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Mechanisms underlying working memory for novel information

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In this Opinion article we describe a theory that the brain mechanisms underlying working memory for novel information include a buffer in parahippocampal cortices. Computational modeling indicates that mechanisms for maintaining novel information in working memory could differ from mechanisms for maintaining familiar information. Electrophysiological data suggest that the buffer for novel information depends on acetylcholine. Acetylcholine activates single-cell mechanisms that underlie persistent spiking of neurons in the absence of synaptic transmission, allowing maintenance of information without prior synaptic modification. fMRI studies and lesion studies suggest that parahippocampal regions mediate working memory for novel stimuli, and the effects of cholinergic blockade impair this function. These intrinsic mechanisms in parahippocampal cortices provide an important alternative to theories of working memory based on recurrent synaptic excitation.

Introduction

Research has demonstrated the existence of multiple memory systems, including working memory, which is defined as a limited capacity system for the temporary storage and manipulation of information for cognitive tasks [1,2]. Many initial fMRI studies of working memory in humans used highly familiar stimuli such as letters and words, and focused primarily on a system that includes prefrontal cortex and parietal cortex [1–3]. However, electrophysiological and lesion studies in animals and recent imaging studies suggest that temporal lobe structures play a crucial role in working memory [4–6]. Here we present the theory that working memory for novel information differs from working memory for familiar information, proposing that novel stimuli require additional cellular mechanisms within the entorhinal and perirhinal cortex, whereas prefrontal and parietal systems are sufficient for maintaining familiar stimuli in working memory. We are not proposing a double dissociation between the systems, but instead we suggest that the prefrontal–parietal system alone is insufficient for maintaining information that has no prior representation in the brain. We hypothesize that cholinergic activation of these single neuron mechanisms results in persistent spiking activity without excitatory synaptic transmission between neurons (Figure 1 and Box 1). This theory provides an alternative to many physiological models of working memory that use recurrent excitation between neurons to maintain persistent spiking [7]. Those other models, based on recurrent excitation, can only maintain information consistent with previously formed representations (i.e. familiar information).

In this article, we evaluate experimental data [6,8–10] and computational modeling [11–13] that support the proposal that working memory for novel stimuli requires additional cellular mechanisms activated by acetylcholine in the entorhinal cortex and other parahippocampal cortices and that differ substantially from the mechanisms required for working memory for familiar stimuli. In each section we first evaluate evidence for the role of this cellular mechanism in the active maintenance of novel stimuli for working memory, and, if evidence is available, we consider a role for this mechanism in encoding long-term memories.

Lesion studies

Working memory

Lesion studies suggest an important role for parahippocampal regions in working memory for novel stimuli. Although cortical regions including prefrontal cortex and parietal cortex show activity during working memory for novel stimuli [14], these regions do not seem to be sufficient to perform working memory for novel stimuli at normal levels when parahippocampal regions are lesioned, although they are sufficient to maintain normal working memory for familiar stimuli. Many studies test working memory with delayed match to sample (DMS) or delayed non-match to sample (DNMS) tasks, in which a stimulus is presented as a sample, and after a delay period, the effective maintenance of the sample information is evaluated by presenting a test stimulus and requiring subjects to indicate whether the test matches the sample. Lesions of parahippocampal regions in monkeys do not cause impairments on DMS tasks with small numbers of highly familiar stimuli [15,16], and parahippocampal lesions in humans also do not cause impairments on tasks using highly familiar stimuli such as the digit span task [17]. By contrast, parahippocampal lesions in monkeys and humans do cause impairments when large sets of trial-unique (i.e. novel) stimuli are used in DMS [18] and DNMS [19] tasks, even at delays as short as 8–10 s. This occurs even though matching tasks are easier (show lower error

