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Memory allocation mechanisms underlie memory linking across time

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ABSTRACT

Memories are dynamic in nature. A cohesive representation of the world requires memories to be altered over time, linked with other memories and eventually integrated into a larger framework of sematic knowledge. Although there is a considerable literature on how single memories are encoded, retrieved and updated, little is known about the mechanisms that govern memory linking, e.g., linking and integration of various memories across hours or days. In this review, we present evidence that specific memory allocation mechanisms, such as changes in CREB and intrinsic excitability, ensure memory storage in ways that facilitate effective recall and linking at a later time. Beyond CREB and intrinsic excitability, we also review a number of other phenomena with potential roles in memory linking.

1. Introduction

Real world memories are rarely isolated entities, and instead are typically part of other related memories. This rich interrelatedness of memory is critical for our ability to navigate an endlessly complex and ever-changing world. Most molecular, cellular and circuit studies of memory have focused on mechanisms such as Hebbian learning to investigate the association of stimuli that are closely juxtaposed in time. In contrast, comparatively little is known about the mechanisms that associate or link information across time spans of hours/days, a phenomenon referred to as memory linking (Cai et al., 2016), the subject of this review. Beyond memory linking, we will also review here a number of other phenomena with critical roles in memory linking.

2. Memory allocation

The concept of memory linking has its roots in the closely related concept of memory allocation (Silva, Zhou, Rogerson, Shobe, & Balaji, 2009). Memory allocation refers to the concept that newly acquired information is not randomly assigned to synapses (Kastellakis, Cai, Mednick, Silva, & Poirazi, 2015) or neurons (Kastellakis, Silva, & Poirazi, 2016) in a network (Rogerson et al., 2014). Instead, specific molecular, cellular and circuit mechanisms determine which specific synapses and neurons within a network will go on to store a certain memory. Memory allocation mechanisms can ensure sparse encoding (Olshausen & Field, 2004), a seemingly universal rule of memory formation found across systems and organisms (Spanne & Jorntell, 2015). Furthermore, it is reasonable to propose that where and how memories are stored may affect how they are subsequently used. For example, memory allocation mechanisms can regulate which memories are retrieved together. This can facilitate and be critical for a number of higher order cognitive processes, including memory linking, schema formation and perhaps even creativity.

Although within a particular network, a large percentage of neurons may have access to incoming information, only a small percentage of these neurons normally go on to participate in the encoding of that information. In the amygdala, for example, about seventy percent of neurons respond to an auditory stimulus during fear conditioning (Repa et al., 2001). However, only twenty to thirty percent of these neurons are actually engaged in storing a given tone fear memory (Rumpel, LeDoux, Zador, & Malinow, 2005). Similar results have also been obtained in the visual cortex (Jia, Rochefort, Chen, & Konnerth, 2010) and hippocampus (Lee, Lin, & Lee, 2012). These data point towards the presence of memory allocation mechanisms that determine which subgroup of neurons with a network is engaged in storing a particular memory.

The concept of memory allocation was first investigated using tone fear conditioning in the lateral amygdala (Han et al., 2007; Han et al., 2009; Zhou et al., 2009). In tone fear conditioning experiments, a tone (conditioned stimulus or CS) is paired with a footshock (unconditioned stimulus or US) such that the tone elicits the same response as the footshock. This association between the tone and the footshock is mediated by the lateral amygdala (Johansen, Cain, Ostroff, & LeDoux, 2011; Schafe, Doyere, & LeDoux, 2005). As mentioned above, during

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tone fear conditioning, more than 70% of lateral amygdala neurons are engaged by either the tone (Repa et al., 2001) or the US or both (Johansen, Tarpley, LeDoux, & Blair, 2010), but a much smaller number of neurons go on to store the fear memory (Quirk, Repa, & LeDoux, 1995; Rumpel et al., 2005). Therefore, tone fear memory is allocated to a small subset of neurons that have access to the relevant information. Studies with the transcription factor CREB (Silva, Kogan, Frankland, & Kida, 1998b) demonstrated that this protein has a central role in memory allocation within amygdala as well as multiple other brain regions (Rogerson et al., 2014).

