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The role of intrinsic excitability in the evolution of memory: Significance in memory allocation, consolidation, and updating

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ABSTRACT

Memory is a dynamic process that is continuously regulated by both synaptic and intrinsic neural mechanisms. While numerous studies have shown that synaptic plasticity is important in various types and phases of learning and memory, neuronal intrinsic excitability has received relatively less attention, especially regarding the dynamic nature of memory. In this review, we present evidence demonstrating the importance of intrinsic excitability in memory allocation, consolidation, and updating. We also consider the intricate interaction between intrinsic excitability and synaptic plasticity in shaping memory, supporting both memory stability and flexibility.

1. Introduction

The question of how memories are formed and stored has intrigued and inspired neuroscientists for more than a century. Diverse theories have been proposed to describe the fundamental mechanisms underlying learning and memory at the molecular, cellular, and network levels. Following the Hebbian hypothesis (Hebb, 1949), numerous studies over several decades of research have shown that memory storage involves the induction of synaptic plasticity, defined as an activity-dependent modification of the strength of synaptic connections (Bliss and Collingridge, 1993, 2013; Citri & Malenka, 2008; Levy & Steward, 1979; Mayford, Siegelbaum, & Kandel, 2012; Takeuchi, Duszkiewicz, & Morris, 2014). Immediately after learning, newly formed memories are stabilized through the induction of synaptic plasticity, which typically takes the form of long-term potentiation or depression (LTP or LTD) (Bliss & Lømo, 1973; Ito & Kano, 1982). The mechanisms that govern synaptic plasticity have been the subject of extensive investigation. Here, we will focus on another critical, yet much less understood mechanism underlying learning and memory: the modulation of neuronal intrinsic excitability (Coulter et al., 1989; Daoudal & Debanne, 2003; Disterhoft and Oh, 2006a, 2007; Disterhoft, Coulter, & Alkon, 1986; Kuo, Lee, McKay, & Disterhoft, 2008; Oh & Disterhoft, 2015; Oh et al., 2010, 2016; Sehgal, Song, Ehlers, & Moyer, 2013; Thompson, Moyer, & Disterhoft, 1996; Zhang & Linden, 2003). Neuronal intrinsic excitability is a neuron's tendency to generate action potentials (APs) upon synaptic integration and is dictated primarily by the distribution and function of voltage-gated ion channels (see Box 1). Specifically, we will highlight several ways in which intrinsic excitability plays a fundamental role in memory formation and memory updating. First, intrinsic excitability regulates the allocation of memory to a specific ensemble of neurons. Next, learning-induced increases in intrinsic excitability likely promote memory consolidation by facilitating the induction of long-term synaptic plasticity. Finally, intrinsic excitability supports the dynamic processes of memory updating, contributing to memory flexibility. In this review, we will examine the current literature supporting a role for neuronal intrinsic excitability across these different phases in the evolution of memories and propose future studies that can advance our understanding of the role of intrinsic excitability in the dynamic processes underlying learning and memory.

2. Intrinsic excitability and memory allocation

In the early twentieth century, Richard Semon introduced the term "engram" to describe the physical manifestation of memory, defined as "the enduring though primarily latent modification in the irritable substance produced by a stimulus" (Semon, 1921). The biological basis for the engram was elusive, however, as Karl Lashley was unable to find a specific engram within the cortex (Lashley, 1933, 1935). In recent years, new technologies for identifying and controlling cellular activity have enabled us to deepen our understanding of the possible physical "trace" of memory (Josselyn, 2010; Sakaguchi & Hayashi, 2012; Josselyn et al., 2015, 2017; Tonegawa, Pignatelli et al., 2015; Tonegawa, Liu et al., 2015; Eichenbaum, 2016; Poo, 2016). Several studies have shown that memories are initially encoded in a sparse

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Box 1
Experimental quantification of intrinsic excitability.

Experience-dependent alterations in neuronal intrinsic excitability are primarily measured using *in vitro* whole-cell patch-clamp recordings in brain slices, where changes are reflected in several electrophysiological parameters outlined in Table 1. Overall, excitability is defined as the neuron's capability to generate APs in response to stimuli (such as somatic current injections or synaptic stimulation). While a simple measurement of the resting membrane potential could reflect excitability, even neurons with the same resting potential could have different excitability. Therefore, studies usually measure other key parameters that may affect AP generation while holding the membrane potential at a certain level (such as −60 mV or −70 mV).

One important parameter to determine intrinsic excitability is the afterhyperpolarization (AHP), which is a hyperpolarized phase after a single or a train of APs where the membrane potential is below the neuron's resting membrane potential. There are three types of AHPs (Table 1; Fig. 1): the fast AHP (fAHP) that occurs after each AP and lasts 2–5 ms, and the medium (mAHP) and slow (sAHP) AHP, which are evoked after a burst of APs and last 50–300 ms and 1–2 s, respectively. Since postburst AHP is generated independent of synaptic transmission, it is considered to be an intrinsic neuronal property (Coulter et al., 1989; Power, Wu, Sametsky, Oh, & Disterhoft, 2002). Both mAHP and sAHP are mediated largely by calcium-dependent outward K^+ currents. The channels that underlie mAHP are generally considered to be a sub-family of Ca^{2+}-dependent K^+ channels called apamin-sensitive SK channels (Bond et al., 2004; Stocker et al., 1999; Stocker, 2004), while those that underlie sAHP are not clearly known (Sah & Faber, 2002; Disterhoft & Oh, 2006a; Oh et al., 2010). A reduction in the size of the postburst AHP is considered to indicate an increase in intrinsic excitability, and vice versa. Importantly, changes in mAHP and sAHP have been observed after learning and in age-related cognitive deficits (Disterhoft and Oh, 2006b, 2006a, 2007; Oh, Simkin, & Disterhoft, 2016; Ohno, Sametsky, Silva, & Disterhoft, 2006).

In addition to postburst AHP, spike frequency accommodation (referred to as accommodation from here forward) is an additional parameter reflecting intrinsic excitability (Table 1). Accommodation is defined as a reduction in AP firing frequency in response to a sustained depolarizing step or a train of depolarizing stimuli. It results from the adaptation of various ionic currents that affect the generation of APs, including the AHP current mediated by Ca^{2+}-dependent K^+ channels (Madison & Nicoll, 1984), and is usually considered to be an intrinsic property of a neuron. A reduction in accommodation (i.e. more APs induced by a sustained stimulus) reflects an increase in excitability, and vice versa. Besides the size of postburust AHPs and accommodation, Researchers have also used other parameters associated with APs as indicators of neuronal intrinsic excitability (see Table 1). Alterations in these properties reflect changes in the overall expression, distribution, and function of voltage-gated ion channels and are used to quantify changes in intrinsic excitability (Aizenman & Linden, 2000; Armano, Rossi, Taglietti, & D'Angelo, 2000; Crestani et al., 2018; Egorov, Hamam, Fransén, Hasselmo, & Alonso, 2002).

population of neurons, or a neural "ensemble" (Guzowski, McNaughton, Barnes, & Worley, 1999; Han et al., 2009; Reijmers, Perkins, Matsuo, & Mayford, 2007; Zhou et al., 2009; Liu et al., 2012; Josselyn, Köhler, & Frankland, 2015; Tonegawa, Liu et al., 2015, Tonegawa, Pignatelli et al., 2015). Artificially reactivating the neural ensemble originally activated during memory encoding leads to memory retrieval (Cowansage et al., 2014; Frankland, Josselyn, & Köhler, 2019; Garner et al., 2012; Liu et al., 2012; Ramirez et al., 2013; Rogerson et al., 2016; Ryan, Roy, Pignatelli, Arons, & Tonegawa, 2015; Yiu et al., 2014). Furthermore, memory allocation, the process of recruiting neurons to form an ensemble representation of the memory, is not random. Rather, neurons with elevated excitability have a higher probability of being recruited into a memory ensemble (Lisman, Cooper, Sehgal, & Silva, 2018; Silva, Zhou, Rogerson, Shobe, & Balaji, 2009). Here, we review the literature highlighting the role of intrinsic excitability in regulating memory allocation.

