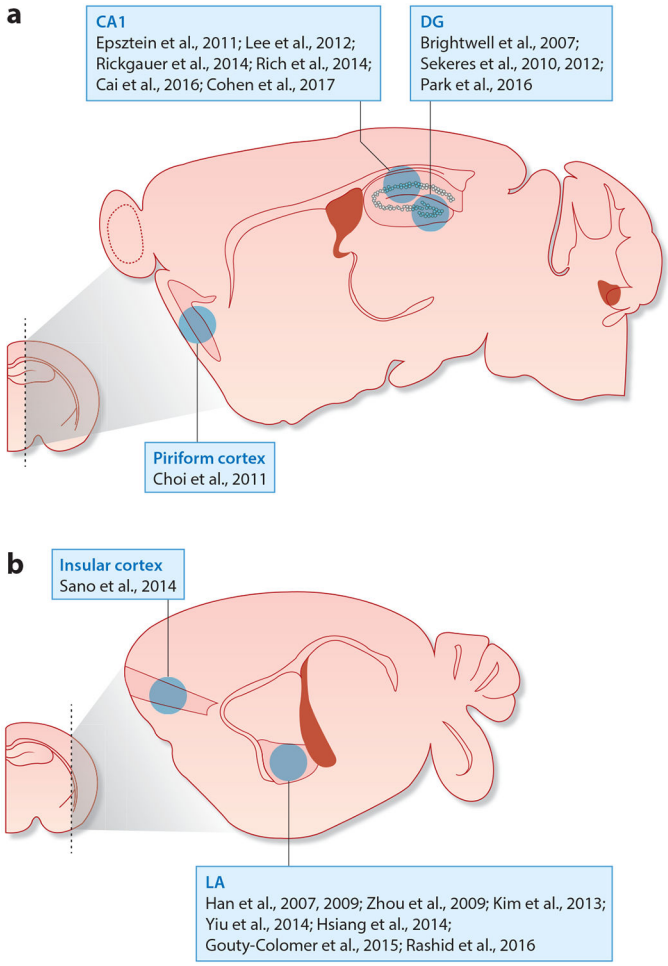

Figure 3.

Allocation has been observed across several brain regions, including the CA1 region of the (*a*) dorsal hippocampus (CA1), dentate gyrus (DG), and piriform cortex, and (*b*) the insular cortex and lateral nucleus of the amygdala (LA). Representative publications are noted.

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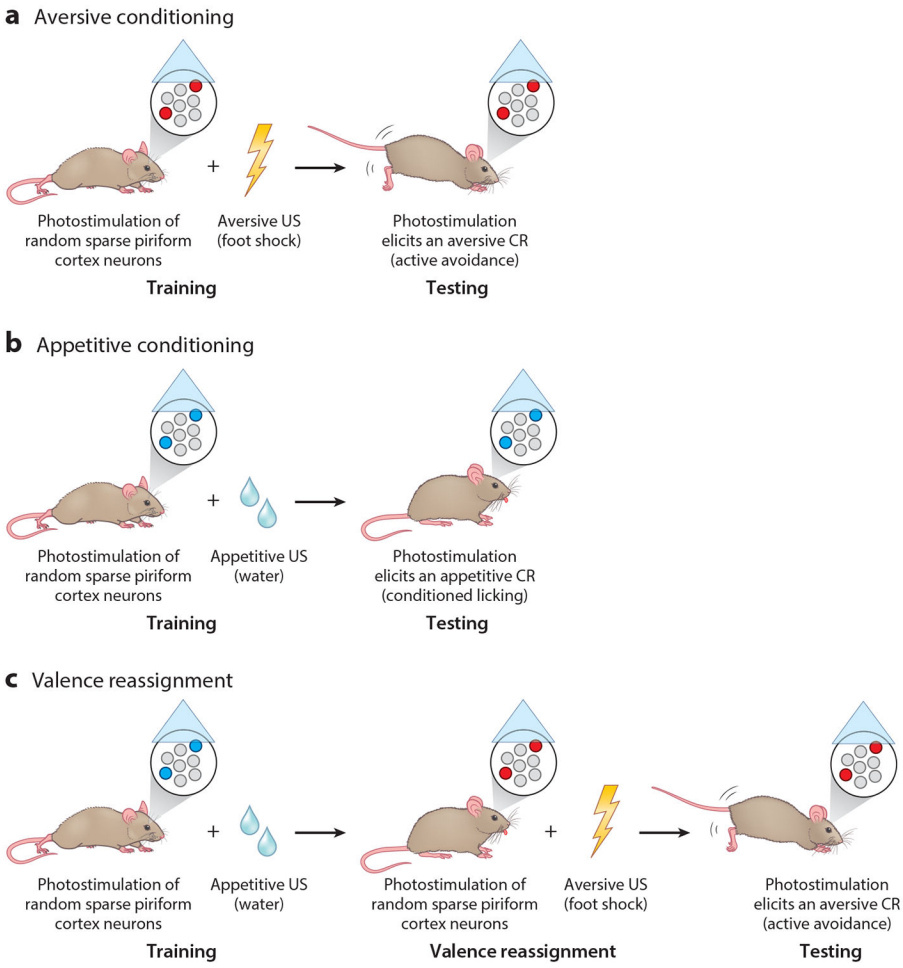

Figure 4.