Early studies used immediate early gene expression to mark the neurons that were activated during memory recall and demonstrated that increasing the levels of CREB (with viral vectors) in a given population of neurons dramatically enhances the probability that these neurons are recruited into encoding a tone fear conditioning memory (Han et al., 2007). Lowering CREB levels has the opposite effect and these neurons are excluded from fear memory allocation (Han et al., 2007). Importantly, complementary experiments demonstrated that these CREB expressing neurons are critical for memory retrieval, since deleting them with an inducible diphtheria-toxin strategy (Han et al., 2009) or preventing their activation (Zhou et al., 2009) results in clear memory deficits. For example, silencing these lateral amygdala neurons with the allatostatin system (Lechner, Lein, & Callaway, 2002), a strategy that hyperpolarizes these neurons, thus keeping them from being activated during memory retrieval, triggers an amnesia for the acquired tone fear conditioning (Zhou et al., 2009). These results demonstrate the critical role of CREB expression for memory allocation within the amygdala.

Since then considerable evidence has emerged for the role of CREB-dependent memory allocation in other brain regions. Experiments in the insular cortex demonstrated that overexpressing CREB in a subset of insular neurons biased the allocation of a conditioned taste aversion memory to the neurons with higher CREB levels (Sano et al., 2014). Similarly, increasing CREB levels in a subset of retrosplenial cortex neurons also modulates spatial and contextual memory allocation to CREB overexpressing neurons (Czajkowski et al., 2014). Within the hippocampus, chemogenetically (with an inhibitory DREADD receptor) or optogenetically silencing CREB-overexpressing dentate gyrus neurons results in retrieval deficits in contextual fear conditioning, whereas turning off a similar number of random neurons that do not overexpress CREB has no effect (Park et al., 2016). Together, these results demonstrate that CREB-dependent memory allocation is a general property of a wide range of brain circuits.

3. How CREB modulates memory allocation?

There is compelling evidence that although CREB is known to affect multiple neuronal processes, its role in memory allocation is due to its known function in modulating intrinsic neuronal excitability (Benito & Barco, 2010; Dong et al., 2006). Intrinsic excitability can be highly plastic, reflecting dynamic alterations in the number, distribution and properties of ion channels (Disterhoft & Oh, 2006; Kim & Linden, 2007; Mozzachiodi & Byrne, 2010; Sehgal, Song, Ehlers, & Moyer, 2013; Zhang & Linden, 2003) that do not necessarily involve changes in synaptic transmission. Instead, intrinsic plasticity mechanisms alter the responsiveness of neurons to synaptic activation. Since CREB can affect neuronal excitability, which in turn could impact the threshold for neuronal activation during learning, it is reasonable to propose that CREB's role in neuronal excitability is the mechanism underlying its ability to affect memory allocation.

Several complementary experiments support the idea that CREB modulates memory allocation by regulating intrinsic excitability. First, increasing CREB levels in a subset of amygdala neurons enhances the intrinsic excitability of these neurons and modulates memory allocation (Zhou et al., 2009). Following auditory fear conditioning, these CREB-overexpressing amygdala neurons have higher synaptic strength, a reflection of learning-related plasticity (Zhou et al., 2009). Thus, CREB could modulate memory allocation by increasing intrinsic excitability, which increases the probability that these neurons undergo synaptic changes needed for memory storage. Second, manipulating neuronal excitability using voltage-dependent potassium channels also affected neuronal allocation: neurons with higher excitability are preferentially recruited into the tone conditioning memory trace (as measured by the expression of immediate early gene *Arc*) (Yiu et al., 2014). Third, increasing neuronal excitability with a special light-activated channel called a step function opsin, also determines which amygdala neurons are preferentially recruited into encoding a tone fear memory (Rogerson et al., 2016). Importantly, activating these amygdala neurons optogenetically can trigger retrieval of the tone conditioning memory. More indirect evidence for the role of intrinsic excitability in memory allocation comes from a study using a fluorescence-based Arc reporter (Gouty-Colomer et al., 2016). Without a direct manipulation of CREB or excitability, this study demonstrates that these Arc-expressing neurons in the lateral amygdala have increased intrinsic excitability. This increased excitability can bias these neurons to be preferentially recruited into a fear memory trace, which is consistent with our memory allocation hypothesis. All together, these findings argue that intrinsic neuronal excitability modulates which neurons in a neuronal network go on to encode a given memory.

