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# Acetylcholine and the complex interdependence of memory and attention

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Long-standing theories propose that acetylcholine biases memory by slowly shifting hippocampal dynamics to favor encoding or retrieval. However, recent characterizations of acetylcholine functions across multiple spatiotemporal scales suggest that its mnemonic influence is both broader in space, coordinating networks of regions, and narrower in time, having precisely timed consequences, than traditionally thought. Integrating this work, we review evidence for synchronous acetylcholine release across the hippocampus and neocortex, which could favor the encoding of attended and well-represented content during high-cholinergic states. Conversely, we propose that lower acetylcholine levels thought to benefit spontaneous hippocampal retrieval conflict with the high cortical levels necessary for attention-dependent aspects of recollection. We propose that rapid cholinergic mechanisms and neural oscillations may resolve these conflicting retrieval demands.

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## Introduction

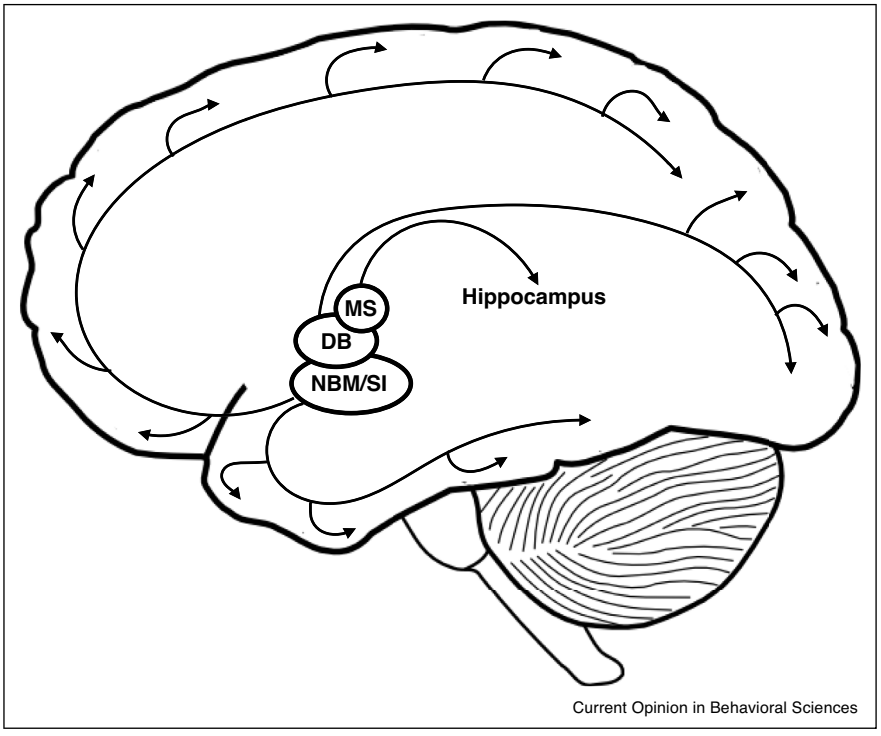
Why do we vividly recall some experiences but forget others? Some formulation of this question remains at the heart of most memory investigations despite decades of fruitful research. Most commonly, memory researchers look to the external world for answers, linking a memory's fate to whether a to-be-remembered experience evokes, for example, emotional responses [1], orientations towards deep semantic or shallow perceptual properties [2], or neural responses in key structures, like the hippocampus [3]. This reactive conception of the brain (and mind) has recently come under criticism [4]. Here too we argue that a more complete picture requires incorporating internally or endogenously sustained states and how they set dynamics to constrain or foster the mnemonic mechanisms evoked by our experiences. To explicate, we concentrate on states associated with one neurotransmitter — acetylcholine — because of its influence over memory processes [5], its fluctuations across multiple timescales [6,7] and its governance over endogenously sustained states [8–10]. We begin by reviewing acetylcholine's effect on core memory mechanisms in the hippocampus in conjunction with long-standing theories relating these physiological effects to memory. Specifically, these theories argue that endogenous fluctuations in acetylcholine resolve distinct requirements of different memory phases (encoding versus retrieval and consolidation) by shifting the hippocampus between modes optimized for each [5,11].