Initial insights into how neuronal excitability modulates memory allocation were derived from a series of studies on the cAMP responsive element-binding protein (CREB), a molecule that plays a key role in the induction of long-term potentiation (LTP) and the consolidation of long-term memory (Alberini, 1999, 2009; Yin & Tully, 1996) (see Box 2). Recent studies found that CREB function regulates memory allocation. Overexpressing wild-type CREB in the amygdala significantly increased the probability of a neuron to be activated during memory encoding

Table 1
Experimental quantification of neuronal intrinsic excitability.

Parameters	Regulators	Measurement	Relationship to excitability
fAHP	BK channel; A-type K + channel ↑ Channel activity ↑ fAHP size	Negative peak after a single AP relative to the holding potential (Fig. 1**A**)	↑ fAHP size ↑ Excitability
mAHP	SK channel ↓ SK channel activity ↓ mAHP size	Negative peak after a train of APs relative to the holding potential (Fig. 1**B**)	↓ mAHP size ↑ Excitability
sAHP	To be identified	Remaining hyperpolarization relative to the holding potential 1-2 s after the AP train (Fig. 1**B**)	↓ sAHP size ↑ Excitability
Spike frequency accommodation	M channel; fast Na^+ channel; regulated by postburst AHP ↓ AHP size ↓ Accommodation	Number of APs elicited during a sustained stimulation	↓Accommodation ↑ Excitability
AP half-width AP frequency	Regulated by fAHP ↑ fAHP ↓ AP half-width ↑ AP frequency	*Half-width*: the width of an AP at its half-maximal value *Frequency*: number of APs per second	↓ AP half-width ↑ AP frequency ↑ Excitability
AP threshold Rheobase	Related to the density of Na^+ channels, Na^+ channel inactivation and K^+ channels	*Threshold*: the membrane potential at which the rising speed of an AP peaks or exceeds a certain value during depolarization *Rheobase*: the minimal current amplitude of an infinite duration to elicit a single AP	↓ AP threshold ↓ Rheobase ↑ Excitability
Input resistance	Determined by the total number and conductance of open channels	Calculated from the I-V curve derived from a series of somatic current injections (R = V/I)	↑ Input resistance ↑ Excitability

Box 2
Molecular factors regulating intrinsic excitability.

In addition to direct modulation by the expression, distribution, and function of various ion channels, the intrinsic excitability is also dependent on protein synthesis and second messenger systems (Cohen-Matsliah, Motanis, Rosenblum, & Barkai, 2010; Daoudal & Debanne, 2003; Saar & Barkai, 2003; Zhang & Linden, 2003), many of which are shared with the induction and maintenance of long-term potentiation (LTP), a major form of long-term synaptic plasticity believed to be essential for memory consolidation (Abel & Lattal, 2001; Citri & Malenka, 2008; Dudai et al., 2015; Dudai, 2004; Kandel et al., 2014; Kandel, 2001).

One important molecule indicated in both synaptic plasticity and intrinsic excitability is the cAMP responsive element-binding protein (CREB), a key regulator in the cAMP-dependent protein kinase A (PKA) signaling pathway. CREB is activated via posttranslational modifications such as phosphorylation, and its activation is synergistically triggered by an increase in intracellular Ca^{2+} and an increase in cAMP (Lonze & Ginty, 2002). CREB has important functions in the nervous system, including learning and memory, which has been demonstrated in various brain regions across different behavior tasks (Alberini, 1999, 2009; Bernabeu, Bevilaqua, Ardenghi, Bromberg, Schmitz, Bianchin, Izquierdo, & Medina, 1997; Impey et al., 1998; Stanciu, Radulovic, & Spiess, 2001; Taubenfeld, Wiig, Bear, & Alberini, 1999; Yin & Tully, 1996). As a well-studied form of long-term synaptic plasticity supporting memory consolidation, the induction of LTP is regulated by CREB. The CRE-mediated gene expression was markedly increased after the generation of long-lasting LTP (Impey et al., 1996), while CREB knockout mice showed memory deficits and impaired LTP (Bourtchuladze et al., 1994). The essential role of CREB activation in LTP induction is now confirmed in a number of studies (Alberini, 1999, 2009; Barco, Alarcon, & Kandel, 2002; Bito, Deisseroth, & Tsien, 1996; Deisseroth, Bito, & Tsien, 1996; Josselyn & Nguyen, 2005; Kandel et al., 2014; Kandel, 2001; Segal & Murphy, 1998). Besides supporting synaptic plasticity, CREB also regulates neuronal intrinsic excitability. Virally overexpressing CREB increased neuronal intrinsic excitability in various brain regions, including the hippocampus, amygdala, locus coeruleus, and nucleus accumbens (Dong et al., 2006; Han et al., 2007; Viosca et al., 2009; Yiu et al., 2014; Yu et al., 2017; Zhou et al., 2009), possibly by decreasing voltage-gated K^+ currents (Dong et al., 2006) and then reducing the size of postburst AHP (Gu, Vervaeke, Hu, & Storm, 2005; Oh et al., 2010). Therefore, both synaptic and intrinsic plasticity (LTP and increased excitability, respectively) are induced after CREB activation. These mechanisms may then work synergistically in promoting memory consolidation.