Schematic depiction of valence-agnostic allocation, summarizing experimental results from Choi et al. (2011). (*a*) A small, random population of principal neurons (PNs) in the piriform (odor) cortex are infected with the excitatory opsin ChR2. Photostimulation of this population (conditioned stimulus, CS) is paired with an aversive shock (unconditioned stimulus, US). Subsequent photostimulation of this population induces conditioned avoidance behavior (conditioned response, CR). Therefore, artificial activation of this random population of neurons alone is sufficient to elicit recall of an aversive memory by activating the engram supporting this memory. (*b*) Photostimulation of a similar small, random population of PNs in the piriform cortex is paired with water (appetitive US). Subsequent photostimulation induces conditioned licking (CR), showing that artificial activation of these neurons alone is sufficient to elicit recall of a rewarding memory. (*c*) The same random population of PNs can become first part of an appetitive memory and then part of an aversive memory. These data suggest that the PNs in the piriform cortex are valence agnostic rather than hardwired or genetically predetermined to be part of an aversive or appetitive memory.

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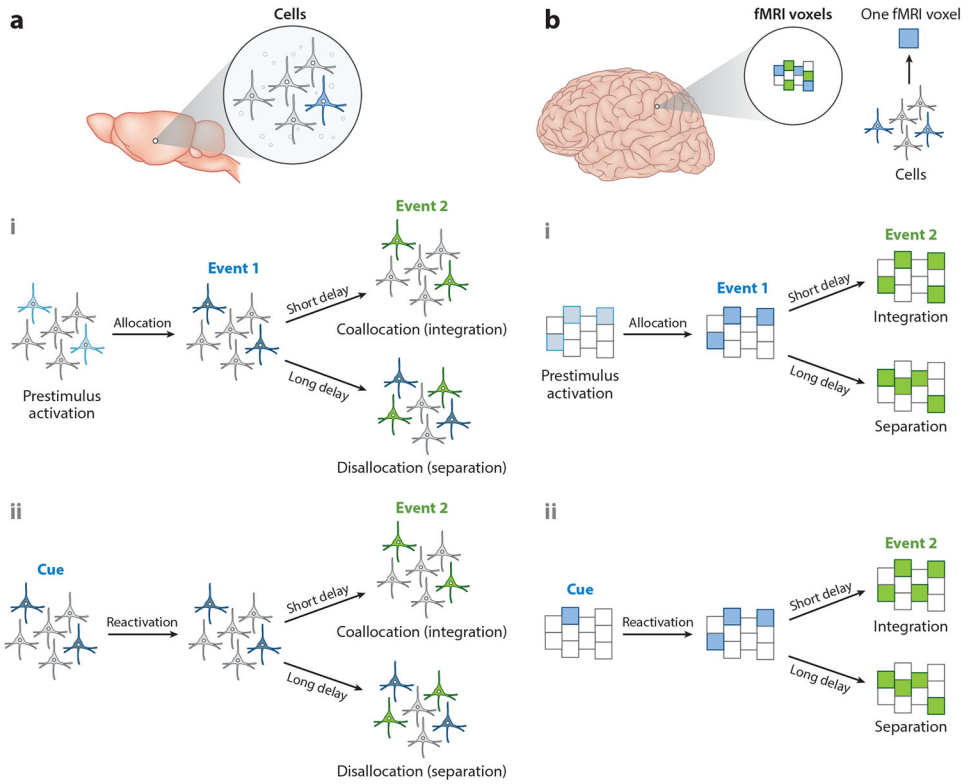

Figure 5.