In the second part, we expand our focus beyond mechanisms traditionally considered mnemonic to explore the relationship between neocortical acetylcholine and attention. Despite informative investigations on how acetylcholine influences attention and memory, there remain several important gaps in developing an integrative framework. In particular, the high-cholinergic cortical states thought to facilitate controlled aspects of episodic retrieval [12] appear at odds with the low-cholinergic hippocampal states thought to facilitate the initial reactivation of memories [13].

## Acetylcholine and hippocampal memory mode switching

The hippocampus' irreplaceable contribution to memory is hypothesized to be related to its capacity for representation transformation [21,22] and rapid synaptic plasticity [23]. First, the representation transformation called *pattern separation* is thought to overcome potential interference between memories storing the similar events comprising our lives [24]. Specifically, entorhinal input, which reflects the similarity of experiences, is thought to be recoded into more orthogonalized representations, particularly within the dentate gyrus (DG) subfield [25,26]. Thus, a new memory could be encoded within a set of neurons which are distinct from those storing memories of related events. As this input travels successively through hippocampal subregions, including CA3 and CA1, connections between coactivated neurons are strengthened through long-term potentiation (LTP). This co-activation and resultant strengthening allows individual experiences to be stored as engrams (memory traces) [27]. When presented with new experiences similar to older memories, these

**Figure 1**



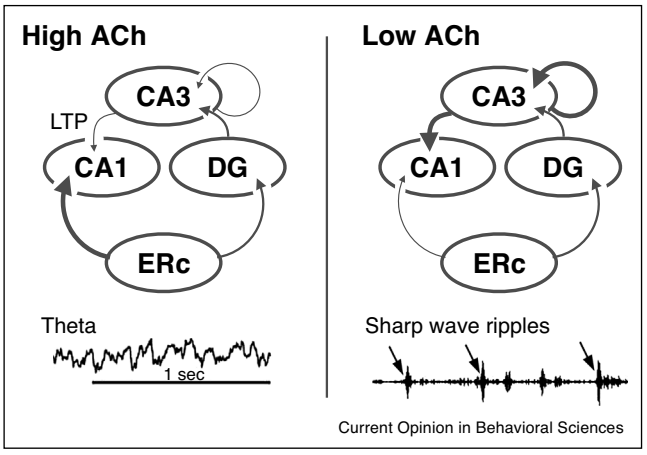

Basal forebrain acetylcholine projections. The hippocampus and neocortex primarily receive acetylcholine input from basal forebrain nuclei [84]. The medial septal nucleus (MS) primarily projects to the hippocampus and entorhinal cortex [85,86]. The nucleus basalis of Meynert (NBM) and related substantia innominata (SI) innervate much of the cortical mantle, particularly prefrontal regions [87], whereas the horizontal and vertical diagonal bands of Broca (DB) innervate primary sensory areas, particularly the visual cortex [88,89].

memories stored in dormant engrams are reactivated via *pattern completion* [25,26]. This reactivation, thus, warps patterns of hippocampal activity to mirror those evoked by the initial experience — a process thought to be supported by recurrent collaterals in CA3 [28]. In a perplexing component of this framework, though, pattern separated DG output must pass through the CA3 network before leaving the hippocampus. Thus, the orthogonalization imposed by DG could be undone by CA3 pattern completion [22,25].