A number of other molecular factors can also alter the expression of ion channels on the membrane, reduce the AHP, and increase intrinsic excitability. Protein kinase A (PKA), protein kinase C (PKC), and calmodulin-dependent protein kinase II (CaMKII), which are major protein kinases within the cAMP-dependent pathway and are involved in different phases of LTP induction (Abel & Lattal, 2001; Abel et al., 1997; Huang, Nguyen, Abel, & Kandel, 1996; Impey et al., 1998, 1999; Kandel, 2001), have been found to be involved in the reduction of AHP (Melyan, Wheal, & Lancaster, 2002; Seroussi, Brosh, & Barkai, 2002; Ohno et al., 2006; de Armentia et al., 2007; Grabauskas, Lancaster, O'Connor, & Wheal, 2007; Oh et al., 2009; Cohen-Matsliah et al., 2010). The activation of muscarinic receptors and metabotropic glutamate receptors has been shown to reduce AHP via PKC and CaMKII (Grabauskas et al., 2007; Malenka, Madison, Andrade, & Nicoll, 1986; Pedarzani & Storm, 1996; Pineda, Bargas, Flores-Hernández, & Galarraga, 1995), while the activation of monoamine receptors reduced AHP via PKA (Grabauskas et al., 2007; Lancaster, Hu, Gibb, & Storm, 2006; Oh et al., 2009; Pedarzani & Storm, 1993).

and recruited into the memory ensemble, and the expression of dominant negative CREB decreased this probability (Han et al., 2007). CREB's regulatory role in memory allocation has since been repeatedly found in the amygdala (Han et al., 2009; Rogerson et al., 2016; Yiu et al., 2014; Zhou et al., 2009), the insular cortex (Sano et al., 2014), and the hippocampus (Park et al., 2016). It was postulated that CREB increased memory allocation through increasing the neuronal excitability, since neurons with enhanced CREB gene expression exhibited increased excitability while those with suppressed CREB expression had decreased excitability (Dong et al., 2006; Viosca, Lopez de Armentia, Jancic, & Barco, 2009; Zhou et al., 2009).

A critical study tested the direct link between intrinsic excitability and memory allocation by manipulating two AHP-related K^+ channels to directly increase and decrease excitability (Yiu et al., 2014). Memory allocation was biased toward neurons with increased intrinsic excitability and away from neurons with decreased intrinsic excitability. Another study used a step function opsin to induce a prolonged depolarization in a subset of amygdala neurons, mimicking a more depolarized resting membrane potential of the hyperexcitable neurons (Rogerson et al., 2016). Fear memory ensembles were biased into the opsin-expressing, depolarized neurons. Beyond experimental findings, theoretical modeling has also supported the potential for excitability to dictate memory allocation. Biophysical modeling of 1000 lateral amygdala cells predicted that principal neurons with higher intrinsic excitability prior to network training on an auditory fear conditioning task were more likely to become "plastic" cells after training (increased response to the conditioned stimulus) compared to cells with lower excitability (Kim, Pare, & Nair, 2013). The results of these various studies point to a direct role for neuronal excitability in guiding memory allocation.

Studies describing how place cells emerge have provided converging evidence for the role of intrinsic excitability in memory allocation. A landmark study found that in the hippocampus a specific subset of cells, now known as place cells, fired when the animal was in a particular location (O'Keefe & Dostrovsky, 1971), contrary to "silent cells", which rarely fired during awake, active behavior (Thompson & Best, 1989). With the advantage of intracellular recording techniques in freely-behaving animals (Lee, Manns, Sakmann, & Brecht, 2006; Lee, Epsztein, & Brecht, 2009), more recent studies started to answer the question of how excitability plays a role in shaping place or silent cells. Place cells exhibited increased excitability compared to silent cells, with lower spiking thresholds and higher burst rates, even before an animal was first introduced to an environment (Epsztein, Brecht, & Lee, 2011). Furthermore, altering the excitability of CA1 pyramidal cells induced place field formation. Increasing the excitability of previously silent CA1 pyramidal neurons by uniformly depolarizing the somatic membrane potential during spatial exploration led to the emergence of spatially-tuned place fields (Lee, Lin, & Lee, 2012), and current injections at specific spatial locations appeared to drive the formation of spatial fields (Bittner et al., 2015; Diamantaki et al., 2018). *In vivo* intracellular recordings have also shown that exploration of novel environments caused increases in measures of intrinsic excitability, such as reduced action potential (AP) threshold and increased subthreshold membrane voltage "hills" that underlie AP bursts and place fields (Cohen, Bolstad, & Lee, 2017). Together, these findings suggest that the formation of place fields not only requires that cells receive specific spatial input, but that those cells must also have higher intrinsic excitability relative to other cells.

In conclusion, converging evidence has demonstrated that memory allocation is not a random process, but is regulated, at least in part, by neuronal intrinsic excitability. Neurons with higher excitability are preferentially recruited into an ensemble, and direct manipulations of excitability are sufficient to drive the ensemble formation (Bittner et al., 2015; Diamantaki et al., 2018; Lee et al., 2012; Rogerson et al., 2016; Yiu et al., 2014).

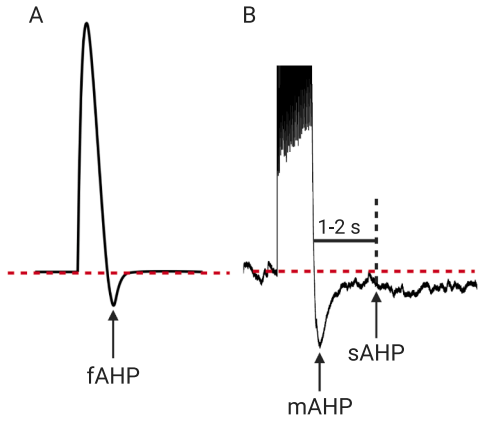

Fig. 1. Three types of afterhyperpolarization (AHP). (A) Fast AHP (fAHP) after a single action potential, measured as the negative peak relative to the holding potential after a single action potential (AP). (B) Medium and slow AHP (mAHP and sAHP, respectively) after a burst of APs, measured as the negative peak relative to the holding potential between 50 and 300 ms (mAHP) or the remaining hyperpolarization at 1-2 s (sAHP) after the AP train.

3. Intrinsic excitability and memory consolidation

After memory allocation, a series of processes follows to stabilize the newly acquired information and transform it into long-term memory. These processes are commonly referred to as memory consolidation, which occurs at the synaptic and systems levels on different time scales (Dudai, 1996, 2004; Dudai, Karni, & Born, 2015; Kandel, Dudai, & Mayford, 2014; McGaugh, 2000). Synaptic consolidation is assumed to last minutes to hours after encoding within the local circuit and synapses. Systems consolidation, on the other hand, is considered to take days to months or even longer and involves the distribution of the memory representations across different brain regions. The two levels of consolidation are closely related, since systems consolidation is assumed to involve waves of synaptic consolidation in interacting brain areas (Dudai, 2012). The mechanisms of memory consolidation are generally thought to rely on synaptic plasticity—the strengthening or weakening of synaptic connections—through activation of signaling cascades leading to modulations in gene expression, post-translational modifications, and protein synthesis (Abel & Lattal, 2001; Alberini, 2008; Dudai et al., 2015; Dudai, 2004; Kandel et al., 2014; Kandel, 2001). Synaptic plasticity has been seen in different forms, with the most extensively studied have been long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus (Citri & Malenka, 2008).

While the synaptic mechanisms of memory consolidation have been the subject of considerable investigation, there is increasing evidence showing that intrinsic excitability may have a significant role in memory consolidation as well. First, learning induces a transient increase in neuronal intrinsic excitability, with a time window coinciding with that of memory consolidation, suggesting a potential role for intrinsic excitability during consolidation. Second, post-learning excitability increase is required for successful learning and may also serve as a general mechanism promoting learning and memory. Last, intrinsic excitability may promote memory consolidation by interacting with LTP, a major form of synaptic plasticity supporting memory consolidation.