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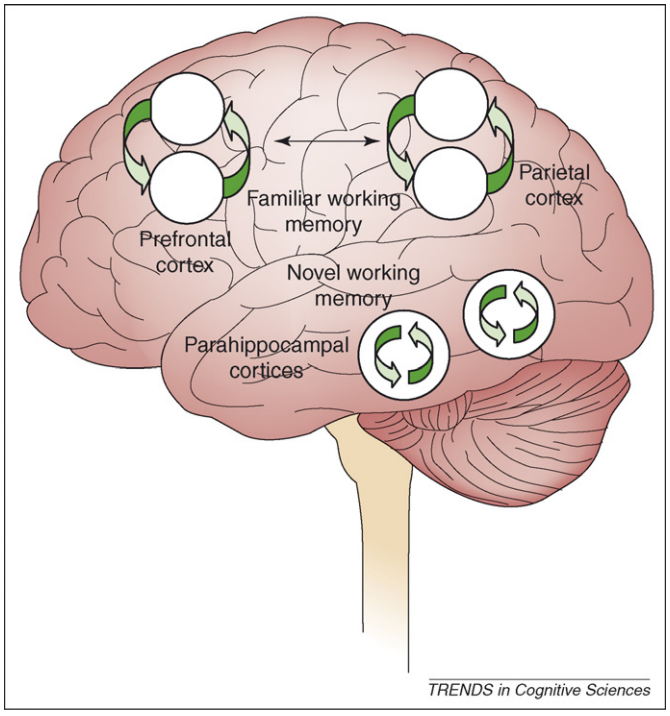

Figure 1. Brain mechanisms underlying working memory for novel and familiar stimuli. Previous work suggests that working memory for familiar stimuli is mediated by excitatory recurrent connections between neurons in prefrontal cortex and parietal cortex, as indicated by the arrows connecting the white discs that represent neurons. We propose that these recurrent connections are insufficient for working memory for novel stimuli. In contrast, we suggest that working memory for novel stimuli is mediated by neurons in parahippocampal cortices. These parahippocampal neurons have intrinsic mechanisms for persistent spiking activity, involving single cell regenerative mechanisms (represented by arrows within the white discs) that do not require prior synaptic modification.

rates) with novel stimuli [5], because there is less interference from previous exposure to the stimuli, and because there is a stronger difference in item familiarity between the sample and the test stimuli. Importantly, parahippocampal lesions cause impairments in working memory for conjunctions and for complex non-verbalizable stimuli even at short retention intervals [20,21] and they disrupt working memory for novel configurations of stimuli in the Brown–Peterson task [17]. Parahippocampal lesions also disrupt memory for novel visual objects (see [22] for a review). These data indicate that parahippocampal cortices are important for mediating working memory for novel stimuli, even over periods of 8–10 s, whereas areas outside of the parahippocampal region seem to be sufficient for normal delayed matching function with small numbers of highly familiar stimuli [15,16], but are not sufficient to support normal working memory for novel stimuli after parahippocampal lesions.

Encoding of long-term memory

The brain mechanisms necessary for working memory for novel stimuli might also be important for encoding new long-term memories. Parametric studies have shown that lesions to parahippocampal structures cause stronger impairments for matching at longer delays (e.g. 1 min, 10 min) than at short delays (e.g. 0.5 s) [18,23]. These data indicate that parahippocampal structures are important for supporting long-lasting representations. Lesions of the hippocampus alone cause anterograde amnesia, as demonstrated by impairments of long-term memory, including free recall and paired associate memory [19], and these effects seem to be stronger in cases in which portions of the entorhinal and perirhinal cortex have also been affected [19]. These data suggest that the entorhinal and perirhinal cortices interact with the hippocampus in the formation of long-term memories, involving the strengthening of synapses to form a long-lasting representation [12,24,25].

In summary, behavioral data show that parahippocampal lesions impair both working memory and encoding of novel stimuli, consistent with the data on fMRI activity in these regions, which is reviewed in the next section.