But what causes the hippocampus to engage in pattern separation over pattern completion, or vice versa? One possibility is that shifting levels of acetylcholine separate these processes in time; when acetylcholine levels are high, hippocampal dynamics could be optimized for encoding distinct engrams via pattern separation. Conversely, low acetylcholine levels could promote pattern completion that supports retrieval [5,11] (for recent reviews see Refs. [29,30•]). Low levels, like those experienced during sleep [31], are similarly argued to support memory replay and systems-level consolidation [5]. Supporting this hypothesis, cholinergic antagonists impair memory formation, particularly in high-interference conditions [32], but minimally impact recall and recognition [32,33]. This dissociation could reflect acetylcholine's impact on neural activity in the hippocampus. In rodents, acetylcholine inhibits DG neurons [34•], which may promote pattern separation by increasing sparse coding. Additionally, acetylcholine inhibits the recurrent collateral activity in area CA3 that mediates pattern completion, but does not inhibit pattern-separated input from DG to CA3 [35]. In area CA3, optogenetic stimulation of acetylcholine neurons and acetylcholine agonist application suppress sharp-wave ripples [36,37] — oscillatory patterns linked to memory reactivation [38], consolidation [39,40], and retrieval [38,41]. Thus, high levels of acetylcholine in the hippocampus may inhibit memory reactivation within CA3, allowing separated DG representations to dominate hippocampal output.

High acetylcholine levels are also thought to promote encoding by biasing the CA1 hippocampal subfield to process environmental input, carried by the entorhinal cortex, rather than recalled memories, carried by CA3 input. In fact, acetylcholine suppresses excitatory transmission from CA3 to CA1 [42] (Figure 2), and manipulations thought to increase acetycholine release similarly shift the strength of different CA1 inputs [43]. Although

**Figure 2**




Schematic illustration of proposed cholinergic modulation of the hippocampus. High cholinergic states suppress recurrent (CA3) transmission and favor entorhinal cortex input to area CA1, biasing the system toward processing externally perceived over internally retrieved signals. Simultaneously, high acetylcholine (Ach) levels facilitate LTP, to encode new experiences, and theta oscillations. Conversely, low cholinergic states favor recurrent (CA3) transmission over entorhinal cortex (ERc) input and are associated with sharp wave ripples. Theta and ripple images adapted from Vandecasteele *et al.* [37].

acetylcholine reduces the driving force of CA3 input, it facilitates LTP between active CA3 and CA1 neurons [44,45] and, in doing so, could promote new memory encoding. In summary, the combined effects of cholinergic modulation in the hippocampus are highly suggestive of a mode switching function, biasing the hippocampus toward encoding distinctive memories during periods of high innervation and reactivating stored memory traces during periods of low innervation.

To confer memory benefits, though, these cholinergic memory states would have to be attuned to the environment in some way so that we perform the right memory operations at the right time. Fortunately, there is evidence that the detection of expectancy violations by the hippocampus could provide precisely this type of control. Area CA1 is positioned to compare expectations stored in memory (generated through CA3 pattern completion) to what's actually happening in our environment (generated through entorhinal input) [46–48]. In turn, hippocampal expectancy violation signals are thought to drive acetylcholine release, promoting new learning. Conversely, when expectations are confirmed (CA3 inputs match entorhinal inputs to CA1), low acetylcholine levels are maintained to promote the further generation of predictions while reducing the encoding of unsurprising — and thus uninformative — outcomes [11,46]. Expectation violation, though, is just one factor influencing acetylcholine release; as described below, the variety of factors influencing cortical acetylcholine release and their consequences raise questions about how cortical and hippocampal acetylcholine levels are coordinated and how their interactions impact memory.

## Cortical acetylcholine and sustained attention

Our capacity to sustain attention is closely linked to fluctuations in neocortical acetylcholine across multiple time scales. The longest shifts in acetylcholine levels coincide with our circadian rhythms: acetylcholine levels gradually rise during active wakefulness and fall during quiet rest and slow-wave sleep [31]. These slow tonic shifts in acetylcholine mirror shifts in our capacity to sustain attention, which peaks in the morning and then declines throughout the day [49]. However, even within the waking phase, tonic acetylcholine levels can change dramatically in response to our activities; acetylcholine levels increase during tasks that require vigilant attention [8–10] and decrease during tasks that require minimal attentional control [8]. Interestingly, higher tonic acetylcholine levels augment the fast phasic acetylcholine release (Box 1) that is necessary for detecting targets in rodents [10]. Thus, slow neuromodulatory release and rapid phasic release appear to be interdependent and together may generate a cascade of effects that ultimately maintains high levels of attention.