Interestingly, the active or phosphorylated form of CREB is responsive to the history of neuronal activity (Sheng, Thompson, & Greenberg, 1991). Therefore, neuronal activation during memory formation would increase CREB levels (and activity) in a subset of neurons within a circuit, which then results in higher neuronal excitability that could affect the allocation of subsequent information. Indeed, learning leads to intrinsic plasticity in many brain structures following various learning paradigms (Disterhoft, Coulter, & Alkon, 1986; Kaczorowski & Disterhoft, 2009; Moyer, Thompson, & Disterhoft, 1996; Saar, Grossman, & Barkai, 1998; Santini, Quirk, and Porter, 2008; Sehgal, Ehlers, & Moyer, 2014; Song, Detert, Sehgal, & Moyer, 2012; Zelcer et al., 2006). It follows that neurons recently activated by one memory, for a time would be more likely to encode a second memory (Silva et al., 2009). Thus, the memory allocation findings reported above predict that two memories acquired close in time are likely to be allocated to overlapping populations of neurons, such that recall of one memory would lead to recall of the other, thus linking the two memories across time (Rogerson et al., 2014).

4. Memory linking

The fundamental idea underlying our hypothesis of memory linking is that temporal or content related memories are stored in overlapping populations of neurons, such that the retrieval of one of the memories can activate the recall of the other. Most of the neuroscience studies of memory have focused on Hebbian synaptic mechanisms that account for associations between stimuli that are closely juxtaposed in time (Elgersma & Silva, 1999; Lee & Silva, 2009). In contrast, the mechanisms underlying associations between memories acquired hours or even days apart remain poorly studied. Connecting information acquired across time has critical evolutionary relevance since it allows for novel predictions and insights.

Results from both human and animal experiments support the idea that memories can be linked and integrated following recall (Schlichting & Preston, 2015). Analyses of human fMRI data with neural decoders using multivoxel pattern analysis (MVPA) showed that reactivation of previously encoded information predicted memory performance in inferential tasks designed to test integrated memories (Zeithamova, Dominick, & Preston, 2012). During scanning, participants were presented with image pairs such as AB and BC but never AC. Performance on inferential association AC (that was never explicitly presented) correlated with the degree of reactivation of previously encoded information (i.e. AB and BC). These findings suggest the

hypothesis that the process of generating novel inferences is critically dependent on reactivating and perhaps linking memories acquired across time. The integration or linking of memories stored at different times could involve the retrieval and recall of an established memory. This retrieval event may render the memory unstable so that it can be easily updated and restored using reconsolidation mechanisms (Nader & Einarsson, 2010; Sara, 2000). A considerable body of data indicates that the retrieval of memory places that information in an unstable state so that it can be modified (Nader & Einarsson, 2010; Sara, 2000).

Experiments in mice demonstrated that neural populations that had been active during training were also reactivated during memory retrieval, and that even partial activation of these ensembles was sufficient to trigger what appeared to be recall (Liu et al., 2012). Interestingly, optogenetic reactivation of these memory ensembles could even be used to generate false memories (Garner et al., 2012; Ramirez et al., 2013). A new memory can be created by the co-activation of two neural ensembles encoding two separate memories (Ohkawa et al., 2015), a result consistent with the idea that the co-activation of memory ensembles can modify and perhaps even connect memories.

The results mentioned in the previous section indicated that the encoding of one memory increases neuronal excitability in the subset of neurons storing that memory. This should bias subsequent memory allocation, such that new memories that engage the same brain networks (e.g., in the hippocampus) would be stored in many of the same neurons that encoded the first memory, a phenomenon we refer to as co-allocation. We propose that co-allocation is central to memory linking, what we call “the allocate-to-link” hypothesis (Silva, 2017).

Early support for neuronal co-allocation of temporally proximate memories came from studies investigating hippocampal place cell dynamics over time. These studies have demonstrated that patterns of hippocampal place cell activity representing an environment change gradually over time such that activity patterns become more dissimilar with time (Mankin, Diehl, Sparks, Leutgeb, & Leutgeb, 2015; Mankin et al., 2012; Rubin, Geva, Sheintuch, & Ziv, 2015; Ziv et al., 2013). Three recent publications provided direct evidence for our allocate-to-link hypothesis (Cai et al., 2016; Rashid et al., 2016; Yokose et al., 2017). The first of these studies showed that overlapping populations of CA1 neurons store the contextual memories of two conditioning chambers encoded close in time (Cai et al., 2016). Mice were placed in two distinct conditioning chambers either 5-h or 7-days apart. Imaging of GCaMP activation signals in dorsal CA1 with head mounted microscopes demonstrated that there is significant overlap in the CA1 neuronal populations representing the memories for the chambers experienced 5-h, but not 7-days apart (Cai et al., 2016). Importantly, these experiments also showed that the overlap between CA1 neuronal populations underlies the behavioral linking between the two memories, so that recall of one memory triggers important elements initially only associated with the other memory: contextual conditioning in one chamber can trigger conditioned responses in a second chamber in which the animals were never conditioned.