After learning, neuronal intrinsic excitability transiently increases, persisting from hours to days. This phenomenon was initially discovered in rabbits after a trace eyeblink conditioning task (Moyer, Thompson, & Disterhoft, 1996, 2000; Thompson et al., 1996). Once rabbits successfully learned the task, postburst afterhyperpolarization (AHP) (see Box 1 and Fig. 1) was reduced in hippocampal pyramidal neurons in CA1 (Moyer et al., 1996, 2000) and CA3 (Thompson et al., 1996), indicating increased excitability. Enhanced excitability was observed as early as 1 h after learning, maximizing at 1 day, and returning to baseline within 7 days (Moyer et al., 1996; Thompson et al., 1996). Enhanced excitability has been observed in rodent hippocampal CA1 after learning various tasks, including trace eyeblink conditioning (Kuo et al., 2008; Matthews, Linardakis, & Disterhoft, 2009; Oh, McKay, Power, & Disterhoft, 2009), trace and contextual fear conditioning (Cai, 2016; Crestani et al., 2018; Kaczorowski & Disterhoft, 2009; Mckay, Matthews, Oliveira, & Disterhoft, 2009; Song, Detert, Sehgal, & Moyer, 2012), Morris water maze (Oh, Kuo, Wu, Sametsky, & Disterhoft, 2003), and an olfactory discrimination task (Zelcer et al., 2006). An important feature of this increase in learning-induced excitability is its transient nature. With induction as early as an hour after learning (perhaps sooner, although this has not been measured), the enhancement of intrinsic excitability temporally overlaps with the critical period of synaptic consolidation (Dudai, 2004). Further, this increase in excitability persists for days after learning (Moyer et al., 1996; Thompson et al., 1996), which may facilitate systems consolidation by supporting synaptic plasticity between interacting brain regions.

Since neuronal hyperexcitability and consolidation processes occur within the same time window after learning, excitability may play a role during the first hours to days to stabilize the memory. Indeed, a number of behavioral observations support this hypothesis. First, the transient increase in excitability correlates with successful learning. Neuronal intrinsic excitability in animals that failed to learn the trace eyeblink conditioning task (non-learners) was comparable to that of control animals and lower than that of successful learners (Kaczorowski & Disterhoft, 2009; Matthews et al., 2009; Moyer et al., 1996, 2000; Oh et al., 2003; Song et al., 2012; Thompson et al., 1996). Further studies of excitability changes with aging supported learning-induced excitability as important for memory consolidation. While middle-aged and aged animals had either similar or lower baseline excitability compared to young animals, it was post-learning excitability that predicted whether aged animals were able to consolidate memories properly (Kaczorowski & Disterhoft, 2009; Matthews et al., 2009; Moyer, Power, Thompson, & Disterhoft, 2000; Tombaugh, Rowe, & Rose, 2005). Animals that recalled the memory had higher learning-induced excitability, regardless of whether the subjects were young or aged. Second, excitability increases in the hippocampus lasted for a shorter period of time than the retention of the memory. While excitability generally returned to baseline within 7 days, the retention of the memory for the trace eyeblink conditioning task lasted for months (Moyer et al., 1996; Thompson et al., 1996). Therefore, it would appear that enhanced excitability is not required to retrieve the memory but is instead involved in the initial stabilizing processes after encoding. It is also possible that hyperexcitability in CA1 facilitates not only synaptic consolidation within the hippocampus, but also systems consolidation in associated cortical areas, rendering the memory hippocampus-independent at a later time point (Kim, Clark, & Thompson, 1995). Whether waves of excitability alterations persist in interacting brain regions after learning, ranging from hours to days and months, remains unclear and will be an exciting area to explore. Taken together, these studies demonstrate that excitability increases after learning may be critical in memory consolidation.

Although a number of studies have shown that the level of intrinsic excitability correlates closely with the quality of learning and memory, there has so far been a dearth of research investigating how intrinsic excitability directly affects consolidation. Several studies do, nonetheless, describe how excitability regulates LTP. As discussed, LTP is a major form of synaptic plasticity contributing to memory consolidation (Abel & Lattal, 2001; Citri & Malenka, 2008; Dudai et al., 2015; Dudai, 2004; Kandel et al., 2014; Kandel, 2001). These studies suggest a mutual relationship between intrinsic excitability and the induction of LTP, which could provide a mechanistic link between learning-induced excitability increases and memory consolidation. Intrinsic excitability is determined by the distribution and function of voltage-gated ion

channels (see Box 1). A sub-class of Ca^{2+}-activated K^+ channels, known as the apamin-sensitive SK channels, are a major determinant of intrinsic excitability through regulation of the postburst AHP (Stocker, Krause, & Pedarzani, 1999; Sah & Faber, 2002; Bond et al., 2004; Stocker, 2004; Disterhoft & Oh, 2006a; Oh, Oliveira, & Disterhoft, 2010). Inhibiting SK channels reduced the size of postburst AHP (Kramár et al., 2004; Stocker et al., 1999), leading to a higher intrinsic excitability, while activation of SK channels led to an enlarged AHP and reduced excitability (McKay et al., 2012; Pedarzani et al., 2001). Besides mediating intrinsic excitability, SK channels also modulated LTP induction. These channels appear to be highly enriched in the postsynaptic density of dendritic spines in pyramidal neurons (Bloodgood & Sabatini, 2007; Faber, 2010; Faber, Delaney, & Sah, 2005; Mulholland, Becker, Woodward, & Chandler, 2011; Ngo-Anh et al., 2005), where they form a negative feedback loop that limits NMDA receptor activation in response to dendritic Ca^{2+} influx. Activating SK channels in the hippocampus reduced excitatory postsynaptic potential and impaired associative learning (McKay et al., 2012), while blocking SK channels in the hippocampus (Behnisch & Reymann, 1998; Kramár et al., 2004; Norris, Halpain, & Foster, 1998; Stackman et al., 2002), amygdala (Faber et al., 2005, 2008)), and cortex (Bock & Stuart, 2016; Bock, Honnuraiah, & Stuart, 2019; Faber, 2010) facilitated LTP induction, increased postsynaptic neuronal excitability, and enhanced spatial and non-spatial memories (Stackman et al., 2002). Therefore, the inhibition of SK channels could conceivably serve as a common mechanism both enhancing intrinsic excitability and facilitating LTP induction after learning. Learning-induced alterations in ion channels directly alter intrinsic excitability and can act as an additional mechanism (besides the classical LTP induction cascade) to further promote the strengthening of synapses. Moreover, maintaining enhanced excitability for a period of time after learning requires protein synthesis and the activation of intracellular signaling pathways, many of which also contribute to the induction and maintenance of LTP (see Box 2). Taken together, these studies suggest a close relationship between the induction and maintenance of intrinsic and synaptic plasticity.