Paralleling its effects within the hippocampus, tonic cholinergic signalling is thought to improve attention by prioritizing feedforward over recurrent neural activity [50,51]. To enhance feedforward processing, acetylcholine increases response gain (selective spiking to a stimulus) in excitatory sensory [52,53] and prefrontal neurons [54] that receive feedforward thalamic input. Furthermore, acetylcholine increases the time-locking of neural responses to attended sensory events [55] which is thought to boost processing of attended input [52,56,57]. On the other hand, acetylcholine desynchronizes local populations of neurons, reducing local

**Box 1 Acetylcholine as a Neurotransmitter or Neuromodulator?**

Acetylcholine projections from the basal forebrain (Figure 1) have historically been considered neuromodulatory, shaping the functions of broad sets of neurons via volume transmission rather than direct synaptic release [14]. In line with this view, ultrastructural studies revealed that cholinergic varicosities rarely form synapses [15] and microdialysis studies showed that extracellular acetylcholine levels slowly fluctuate across seconds to minutes [16]. Recent methodological innovations, however, suggest that acetylcholine may also have more targeted effects at faster timescales. For instance, acetylcholine release following target detection [7] and reinforcement [17], has rapid consequences on cortical function [18]. Improved imaging techniques have also identified thin, previously overlooked synapses at cholinergic varicosities that may mediate rapid responses in the hippocampus [19•]. Interestingly, the authors note that substantial 'spill over' of acetylcholine beyond these small synapses is likely to mediate slower and prolonged effects. Combined, this work suggests that acetylcholine serves as both a targeted neurotransmitter and a sustained neuromodulator [7,20].

field potentials [55,57,58], particularly in low frequency bands [59]. This decorrelated neural activity is thought to reflect suppressed lateral and recurrent transmission, consistent with evidence that acetylcholine suppresses horizontal communication between cortical columns [53]. Combined, these cholinergic effects could enhance processing of important sensory input, while dampening processing of internal and external distractions. Notably, more temporally precise phasic acetylcholine release could further enhance the preferential processing of motivationally relevant stimuli – a speculation consistent with evidence that phasic acetylcholine release in rodents is precisely timed for the detection of target stimuli [10].

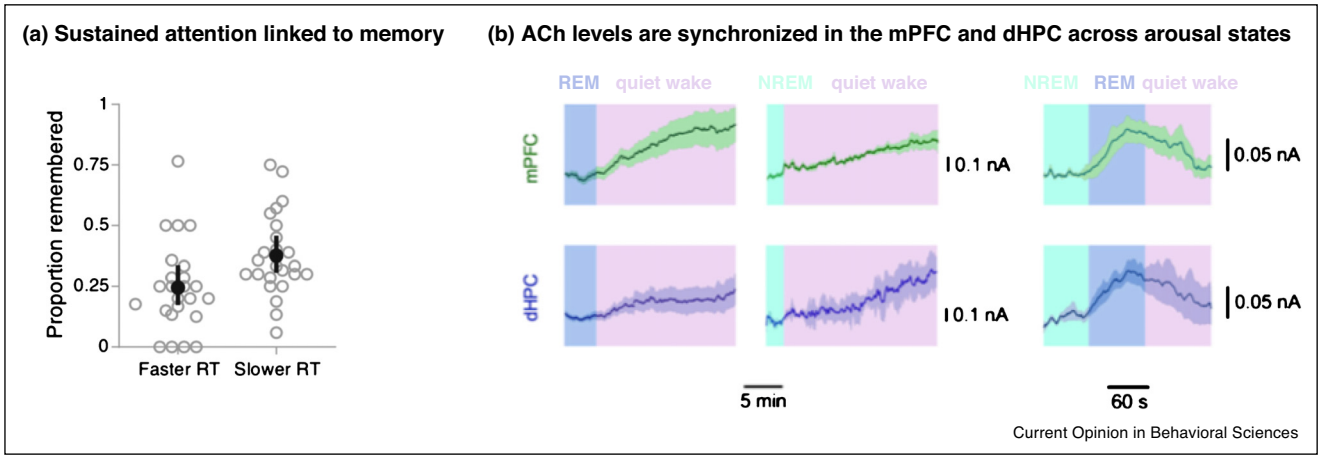
## Selective and sustained attention and memory encoding