Functional magnetic resonance imaging

Working memory

Functional neuroimaging studies support the idea that working memory for novel stimuli requires the additional recruitment of parahippocampal regions. Early functional neuroimaging studies of working memory emphasized the role of prefrontal and parietal cortices, and most studies were carried out using highly familiar stimuli, including letters, words, simple objects and spatial locations [26]. Surprisingly, these early fMRI studies of working memory did not report activity within parahippocampal regions such as perirhinal or entorhinal cortex, although these areas had previously been shown to be necessary for DNMS and DMS tasks in monkeys [18,19,23]. The non-human primate lesion studies motivated an fMRI study by Stern *et al.* [5] that demonstrated differential activation for novel versus familiar stimuli during performance of a 'two-back' working memory task, in which subjects respond if a stimulus matches the stimulus seen two stimuli previously. This study showed that working memory for a highly familiar set of complex visual images primarily activated prefrontal and parietal cortices, whereas the same task using novel (trial-unique) visual images strongly activated parahippocampal structures in addition to prefrontal and parietal cortices [5]. Activation of parahippocampal structures associated with working memory for novel stimuli has also been shown in an event-related fMRI study using novel face stimuli [27,28].

Encoding of long-term memory

Increased parahippocampal activity for novel stimuli might also be important for the encoding of long-term memories. A recent fMRI study by Schon *et al.* showed changes in blood flow in the entorhinal cortex and other parahippocampal cortices during the delay period in a DMS task with novel stimuli [6,29]. This delay period fMRI signal in parahippocampal cortices was correlated with subsequent memory function in a long-term recognition test at the end of the experiment [6] (Figure 2), and might be closely related to the persistent spiking activity described below in the section on cellular physiology [10,30]. Thus, persistent activity might facilitate the encoding of novel stimuli in humans. When subjects were

Box 1. Computational modeling of single cell mechanisms for working memory

The hypothetical link between the cellular data and behavioral data presented here has been described and analyzed in detailed computational models. Lisman and colleagues initially proposed that intrinsic afterdepolarization such as that shown by Klink and Alonso [8] and others forms a cellular basis for working memory [11,56]. This section describes models showing how this cellular mechanism could underlie working memory [11–13,57] and encoding into episodic memory [24,25,56].

Working memory

Biophysical compartmental simulations of layer II non-stellate neurons [13] demonstrate how the Alonso current can underlie the sustained delay period spiking in the entorhinal cortex seen with extracellular unit recording in rats and monkeys during the performance of delayed matching tasks [10,30]. These detailed models extended earlier models showing that afterdepolarization could underlie working memory function [11,56]. Compartmental simulations of layer II neurons were combined in network simulations that included detailed models of inhibitory interneurons [13] to demonstrate the mechanisms for many additional response properties of single neurons recorded in the entorhinal cortex, including match and non-match enhancement and suppression [10,30].

Models also illustrate why intrinsic mechanisms for persistent spiking provide a mechanism for working memory for novel stimuli [40], in contrast to most models using excitatory recurrent connectivity, which are primarily appropriate for familiar stimuli. Familiar stimuli can be retained in a circuit in which Hebbian synaptic modification of glutamatergic synapses has been induced previously, as shown in Figure Ia. Modified connections (arrows) allow reverberatory interactions between neurons in the pattern, causing persistent spiking (Figure Ia). By contrast, the neurons responding to novel stimuli do not have excitatory recurrent connections with other neurons coding the same pattern. However, as shown in Figure Ib, the internal regenerative process mediated by the Alonso current allows maintenance of spiking activity for novel stimuli in the absence of synaptic interactions. Figure Ic shows that blockade of cholinergic receptors will block the cellular mechanisms for persistent spiking, and thereby reduce the capacity to maintain working memory for novel stimuli, as suggested by impairments caused by scopolamine and cholinergic lesions [34,36,40,42].