Similarities between rodent and human imaging data on allocation and memory linking. (*a, i*) In the rodent lateral nucleus of the amygdala (LA), a population of excitatory principal neurons (PNs) is more excitable (*light blue*) than its neighbors (*white*) in the prestimulus period. During event 1, these more excitable neurons are allocated to the engram underlying event 1 (*dark blue*). Once allocated, neurons remain transiently excited for a limited period of time (roughly 6 h). If event 2 occurs within this window of increased excitability, then an overlapping population is allocated to the engram for event 2 (coallocation) (*green*). The memories are linked by virtue of coallocation. Following this period of increased excitation, previously allocated neurons show a decrease in excitability. If event 2 occurs beyond the time window of increased excitability (>6 h), then a new nonoverlapping population of neurons is relatively more excitable and this population is allocated to event 2 (disallocation) (*green*). The memories are separated. (*a, ii*) Coallocation may also occur following cue-induced recall of event 1. Allocated neurons are reactivated and remain transiently more excitable (*dark blue*) than their neighbors (*white*). If event 2 occurs within this window of excitability (<6 h), then an overlapping population is allocated to event 2 (coallocation) (*green*). If event 2 occurs beyond this time window (>6 h), then a nonoverlapping population is allocated to event 2 (disallocation) (*green*). (*b*) A similar process is thought to occur in human brains (Eichenbaum 2000, Schlichting & Frankland 2017). (*b, i*) Activation of a single functional MRI (fMRI) voxel (*square*) represents the average response across a population of neurons. Active voxels (*light blue*), relative to baseline voxels (*white*), are more likely to be allocated to the engram underlying event 1 (*dark blue*). If event 2 occurs after a short delay (*top arrow*), then overlapping populations may be engaged (*green*) and

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the memories may be linked. In contrast, if event 2 occurs after a long delay (*bottom arrow*), then dissimilar activation patterns (*green*) may be engaged (similar to disallocation) and memories may be separated. (*b, ii*) A similar mechanism supports memory integration across events related by shared content. The familiar elements in event 2 serve as a retrieval cue, leading to reactivation of event 1 representation. Event 2 may then be encoded in an overlapping (integrated) (*top arrow*) or nonoverlapping (separated) (*bottom arrow*) neural representation.

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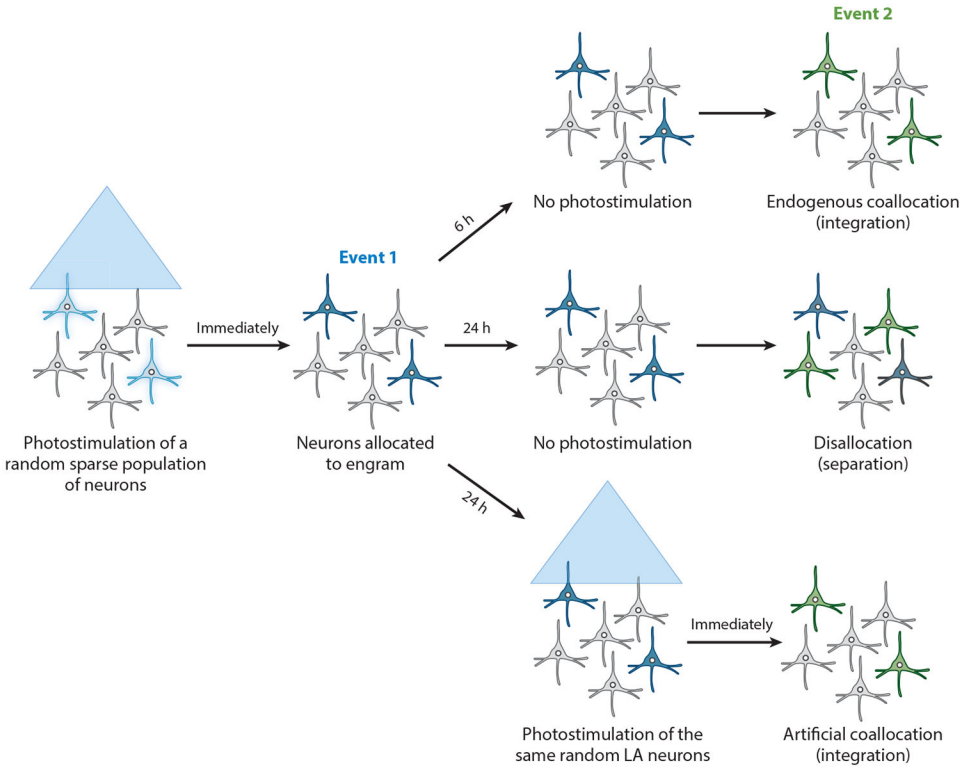

Figure 6.

Coallocation and memory linking are mediated by neuronal excitability, as demonstrated by experimental results from Rashid et al. (2016) (see also Choi et al. 2011). A random small subset of principal neurons in the lateral nucleus of the amygdala (LA) is infected with the excitatory opsin ChR2 (*light blue*). Photostimulation of these neurons immediately before event 1 allocates these neurons to the engram underlying event 1 (*dark blue*). These neurons remain more excitable for roughly 6 h. If event 2 occurs less than 6 h later, then these same neurons are more excitable than their neighbors and coallocated, thus linking the memories. In contrast, if event 2 occurs 24 h later, then a different population of neurons is more excitable and allocated to event 2 (disallocation), thus separating the memories. Two distinct memories acquired 24 h apart may be artificially coallocated and linked if infected neurons are photostimulated prior to both event 1 and event 2.