In summary, a transient increase in intrinsic excitability is correlated with successful learning and may serve as a neuronal mechanism to promote memory consolidation. Moreover, the time course of learning-induced excitability increases occurs within the same time as synaptic and early systems consolidation. Given the highly interconnected relationship between intrinsic excitability and LTP, a well-established proxy of memory consolidation, it is very likely that intrinsic excitability contributes to consolidation processes. Within the hippocampal circuits, a transient increase in excitability may facilitate LTP induction and the initial synaptic consolidation. Brain wide, waves of excitability alterations in interacting brain regions may enhance the strengthening of cross-regional synaptic connections, thus contributing to systems consolidation on a longer time scale as well.

4. Intrinsic excitability and memory updating

In the last few decades, there have been significant advances in our understanding of the mechanisms underlying the formation of single memories (Bliss & Collingridge, 1993; Kandel et al., 2014; Kandel, 2001; McGaugh, 2000). Memory processing, however, involves the integration of multiple memories across time, with single memories affecting how others are processed and stored over time (Cai, 2016; Morton, Sherrill, & Preston, 2017; Rashid et al., 2016; Richards & Frankland, 2017; Schlichting et al., 2015, 2017; Yokose et al., 2017). The brain's ability to organize and integrate different experiences so that it can efficiently 'file' and 'cross reference' information is critical for daily life. Memories need to maintain stability and fidelity, yet new information must be flexibly integrated into past memories to inform future decision making (Kroes & Fernández, 2012; Nadel, Hupbach, Gomez, & Newman-Smith, 2012; Routtenberg & Rekart, 2005; Rule, O'Leary, & Harvey, 2019; Schacter, Norman, & Koutstaal, 1998). The dynamic nature of memory makes it possible to integrate new information during memory updating while reducing the influence of outdated knowledge, which is crucial for memory-guided decision making (Richards & Frankland, 2017). Although different forms of memory integration and updating has been observed in animal and human studies, the exact mechanisms driving these phenomena remain largely unclear. Here, we review the literature on neuronal intrinsic excitability regulating the dynamic memory updating processes. Specifically, we will focus on temporal memory-linking, memory integration during retrieval, and rule and schema learning.

4.1. Temporal memory-linking

We have reviewed several studies showing that the initial memory allocation, which is the process of recruiting neurons to form an ensemble representation of a memory, is not random. Neurons with higher excitability have an increased probability of being recruited into a memory ensemble than neighboring neurons (Han et al., 2007, 2009; Park et al., 2016; Rogerson et al., 2016; Sano et al., 2014; Yiu et al., 2014; Zhou et al., 2009). An important evidence for the memory allocation hypothesis is that memories encoded close in time share an overlapping ensemble, which links temporally close memories together (i.e. temporal memory-linking). Further, learning-induced excitability increases play an important role in regulating the temporal memory-linking process. It has been shown repeatedly in different behavior tasks that after learning, neuronal intrinsic excitability increases transiently within hours and returns to baseline within days (Moyer et al., 1996; Thompson et al., 1996; Zelcer et al., 2006). A contextual memory is encoded into a sparse neural ensemble in the hippocampus (Deng, Mayford, & Gage, 2013; Garner et al., 2012; Guzowski et al., 1999; Liu et al., 2012; Mckenzie, Frank, Kinsky, Porter, & Rivie, 2014). When a second new environment is introduced a few hours later and the excitability of the ensemble neurons from the first memory is still high, the allocation of the second memory should be biased into many of the same neurons as the first one (Dragoi & Tonegawa, 2011; Epsztein et al., 2011; Lee et al., 2012; Yiu et al., 2014; Zhou et al., 2009). Indeed, with *in vivo* calcium imaging, a study showed that the ensemble overlap between two memories encoded 5 h apart was significantly higher than that between two memories encoded 7 days apart (Cai, 2016). Sharing a neural ensemble between two memories had important behavioral consequences; recall of one memory triggered recall of the temporally linked memory (encoded 5 h apart) (Cai, 2016). Similar findings have been observed in the lateral amygdala (LA), where two cued fear conditioning sessions administered 6 h apart were more likely to be encoded by an overlapping population of neurons than those encoded a day apart (Rashid et al., 2016). These memories were also behaviorally linked so that extinguishing one memory also extinguished the other one learned hours apart.

In addition to endogenously changing excitability through learning, other studies artificially manipulated neuronal excitability to examine how excitability may regulate temporal memory-linking. Increasing excitability by virally overexpressing CREB in a sparse population of neurons biased the allocation of two memories encoded 24 h apart to the CREB positive neurons, artificially linking the two memories that would typically be separated (Rashid et al., 2016). Studies have also used neural activity as a proxy for intrinsic excitability and investigated its potential role in temporal memory-linking. Optogenetic activation of a sparse neural ensemble in the lateral amygdala during the encoding of two temporally separated memories was sufficient to drive the linking of the two memories (Rashid et al., 2016). A separate study using middle-aged mice with decreased hippocampal CA1 excitability (Disterhoft & Oh, 2007; Kaczorowski & Disterhoft, 2009; Murphy, Rahnama, & Silva, 2006; Oh et al., 2010) showed decreased ensemble overlap for temporally close memories and a deficit in temporal memory-linking (Cai, 2016). Chemogenetically boosting CA1 neural activity restored normal temporal memory-linking in middle-aged mice

by driving temporally close memories into a shared ensemble (Cai, 2016). These studies suggest that a group of highly active neurons is sufficient to drive the linking processes. While all of these manipulations affect neuronal excitability or activity, off target effects may contribute to linking. Although CREB increases excitability, it also triggers a molecular cascade of events that could mediate linking. Both optogenetic and chemogenetic manipulations serve only as a proxy for intrinsic excitability. Therefore, future studies directly manipulating excitability-related voltage-gated ion channels are critical to dissect how intrinsic excitability links and separates memories across time.

An important finding in temporal memory-linking studies is that when memories were encoded close in time and shared an overlapping neuronal ensemble, the first memory enhanced the strength of the second (Cai, 2016; Rashid et al., 2016). This enhancement effect was also observed in studies artificially driving excitability during encoding (Yiu et al., 2014; Yu, Curlik, Oh, Yin, & Disterhoft, 2017). A possible explanation for this enhancing effect is that the state of transient hyperexcitability of the first memory ensemble drives the allocation of the second memory into a shared ensemble, and, subsequently, increased excitability of the shared neurons further facilitates consolidation of the second memory. The phenomenon of temporal memory-linking serves as a demonstration that memories are not formed in isolation, but rather that the formation of a memory may be influenced by prior experiences, possibly through the modulation of intrinsic excitability.