Encoding of long-term memory

Modeling also demonstrates how these mechanisms could enhance encoding into long-term memory. In particular, the capacity of the entorhinal cortex for maintaining persistent spiking could allow spikes to fall within the narrow time window that is required for spike timing-dependent plasticity [12,24,25], thereby bridging behavioral input that is separated by long time intervals and enabling the formation of associations between sequential patterns. Models of these mechanisms use timing of intrinsic spiking relative to the phase of cortical theta rhythm oscillations to maintain information about the sequential order of an item [12,24,25], consistent with evidence for cholinergic modulation of cortical theta rhythm oscillations. Modeling also demonstrates potential mechanisms for the extended maintenance of graded levels of firing frequency in layer V of entorhinal cortex [58], which could provide a mechanism for maintaining temporal context for memory encoding [59].

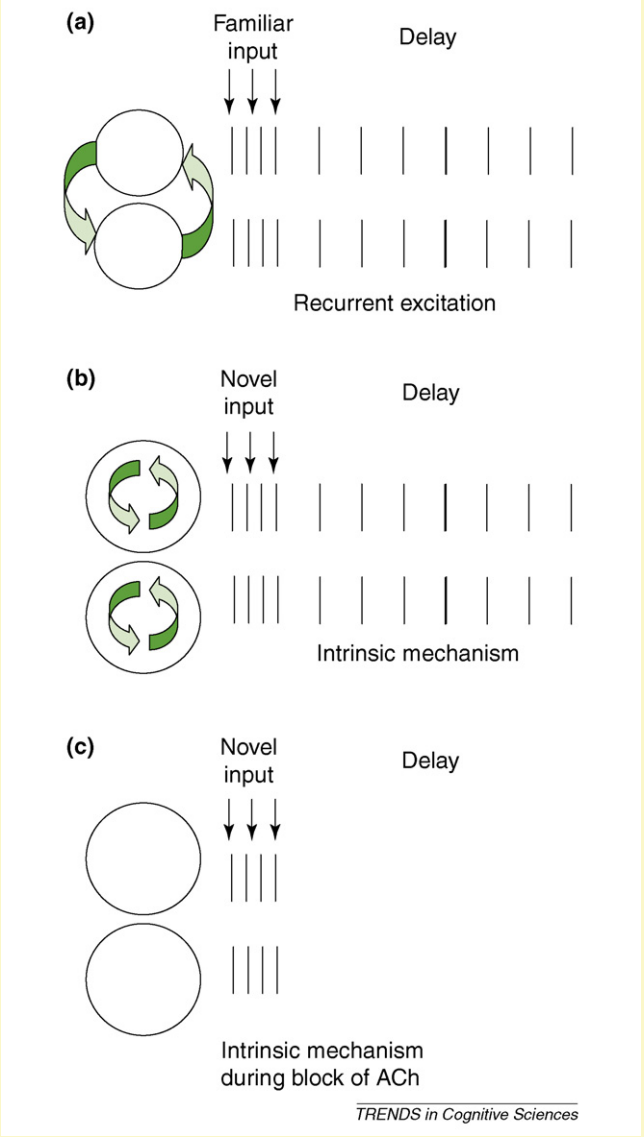

Figure I. **(a)** Maintenance of familiar information does not require acetylcholine, because the familiar input matches the pattern of excitatory glutamatergic connectivity between neurons, allowing maintenance of persistent spiking. The arrows between circles represent excitatory recurrent synapses strengthened by prior learning, which spread activity back and forth between neurons representing the familiar pattern. **(b)** Maintenance of novel information is possible with cholinergic activation of intrinsic mechanisms for persistent spiking (arrows within circles) because individual neurons have internal regenerative mechanisms for spiking without excitatory recurrent connections (discussed in Ref. [40]). **(c)** Blockade of muscarinic acetylcholine receptors (for example by scopolamine) blocks the intrinsic mechanisms for persistent spiking, impairing working memory for novel stimuli.

injected with scopolamine, a muscarinic cholinergic antagonist, fMRI activation in parahippocampal regions that was correlated with subsequent memory was reduced [6], supporting the hypothesis that acetylcholine is necessary for the persistent activity that enhances encoding.

These data indicate that cholinergic modulation in parahippocampal cortices contributes to persistent activity for working memory and encoding of novel stimuli, consistent with results of other cholinergic manipulations reviewed in the next section.