Interestingly, one contextual memory could also strengthen a second contextual memory when the two memories were separated by 5-h but not 7-days apart (Cai et al., 2016). Previous studies have demonstrated that exploration of a new context triggers CREB activation (Viola et al., 2000) and that increases in CREB could trigger enhancements of memory in flies and mice (Silva, Kogan, Frankland, & Kida, 1998a; Yin & Tully, 1996). Since the second memory was stored in many of the same neurons as the first memory, it may be strengthened by the increases in CREB triggered by the first memory. Remarkably, with aging there are decreases both in CREB levels and in intrinsic excitability of CA1 neurons (Yu, Oh, & Disterhoft, 2016). As predicted by the-allocate-to-link hypothesis, such decrease in excitability in aging mice could disrupt both memory linking and the related memory enhancements. Consistent with this, Cai et al. observed that middle-aged mice that acquired and stored single contextual memories normally, were impaired in memory linking and linking-related memory enhancement normally observed in young mice. Remarkably, artificially increasing excitability in a subgroup of neurons in CA1 right before encoding of two contextual memories was sufficient to restore memory linking and memory strengthening in aged mice, demonstrating the importance of intrinsic excitability in memory linking, an important feature of the allocate-to-link-hypothesis.

Compelling evidence for the allocate-to-link hypothesis was also provided in a different brain region by two other groups using different behaviors (Rashid et al., 2016; Yokose et al., 2017). Studies with tone fear conditioning in the amygdala demonstrated that memories for two distinct tone fear conditioning events, separated by either 1.5 or 6 h, but not by longer intervals (18 or 24 h), are stored by overlapping populations of lateral amygdala neurons (Rashid et al., 2016). These results also revealed that the acquisition of one memory also activates GABA-mediated inhibition that constrains subsequent memory allocation to previously active neurons in the lateral amygdala, thus ensuring the overlap between the neuronal ensembles encoding memories acquired close in time (Rashid et al., 2016).

Remarkably, another independent set of experiments in the amygdala demonstrated that specifically inhibiting the overlapping neurons between two distinct amygdala-dependent memories (conditioned taste aversion or CTA, and tone conditioning) did not disrupt recall of either memory, but it did interfere with the ability of one memory to trigger the recall of the other (Yokose et al., 2017). Following acquisition of the CTA and tone memories, mice were repeatedly re-exposed to the conditioned stimuli associated with each of the two memories simultaneously (saccharin and an auditory tone), such that exposure to saccharin appear to trigger recall of the tone conditioning (i.e., the mouse exposed to saccharin demonstrated freezing responses similar to that in response to the conditioned tone). This result demonstrated that the two memories were linked, since retrieval of the CTA memory triggered by exposure to saccharin appeared to cause the recall of the tone conditioning memory (i.e. the mice were freezing), an interpretation supported by imaging studies that demonstrated a significant overlap between the populations of amygdala neurons activated by these two tasks. Remarkably, optogenetic silencing of the ensemble of neurons activated by both CTA and tone conditioning did not affect either learning task, but did disrupt memory linking (exposure to saccharin no longer triggered freezing responses), demonstrating the importance of memory co-allocation in memory linking.

Cortical networks may also be able to link information stored at different timescales. For example, it is conceivable that semantic knowledge can emerge from related information stored across multiple episodes. The brain may use frameworks to organize long-term storage of related information. Information consistent with pre-existing frameworks or schemas may be easily learned and integrated with existing information (Bartlett, 1932; Piaget, 1929). Experiments with rodents have suggested that neocortical-hippocampal networks are key for the formation of schemas (Tse et al., 2007, 2011). Single unit electrophysiological studies in rat hippocampal CA1 demonstrated that updating a preexisting schema with new information results in the previously engaged neurons to be re-recruited but these representations change gradually to allow discrimination between related information in the schema (McKenzie, Robinson, Herrera, Churchill, & Eichenbaum, 2013). This suggests that during schema formation and updating, memory allocation mechanisms modulate the process by which the neurons that encode the existing framework are committed to storing new related information, and may be responsible for the gradual neuronal network refinements that allow discrimination between multiple memories learned on different occasions. This allows memories to be linked and still remain distinct.