4.2. Memory integration during retrieval

The studies reviewed thus far demonstrate that intrinsic excitability appears to play a key role in guiding memory allocation and facilitating memory consolidation, leading to the temporal linking of memories. Intrinsic excitability is not only transiently increased after the initial encoding of a memory, but also after memory retrieval, providing a mechanism by which memories can be updated through the integration of new information. A recent study investigated changes in the intrinsic excitability of dentate gyrus granule cells after mice recalled a contextual fear memory (Pignatelli et al., 2019). On Day 1, mice were exposed to a contextual fear conditioning task, when ensemble neurons were tagged with EYFP using the TetTag approach (Reijmers et al., 2007). On Day 2, mice were re-exposed to the conditioned context to elicit memory retrieval. Researchers prepared acute brain slices from mice that underwent retrieval and observed that EYFP-tagged cells (ensemble cells) exhibited enhanced excitability compared to neighboring non-tagged cells (non-ensemble cells), demonstrated by increased input resistance and decreased rheobase. Interestingly, optogenetic activation of the ensemble cells while animals were in a novel context did not alter their intrinsic excitability, suggesting that the observed heightened excitability was specific to retrieval-induced reactivation but not artificial activation. Heightened excitability lasted approximately 1 h during which the animals' ability to discriminate between the conditioned context and a similar unconditioned context (i.e. pattern separation) was enhanced. Also, the retrieval of a neutral contextual memory enabled the animals to more rapidly associate the neutral context with a foot shock during an immediate shock protocol. To demonstrate that elevated excitability is essential to these enhancements, researchers then expressed exogeneous Kir2.1 ion channels, which suppresses intrinsic excitability, specifically in the ensemble neurons. Suppressing the excitability of ensemble neurons abolished the enhancement in pattern separation and memory integration after retrieval (Pignatelli et al., 2019). Another study also showed the effect of memory retrieval on encoding of a subsequent memory, without, however, measuring excitability. Recalling a fear memory 6 h but not 1 day before encoding a new memory enhanced the new memory (Rashid et al., 2016). Together, these studies show that recalling a memory can facilitate the integration of new information into the recalled memory. Furthermore, similar to learning-induced excitability increases, retrieval-induced excitability increases may also enhance the encoding and consolidation of a memory formed following the recall.

When two memories are encoded close in time, they can be behaviorally linked (Cai, 2016; Rashid et al., 2016). Similarly, memories that were initially encoded as separate memories can also be linked during memory retrieval. When mice were trained independently on two different conditioning tasks with distinct unconditioned stimuli (US 1: LiCl injection; US 2: foot shock) and distinct conditioned stimuli (CS1: saccharin solution; CS2: tone), repeated co-retrieval with the presence of the conditioned stimuli caused the two conditioned responses to be co-represented by a shared neural ensemble and also linked behaviorally: the saccharin solution (CS1) triggered freezing (response to CS2) (Yokose et al., 2017). We see here that memories can be linked not only during initial memory encoding (Cai, 2016; Rashid et al., 2016) but also during retrieval. Transiently increased excitability may increase the overlap between two originally independent ensembles during repeated co-reactivation.

In conclusion, studies suggest that recall of an existing memory transiently triggers an increase in the excitability of ensemble neurons, which then opens up a temporal window both for memory enhancement and integration of new information into the existing memory. Memory integration during retrieval is a further demonstration of the dynamic nature of memory, and retrieval-induced intrinsic excitability increases may play an important role in mediating this process.

4.3. Rule and schema learning

We have thus far described how memory encoding and retrieval influence the formation of a temporally close memory and the integration of new associations into an existing memory. We can think of this process as the use of past information or experience to guide the formation of new memories and the update of old memories, which is critical for survival. There are, at the same time, other types of learning that appear to associate past and new information. In "rule learning" and "schema learning", two separately discovered but closely related behavioral phenomena in rats, a rule or schema is created through repeated training. When similar information is subsequently encountered, the brain can utilize the established rule or schema to achieve more efficient learning. Here, we review studies of rule and schema learning and consider how neuronal intrinsic excitability in interacting brain regions may play a role in establishing and maintaining a rule or schema after a sufficient amount of training.

Rule learning describes the phenomenon of an abrupt increase in the learning rate of new cue-reward associations after animals acquire the first one or two associations in the same training paradigm. The behavioral evidence for rule learning came from a series of studies on an odor discrimination task, during which water-deprived rats learned to distinguish between pairs of odors in order to obtain a water reward (Chandra & Barkai, 2018; Quinlan, Lebel, Brosh, & Barkai, 2004; Saar & Barkai, 2003; Saar et al., 1998, 1999, 2001, 2002; Staubli, Fraser, Faraday, & Lynch, 1987; Zelcer et al., 2006). In general, rats were presented a multi-arm radial maze in which odors were released into two arms, one with a positive odor and a water reward, the other with a negative odor and no reward. Rats needed to learn that water reward was associated with the positive odor. Twenty trials were conducted per session per day, and the criterion for completion of learning on an odor pair was at least 80% positive-cue choices in the last 10 trials of a training session. Researchers found that learning occurred in two distinct phases: a first phase of 7–8 sessions for the animals to learn to discriminate the first pair of odors and get the water reward, and a second phase during which animals could learn to associate a new odor with water reward within one session after being well trained on the first odor pair (Chandra & Barkai, 2018; Saar & Barkai, 2003; Saar et al., 1998, 1999). It was proposed that the animals learned the general rule during the first phase ("rule learning"), which enhanced their capability for learning new cue-reward associations. Notably, the enhancement in learning capability was significant and abrupt immediately after the

rule learning phase.

Evidence for how excitability may modulate rule learning comes from studies in the piriform cortex. It has been shown that in the piriform cortex, which receives direct input from the olfactory bulb (Haberly, 1990; Schoenbaum & Eichenbaum, 1995), neuronal intrinsic excitability is strongly correlated with rule learning. Electrophysiology studies revealed that neuronal intrinsic excitability of piriform cortex pyramidal neurons was increased after rule learning, demonstrated by a reduction in both the postburst AHP and the spike accommodation (Saar and Barkai, 2003, 2009; Saar, Grossman, & Barkai, 1998). This state of hyperexcitability was sustained as long as training continued, and lasted another 1–3 days after training was stopped (Saar et al., 1998). During this time of increased excitability, there was enhancement in the learning rate in discriminating new odor pairs. If the training was suspended for 4 or more days (when excitability had returned to baseline levels), there was no benefit from rule learning and animals behaved as if they had not been trained (Saar et al., 1998). This finding suggests that excitability increases in the piriform cortex may be important in maintaining the rule and essential for enhancing the animals' ability to learn new associations in the same training paradigm.

A similar yet more complex behavior phenomenon was observed in rats, defined as schema learning (Tse, Langston, Kakeyama, Bethus, & Spooner, 2007). Briefly, rats were trained to dig for flavored food pellets hidden in sand wells placed at specific locations in a familiar arena. Before the start of each trial, rats were cued with a flavor to orient to and dig into a specific sand well for pellets of the same flavor. The rats' performance was evaluated by the number of incorrect digs before going to the correct well during training sessions, and by the time spent digging at the correct well during probe tests (rats cued but no reward in the sand well). Performance was enhanced incrementally during training across the first 13 sessions. Remarkably, only a single training was required for rats to remember a new paired-associate (new food flavor and new sand well location) after they mastered the task. Moreover, a hippocampal lesion only 24 h after learning the new pair associations did not disrupt the newly formed memory. This was a surprising finding as this type of paired-associate learning is likely to be initially mediated in the hippocampus (Bunsey & Elchenbaum, 1996; Kesner, Hunsaker, & Gilbert, 2005; Wirth et al., 2003) and later consolidated in the neocortex (Miyashita, 2004; Sakai & Miyashita, 1991), and systems consolidation generally requires more than 48 h to be completed (Anagnostaras, Maren, & Fanselow, 1999; Bayley, Gold, Hopkins, & Squire, 2005; Kim & Fanselow, 1992; Zola-Morgan & Squire, 1990). Together, these results indicate that prior learning of an associative schema may facilitate faster encoding and systems consolidation when learning new associations (Tse et al., 2007).