Cholinergic manipulations

Working memory

Studies of the behavioral effects of drugs that block muscarinic acetylcholine receptors support a role for cholinergic modulation in the entorhinal cortex in the short-term retention of novel memories. Systemic injections of muscarinic acetylcholine blockers such as scopolamine impair DMS performance in monkeys at delays on the order of several seconds [31], and impair the arm choice behavior of rats in an eight-arm radial maze

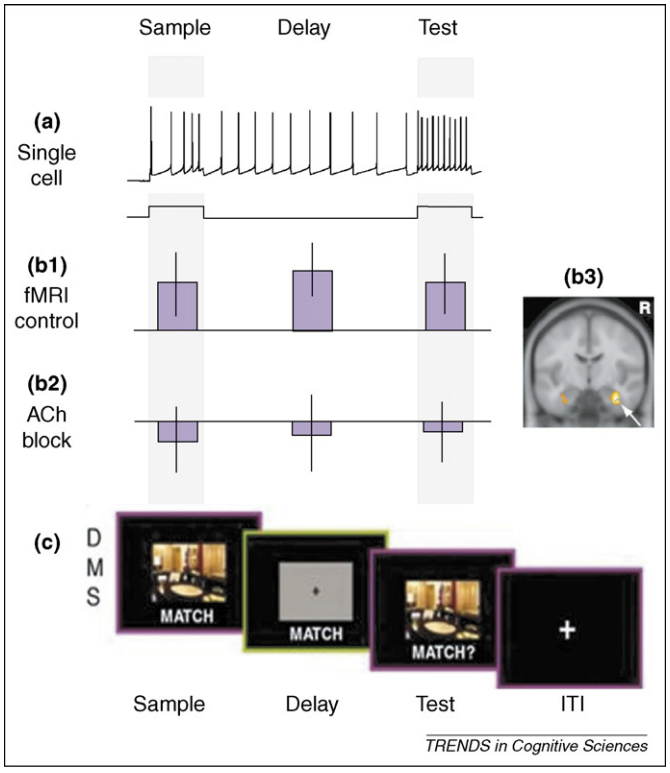

Figure 2. Effect of scopolamine on delay period activity [6,29] in a DMS task, which includes sample, delay and test periods. **(a)** Proposed pattern of delay period spiking activity that could underlie changes in blood flow detected by fMRI during performance of the task. **(b1)** Histogram bars show high levels of fMRI activity in parahippocampal regions during the sample, delay and test periods, which are correlated with performance on the post-scan recognition test. **(b2)** Blockade of acetylcholine (ACh) receptors with scopolamine greatly reduces the activity in perirhinal and entorhinal regions correlated with performance on the post-scan recognition memory task. **(b3)** Location of significant activation in the perirhinal and entorhinal region. **(c)** Scanning occurred during performance of a DMS task, which includes sample, delay and test periods, with inter-trial intervals (ITIs). After scanning, subjects were tested on a post-scan recognition memory task for the individual stimuli.

when there is a delay between the individual choices [32]. In mice, selective knockouts of the m1 muscarinic receptor also cause deficits in DNMS behavior [33].

Muscarinic blockade with drugs such as scopolamine in humans also causes deficits on DMS and n-back tasks [34–36], and on the Brown–Peterson task when letter trigrams that involve novel combinations of well-known elements are used [37]. However, scopolamine injections do not lead to impairments on simple measures of short-term memory such as digit span [38] and the recency component of a serial position curve [39], suggesting a lack of effect on working memory for highly familiar stimuli such as words or numbers. For these stimuli, previously modified synaptic connections might be sufficiently strong to maintain activity without cholinergic modulation.