Although many lines of evidence (including those discussed above) support co-allocation of memories acquired close in time, some studies suggest that memories acquired simultaneously may be encoded by non-overlapping ensembles (McKenzie et al., 2014; Schlichting, Mumford, & Preston, 2015). For example, Schlichting et al., 2015 use a

prospective inference design (described before during a discussion of Zeithamova et al., 2012) to demonstrate that memories presented one after another have increasingly similar neural representations within anterior hippocampus but when these memories are presented simultaneously their neural representations diverge and become more separate from one another. This separation is indicative of a tendency to trigger pattern separation (rather than pattern completion) during active differentiation when similar unrelated memories need to be studied and retrieved in alternation (Hsieh, Gruber, Jenkins, & Ranganath, 2014). Since, both simultaneous as well as sequential encoding of memories supports prospective inference, there must be mechanisms other than neuronal co-allocation (active during simultaneous encoding of memories) that support memory integration needed for prospective inference. Similarly, there is strong correlation in hippocampal representations of items that share features across training sessions but the items that co-occurred within a training session lack representational overlap (McKenzie et al., 2014). These data indicate that a balance between neuronal overlap and separation may be an important factor controlling memory linking and discrimination witnessed on the timescale of minutes and hours. We expect that future research would improve our ability to understand many such questions.

Weak and strong memories may also be linked using synaptic tagging and capture mechanisms such that recall of one may trigger the recall of another (Frey & Morris, 1997; Martin et al., 1997). Memories that would otherwise be forgotten (i.e., weak memories) can be remembered when acquired in the proximity of strong memories (e.g., within one hour). Molecular components provided by the consolidation of a strong memory can be shared with the weak memory, and therefore stabilize synaptic potentiation processes needed for the weak memory storage (Frey & Morris, 1997; Martin et al., 1997). During memory acquisition, synaptic molecular mechanisms tag activated synapses associated with both the weak and strong memories. Although the weak memory cannot activate the synthesis of proteins needed for memory consolidation, it can utilize these proteins when they are produced as a result of a strong memory, as long as the strong memory is acquired within temporal proximity of the weak memory (e.g., few hours). Since both memories should be encoded in overlapping neuronal populations (otherwise they would not be able to share proteins), synaptic tagging and capture mechanisms should also result in the linking of the weak and strong memories (Kastellakis et al., 2015) (Rogerson et al., 2016) (Kastellakis et al., 2016).

Behavioral studies (Moncada & Viola, 2007) confirmed a key behavioral prediction of the synaptic tagging and capture hypothesis: a weak memory for a spatial learning task, that would have normally be forgotten, could be strengthened and consolidated by exposing the rodents to a strong spatial learning episode (i.e., novel open field exploration) one hour before or after training on the weak memory. Similarly, exploration of a novel context strengthened the consolidation of a weak object recognition task (Ballarini, Moncada, Martinez, Alen, & Viola, 2009). Successful behavioral tagging, that rescues a weak novel object recognition memory, is accompanied by an increase in the number of overlapping neurons in the CA1 region of hippocampus, i.e., neuronal co-allocation accompanies behavioral tagging (Nomoto et al., 2016).

It should be noted that memories acquired close in time do not always strengthen each other. For example, when rodents are exposed to a novel environment one hour following inhibitory avoidance, their memory for inhibitory avoidance is weakened (Izquierdo, Schroder, Netto, & Medina, 1999). It is possible that two memories acquired very close in time (for example, within one hour) can compete for limited synaptic proteins and consequently weaken one another (Govindarajan, Israely, Huang, & Tonegawa, 2011). Consistent with this, when preceded by an open field task for 15 min or 1 h, a weak inhibitory avoidance memory was made stronger at a cost to the open field exploration memory (Martinez, Alen, Ballarini, Moncada, & Viola, 2012). These effects on the memory of open field exploration were seen if the two memories were encoded within 15 min or 1 h of one another but not if open field exploration occurred 4 h before inhibitory avoidance training. Experiments with Arc antisense oligonucleotides demonstrated that memory impairment was observed under regimes with limited Arc synthesis and competition for plasticity related proteins (PRPs), such as Arc, could underlie these effects. The studies of how memories interact over time are just starting. However, the impact of these studies will shape how we understand memory and associated disorders.

5. Conclusions

The studies reviewed here mark a new exciting era in the field of learning and memory research. We are slowly transitioning from studying single memories to understanding how multiple memories are linked, integrated and bound within an existing framework. In the coming years, with better tools to track and manipulate memory allocation mechanisms in real time, in specific neuronal compartments and circuits we are bound to transform our understanding of memory and its disorders.

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