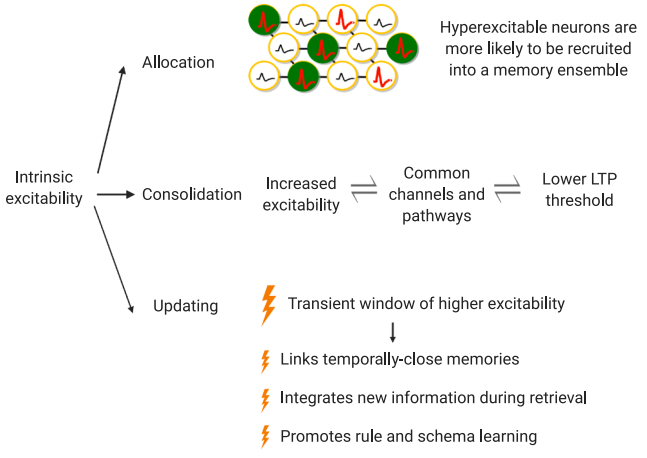

Fig. 2. The contribution of intrinsic excitability in memory allocation, consolidation, and updating. Allocation: neurons with a higher excitability at the time of learning have a higher probability to be recruited into a memory ensemble. **Consolidation**: increases in neuronal intrinsic excitability lower the threshold for LTP induction, through common underlying voltage-gated ion channels (such as SK channels) and signaling pathways. **Updating**: excitability is important for memory integration during memory updating. Especially, we have highlighted the role of heightened excitability in three processes: temporal memory-linking, memory integration during retrieval, and rule and schema learning.

No studies have directly characterized intrinsic excitability profiles during schema learning and how excitability may facilitate systems consolidation and faster learning. However, excitability changes in hippocampal CA1 during rule learning may have implications for the potential role of excitability in schema learning. The excitability of hippocampal CA1 pyramidal neurons remained unchanged until it increased 1 day before rats acquired the rule, and returned to baseline only 1 day after rule learning, regardless of whether training continued (Zelcer et al., 2006). Compared to learning-induced hyperexcitability in the piriform cortex, which was sustained as long as training continued and could last another 1–3 days if training was stopped (Saar and Barkai, 2003, 2009; Saar et al., 1998), the hippocampus and piriform cortex may have different roles in rule learning. Hippocampal CA1 excitability may drive the local circuit processes essential for learning the initial pairs of associations while sending signals to interacting neocortical regions to enhance excitability and facilitate the establishment of a rule or schema representation in the cortex. Subsequently, the excitability of cortical neurons may increase and further help to stabilize ensembles in cortical structures.

It remains largely unknown whether and how excitability fluctuations in different brain regions mediate rule or schema learning. We speculate that similar to learning-induced and retrieval-induced hyperexcitability promoting memory strength and integration, rule learning through repeated trainings may lead to the formation of a stable ensemble representation with sustained higher excitability that lasts several days. During this temporal window, additional learning may be facilitated by recruiting overlapping neurons from the hyperexcitable ensemble with already established synaptic connectivity. Further, enhanced excitability may promote information flow between interacting brain regions and facilitate systems consolidation and the establishment of schema representations in the neocortex.

5. Conclusion and future directions

In this review, we have summarized studies that examine how neuronal intrinsic excitability may regulate three fundamental phases of memory: allocation, consolidation, and updating (Fig. 2). First, neurons with higher intrinsic excitability are more likely to be recruited into a neural ensemble during learning. Second, learning induces an increase in the excitability of ensemble neurons, and this higher excitability might work synergistically with synaptic plasticity mechanisms to facilitate memory consolidation. Third, intrinsic excitability may also contribute to multiple memory updating processes, such as temporal memory-linking, memory integration during retrieval, and rule and schema learning.

A particularly intriguing characteristic of learning-induced increase in excitability is its transient, or dynamic, nature. The time course of excitability after learning can vary across distinct behavioral tasks, different brain regions and cell types, and the diverse experimental methods used to measure it. In a trace eye-blink conditioning task, the excitability in rabbit hippocampal CA1 and CA3 pyramidal neurons maximized after 24 h and returned to basline within 7 days, as shown by a reduction in the size of postburst AHP in slice preparations, while the reduction in spike accommodation (also indicating higher excitability) lasted as long as 3 days after conditioning (Disterhoft & Oh, 2007; Moyer et al., 1996; Thompson et al., 1996). In rodent studies using a contextual fear conditioning paradigm, hippocampal CA1 neurons had higher excitability in brain slices prepared as long as 2 days after the last training session (Crestani, Krueger, Barragan,

Nakazawa, Nemes, Quillfeldt, Gray, & Wiltgen, 2018; Mckay et al., 2009), while a recall of fear memory induced hyperexcitability in dentate granule cells persisted for only 1 h (Pignatelli et al., 2019). *In vivo* electrophysiology recordings and population activity analyses have revealed that different hippocampal subregions varied in terms of how quickly neural ensemble activity turned over across time (Mankin et al., 2012, 2015; Rangel et al., 2014). Studies have shown that CA1 and CA2 population activity patterns changed dramatically with increasing temporal distances of encoding, while CA3 representations stayed relatively stable across time (Mankin et al., 2012, 2015). Interestingly, the dentate gyrus might recruit populations of hyperexcitable new-born granule cells to organize memories across weeks (Aimone et al., 2006, 2009; Rangel et al., 2014). Nevertheless, we still lack a comprehensive analysis of the time course of excitability change in brain regions involved in learning a particular task (e.g. the amygdala-hippocampus-prefrontal cortex circuit in a contextual fear conditioning paradigm), which will be critical to further understand the dynamic integration and updating of memories, and how the brain organizes and stores memories over time. A caveat in systematically studying excitability alteration patterns is that the tools used to measure excitability may influence the results. Therefore, it is important to consider the methods used when interpreting the results.

Besides serving as a regulator for local ensembles in various brain regions, intrinsic excitability potentially also serves as a link between ensembles across brain regions. Intracellular and extracellular oscillations may bind information processing across brain regions by synchronizing windows of memory allocation and plasticity. For instance, short bursts of excitability changes, such as those driven by intracellular theta oscillations, may mediate learning in a similar way to the longer-term fluctuations in excitability discussed above. Indeed, the coherence between local oscillations in interactive brain regions enhanced the information flow between them (Akam and Kullmann, 2010, 2014; Bosman et al., 2012; Fries, 2005; Von Stein & Sarnthein, 2000) and this process might be mediated by fluctuations in excitability. Interestingly, in CA1 place cells, intracellular theta increased in frequency and power as the animal entered the cell's place field (Harvey, Collman, Dombeck, & Tank, 2009), which might amplify the effect of oscillations on memory processes. In addition, cells with a higher excitability had stronger intracellular theta both inside and outside of their place fields (Lee et al., 2012) indicating that hyperexcitable cells might be more sensitive to global oscillations, further enhancing their impact on learning. Finally, beyond place cells, the hyperexcitable cells recruited into ensembles across brain regions may engage in coherent oscillations from interacting regions and facilitate the synchronization of dispersed ensembles into systems.