An experiment by McGaughy *et al.* directly tested the hypothesis that cholinergic modulation regulates memory for novel but not familiar stimuli by analyzing DMS performance in rats that were given injections of a neurotoxin into entorhinal cortex, which selectively lesions the cholinergic innervation to this region [40]. These selective lesions did not impair DNMS function for familiar odors at delays of 15 min, but did cause a significant and selective deficit at 15 min for odors that were novel to the rats. This impairment could be due to loss of the cholinergic modulation of persistent spiking activity, coupled with a loss of cholinergic enhancement of synaptic modification [41]. In monkeys, selective lesions of the cholinergic innervation to the perirhinal cortex caused impairments in DNMS performance at a delay of 30 s for novel visual stimuli [42]. Parahippocampal neurons can maintain persistent spiking for periods longer than 15 min (L.M. Giocomo, B. Tahvildari and M.E. Hasselmo, unpublished) but in the behavioral tasks with long delays it is likely that cholinergic regulation of persistent activity also enhances encoding of novel stimuli through long-term synaptic modification so that later matching can be performed even after persistent activity terminates.

Encoding into long-term memory

The cholinergic lesion studies extend earlier work in monkeys demonstrating that injections of scopolamine into the perirhinal cortex (which probably also affect the entorhinal cortex [43]) impair the encoding of new visual stimuli but not the recognition of stimuli learned before the scopolamine injection [43,44]. By contrast, infusion into the inferotemporal cortex or dentate gyrus did not cause impaired performance [43]. Crossed lesions of cholinergic innervation and cortical regions similarly impair learning of new scenes and objects [45]. Consistent with these data, systemic injections of scopolamine in humans strongly impair the encoding of new words into memory for subsequent free recall or paired associate memory, without affecting the recall of words learned before scopolamine injections [46]. In line with the effects of scopolamine, damage to the hippocampus does not impair digit span [17] but does impair performance on tasks requiring longer retention or retention of complex non-verbalizable stimuli [21]. The data summarized above indicate that scopolamine might be blocking a necessary mechanism for the formation of long-term memories involving novel stimuli in the hippocampus, possibly by inhibiting sustained spiking activity in the entorhinal cortex, which provides input necessary to modify synapses in the hippocampus [25].

In summary, reductions in cholinergic modulation impair working memory for novel stimuli, possibly owing to a blockade of cellular effects that are reviewed in the next section.

Cellular physiology

The proposal of a working memory system for novel stimuli presented here was initially motivated by intracellular single-cell recordings of memory mechanisms [8,47]. Recordings in the laboratory of Angel Alonso demonstrated that single neurons in layer II of slice preparations of the entorhinal cortex, isolated from other neurons by pharmacological blockade of excitatory and inhibitory synaptic transmission, can maintain memory for prior input in the form of persistent spiking activity (Figure 3). This maintenance of persistent spiking depends on the application of acetylcholine or other drugs that activate muscarinic acetylcholine receptors [47] and is blocked by muscarinic antagonists such as atropine [8]. In the absence of acetylcholine, a depolarizing intracellular current injection causes the neuron to fire a train of spikes during the depolarization, but when the current injection is stopped,

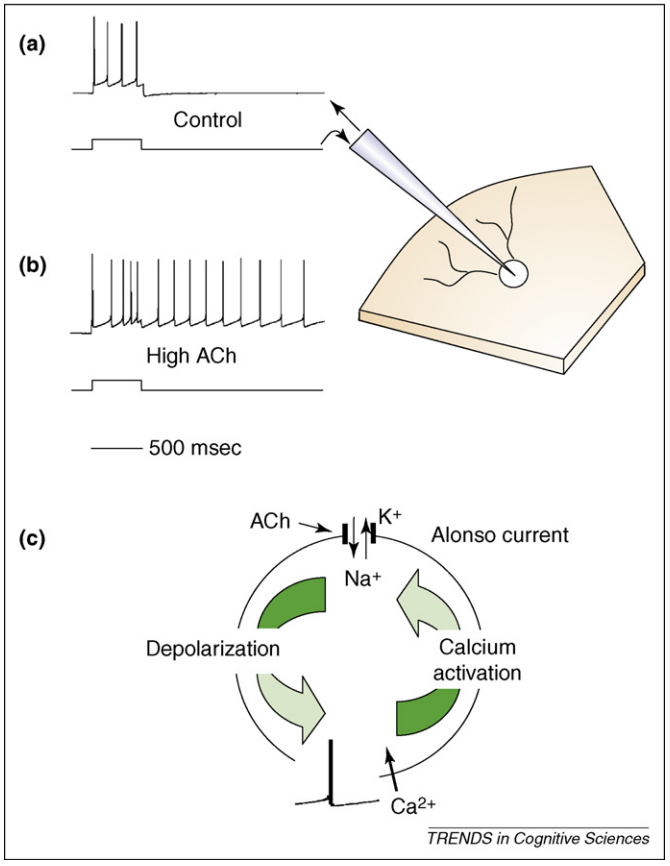

Figure 3. Schematic of persistent spiking observed with intracellular recording from neurons in layer II of entorhinal cortex slices. **(a)** In control conditions, an entorhinal cortical neuron responds to a brief current injection by spiking during the current injection, and falling silent after the current injection ends. **(b)** With activation of acetylcholine (ACh) receptors, the same neuron responds to a current injection with spiking, which persists for many seconds or minutes after the end of the current injection. **(c)** Intrinsic mechanisms of regenerative spiking. The Alonso current is activated by a combination of extracellular ACh and by spiking activity induced by current injection. Spiking activates voltage-sensitive calcium channels that increase intracellular calcium. Calcium activates the Alonso current, which increases Na^+ influx and causes more depolarization. This depolarization causes further spiking activity, which causes calcium influx and further activates the Alonso current, completing a cycle that could underlie persistent spiking.

the membrane potential of the cell falls back to resting potential and the firing stops. However, in the presence of acetylcholine, a current injection of only a few hundred milliseconds in layer II causes the membrane potential to remain depolarized after the current injection is stopped, and the cell continues to generate spikes for an extended period of many seconds or even minutes without current injection or synaptic input.

The phenomenon underlying self-sustained spiking is sometimes referred to as an afterdepolarization or plateau potential. This phenomenon continues even when both excitatory and inhibitory synaptic transmission are blocked, indicating its dependence on intrinsic mechanisms in a single neuron, rather than on excitatory recurrent connectivity between neurons [8]. The effect can return after brief periods of hyperpolarizing current injection, indicating resistance to transient distractors. A similar plateau potential phenomenon has also been described in layer V of prefrontal cortical slices [48]. However, the prefrontal cortex is not sufficient to mediate working memory performance for novel stimuli after parahippocampal lesions [19,22], which suggests that, without prior familiarization, prefrontal cortex neurons might not receive sufficient synaptic input to represent novel sensory stimuli, consistent with a weaker spiking response to novel stimuli compared to familiar stimuli in some experiments [49].

In the entorhinal cortex, plateau potentials seem to arise from a calcium-sensitive non-specific cation current [8,13] that strongly depolarizes neurons. Here we refer to this current in entorhinal cortex as the Alonso current, after Professor Angel Alonso, who died in 2005. This mechanism for intrinsic working memory relies on the conjunction of acetylcholine and cellular spiking [8]. Current injection in the absence of acetylcholine does not initiate sustained spiking. However, in the presence of acetylcholine, the generation of spiking by intracellular current injection or synaptic stimulation causes the neuron to enter an internal regenerative cycle of sustained spiking. Each new spike activates voltage-sensitive calcium channels, and the new influx of calcium activates the Alonso current [13]. This current causes additional depolarization, leading to another spike that again activates voltage-sensitive calcium channels that further perpetuate the cycle (Figure 3c). Box 1 summarizes computational modeling of these single-cell mechanisms for working memory.

In summary, the cellular processes in parahippocampal cortices provide a mechanism of persistent spiking suitable for working memory for novel stimuli, which could also underlie some of the data from unit recording studies in parahippocampal structures reviewed in the next section.