Additional insights into excitability and oscillations come from theoretical studies. Computational models have suggested a relationship between intrinsic excitability and gamma oscillations (40–100 Hz), where gamma-paced excitation and inhibition selected the most highly excited cells in a given network to fire during gamma cycles (De Almeida et al., 2009a, 2009b). An explicit parameter in this computational model was the AHP, which varied across brain regions and even across cells within a region. The magnitude of this AHP could influence the oscillatory spiking patterns of a single cell, which then results in different patterns of excitation to downstream regions and leads to activation of different memory ensembles. Thus, the heterogeneous intrinsic excitability of neural populations may dictate the identity of neurons active in an ensemble during oscillatory network states.

As we have reiterated throughout this review, there is much research yet to be done to achieve a deeper, more comprehensive understanding of intrinsic excitability across the distinct phases of memory. Currently existing experimental tools have separately provided us with an understanding of the dynamics of single-neuron excitability (whole-cell patch clamp), synaptic integration within a neuron (dendritic patch clamp, dendritic calcium imaging, neurotransmitter release imaging), and population-level activity (IEG expression, TetTag, neuronal calcium imaging, *in vivo* electrophysiology recordings). Although these techniques can directly or indirectly measure excitability, they all have limitations. Patch-clamp recording can provide direct and accurate quantification of intrinsic excitability but is relatively low throughput. Techniques based on IEG expression, such as TetTag and catFISH, enable visualization of populations of cells, but are done *in vitro* and can only report cell activation that may or may not be a direct result of changes in excitability. Calcium imaging can indirectly indicate excitability in a large group of neurons but lacks temporal resolution. The advent of large-scale recording techniques that allow simultaneous recording of neuronal and dendritic excitability in a population of neurons *in vivo* would allow scientists to broadly probe intrinsic excitability changes and structural reorganization dynamically, and provide us with better insight into the neural mechanisms underlying the dynamic processes of memory formation and integration.

While no tool exists that covers the entire breadth of these investigations, promising new technologies have already been developed to advance research in intrinsic excitability. Genetically encoded voltage indicator (GEVI) imaging offers the unique ability to optically record changes in voltage within individual neurons across populations, with a time-scale significantly more sensitive than the current standard of optical imaging (e.g. calcium-based imaging) (Adam, 2019; Cao et al., 2013; Chamberland et al., 2017; Fan et al., 2020; Piatkevich, Murdock, & Subach, 2019; Piatkevich, Bensussen, et al., 2019; St-Pierre et al., 2014; Yang et al., 2016; Villette et al., 2019). Moreover, GEVIs have the ability to capture both subthreshold and suprathreshold activities and have fluorescence modulation across the physiological range of membrane potentials, including hyperpolarization. GEVIs are ideal candidates to monitor changes in intrinsic excitability parameters, such as postburst AHP and single AP properties, in a large population of neurons in awake behaving animals (Adam, 2019; Fan et al., 2020; Piatkevich, Bensussen, et al., 2019; Villette et al., 2019), which is difficult to achieve with traditional electrophysiological methods. The recent development of new generations of GEVIs and corresponding ultra-fast two-photon imaging methods have made it possible to further examine alterations in the excitability of subcellular compartments *in vivo* such as dendritic backpropagating APs (Adam, 2019; Piatkevich, Bensussen, et al., 2019; Villette et al., 2019). Combined with synaptic level tools, including the tagging and manipulation of highly active individual synapses during specified time windows (Gobbo et al., 2017; Hayashi-Takagi et al., 2015), these novel technologies will enable investigation of how synaptic and intrinsic plasticity integrate and interact at a population level and how they correlate with animal behavior.

Finally, while numerous models and theories have been proposed to describe the formation and transformation of memory in animal research, it will be important to test and validate these ideas in the human brain. Recent studies using functional magnetic resonance imaging (fMRI) have provided evidence that memory dynamics observed in rodent studies across time also existed in the human brain (Schlichting & Frankland, 2017). Hippocampal activation patterns evoked by specific encoding events have been shown to be more similar for those encoded close in time than those encoded at distant times in human subjects (Schapiro, Kustner, & Turk-Browne, 2012), and neural pattern similarity predicted a person's later subjective judgment of the temporal proximity of memories (Ezzyat & Davachi, 2014). Moreover, temporal proximity of memory encoding could both increase the efficiency and accuracy of inferential judgements and enhance the integration of memories in the human brain (Zeithamova & Preston, 2017). Another recent study in humans demonstrated that temporally close memories (encoded 3 h but not 7 days apart) were linked using a fear conditioning paradigm (Yetton, Cai, Spoormaker, Silva, & Mednick, 2019) comparable to the behavioral paradigm used in rodent studies (Cai, 2016; Rashid et al., 2016). Another form of memory integration observed in animals, memory schemas (a process of incorporating new information into pre-existing knowledge) (Tse et al., 2007), has also

been observed in humans through longitudinal studies using fMRI to track the brain regions and activity involved in their development (Sommer, 2017).

While these studies provide evidence of similar processes in humans to those observed in animals, recording methods with higher spatial and temporal resolution are needed to address a number of important questions, such as how single neuron activity and excitability may be involved in memory formation and updating. The invasive nature of currently available techniques has restricted the recording of single neuron activity in awake behaving humans to a very limited number of circumstances, such as in drug-resistant epileptic patients or with the implantation of a deep brain stimulation device for the treatment of psychiatric or movement disorders (Rutishauser, 2019). Novel minimally invasive techniques that will enable investigations at a higher resolution are needed to achieve a fuller understanding of the dynamic processes of memory in the human brain.

Intrinsic excitability is more than simply a byproduct of neural activity. The fluctuating intrinsic excitability results from the regulation of signalling pathways and protein syntheses and is primarily determined by the distribution and function of somatic and dendritic ion channels. As we have discussed throughout this review, the intrinsic excitability exerts lasting effects on memory from the initial encoding to consolidation. Moreover, its transient nature makes intrinsic excitability an ideal cellular property governing the dynamic process of integration during memory updating. Intrinsic excitability promotes both the stability and flexibility of memories, helping to shape, update, and organize memories accumulated across a lifetime.

CRediT authorship contribution statement

Lingxuan Chen: Conceptualization, Writing - original draft, Writing - review & editing. **Kirstie A. Cummings:** Writing - original draft, Writing - review & editing. **William Mau:** Writing - original draft, Writing - review & editing. **Yosif Zaki:** Writing - original draft. **Zhe Dong:** Writing - original draft. **Sima Rabinowitz:** Writing - original draft, Writing - review & editing. **Roger L. Clem:** Writing - original draft, Writing - review & editing. **Tristan Shuman:** Writing - original draft, Writing - review & editing. **Denise J. Cai:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition.

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