Recording of spiking activity during behavior

The theory that the Alonso current in the entorhinal cortex contributes to the maintenance of working memory is supported by recordings of the spiking activity of single neurons in animals performing delayed matching tasks. Sustained spiking activity during delay periods has been shown for neurons in parahippocampal cortices, including the entorhinal cortex, in rats performing a continuous DNMS task with odors [10] and in monkeys during performance of DMS tasks with complex visual stimuli [30]. Delay activity in the entorhinal cortex proves resistant to distractor stimuli presented between the sample and match stimulus [30]. This is consistent with data from entorhinal cortex slices showing that the spiking activity of single cells will restart after a brief hyperpolarizing current injection [8,13]. Delay activity in the perirhinal cortex does not, however, persist after intervening distractors [50]. No electrophysiological study has yet looked at effects of cholinergic blockade on persistent spiking for novel stimuli in the parahippocampal cortices.

In addition to sustained activity during delay periods, some entorhinal neurons show enhancement of spiking activity for a match stimulus relative to the response to the same stimulus presented as sample, whereas most neurons show suppression of activity in response to a match [10,30] and to repetitions of distractor stimulus [30,50,51]. Thus, there are multiple possible mechanisms for making a memory-guided decision in a matching task – including sustained delay activity, match enhancement

and repetition suppression – that are not mutually exclusive. There is additional suppression as a novel stimulus becomes familiar [52], which might play a crucial role in selectively gating parahippocampal activity to only maintain novel stimuli [53,54]. In summary, unit recording data support the idea that sustained spiking in parahippocampal cortices could provide working memory as a result of cellular mechanisms of persistent spiking.

Summary and future directions

The experimental data and computational modeling reviewed here support the hypothesis that intrinsic single neuron mechanisms in parahippocampal cortices mediate working memory for novel stimuli. Studies using techniques at several different levels support this hypothesis. However, further work at the behavioral level is needed to test whether blockade of cholinergic receptors will selectively impair active maintenance of novel but not familiar stimuli in the same task in humans, possibly by using experimental designs that are similar to those used to show impairments of memory for novel visual objects in amnesic subjects [22].

The work presented here also generates specific predictions about the nature of unit activity in parahippocampal structures. In particular, during the delay period of a DMS task, unit activity should be more sensitive to muscarinic antagonists such as scopolamine for novel than for highly familiar stimuli. Studies have shown that scopolamine does not reduce repetition suppression of unit responses [55], but have not tested scopolamine effects on match enhancement or delay activity (Box 2). Unfortunately, the ability to quantify firing-rate responses to stimuli usually requires showing them repeatedly, thereby reducing their novelty [30], but the effect could be analyzed with a large set of novel stimuli.

The cholinergic mechanisms in parahippocampal structures described here could act as a buffer for long-term encoding [1,12], which has the capacity to integrate and hold information from multiple modalities, to maintain information about the order of items in working memory, and to feed information into long-term episodic memory. The episodic buffer could be supported by a selected subset of neurons firing in response to the multimodal convergent input to the entorhinal cortex. The Alonso current could allow entorhinal neurons coding multimodal components of an episodic memory to persist in activity, representing the distinct relationship between events and items in a novel episode, and allowing encoding into episodic memory in the hippocampus.

The data described here provide a link between the behavioral function of working memory and possible mechanisms at the cellular and circuit level for holding a sustained representation of novel information across a temporal delay. Understanding these physiological mechanisms and relating them to behavior is crucial for our understanding of working memory.

Box 2. Outstanding questions

- Do systemic injections of scopolamine cause stronger impairment of working memory for novel versus familiar stimuli in the same study in humans?
- Does local infusion of scopolamine into entorhinal and perirhinal cortex selectively impair working memory for novel stimuli but not familiar stimuli in rats?
- Does systemic or local infusion of scopolamine reduce single neuron spiking activity in parahippocampal cortices during the delay period of DMS tasks using novel stimuli, but not familiar stimuli?
- Do mechanisms of persistent spiking shown with intracellular recording *in vitro* interact with *in vivo* theta rhythm oscillations in parahippocampal structures [12,25,60]?

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