At a cognitive level, memory encoding depends on selective attention. Taxing attentional resources during encoding with a secondary task impairs memory formation [60,61]. Moreover, selectively attending to specific features of the environment improves memory for attended input at the cost of memory for unattended input [62,63].

While the relationship between selective attention and memory is well established, we are only beginning to understand how fluctuations in sustained attention impact memory encoding. Recently, deBettencourt *et al.* [64•] showed that fluctuations in sustained attention, indexed by patterns of reaction time within individuals, predicted whether people formed memories, such that people were less likely to form memories during attentional lapses (Figure 3). To-be-remembered images in this study were presented one at a time; but fluctuations in our attentional state may modify the encoding of complex experiences in everyday life even more profoundly. Indeed, sustained attention could support our capacity to selectively attend to and form rich and detailed memories for motivationally relevant input. However, heightened attention might carry a cost to encoding less relevant information. This interaction between sustained attentional states and selective attention may be particularly relevant for children and older adults who cast a broader attentional net and better remember less relevant information [65,66].

From a physiological perspective, sustained attention and memory encoding may, in part, be linked by global fluctuations in acetylcholine [51,67] (Figure 3). Recent work suggests that acetylcholine levels in the hippocampus and cortex are synchronized during tasks and throughout sleep-wake cycles [68•] (Figure 3). This coordination may be adaptive, ensuring that high fidelity cortical representations of relevant content are encoded by the hippocampus [67]. This also raises the possibility that the apparent dependence of memory on sustained attention reflects coordinated release of acetylcholine in the hippocampus and cortex, rather than attention directly supporting memory formation. Notably, understanding the physiological links between memory and attention could inform classic theories that propose attending to input is sufficient to drive memory encoding in the hippocampus [69].

**Figure 3**




**(a)** Participants were more likely to later remember images presented during a good attentional state (indexed by preceding periods of slow RTs) as compared to a poor attentional state (indexed by preceding periods of fast RTs) from deBettencourt *et al.* [64•]. The grey open circles represent individual participants, whereas the solid black circles and error bars represent the sample mean and 95% confidence intervals of the mean. **(b)** A representative example of tonic choline currents for different arousal states and state transitions in the medial prefrontal cortex (mPFC; top) and dorsal hippocampus (dHPC; bottom). Figure is adapted from Teles-Grilo Ruivo *et al.* [68•]. Color coding represents different measured states (i.e., REM sleep, non-REM sleep, quiet wakefulness). Choline activity levels were remarkably coordinated in the mPFC and the dHPC across arousal states and arousal state transitions.

## High cortical acetylcholine could promote strategic components of retrieval

The effects of cortical acetylcholine on episodic retrieval are less straightforward than its effects on encoding. This is due to the diversity of processes supporting retrieval, including memory search, evaluation, monitoring, and reactivation. Indeed, while memory retrieval can occur spontaneously in the absence of controlled attention (e.g., recognizing that we've seen a flower), retrieval is often effortful and goal-driven (e.g., trying to recollect where exactly we saw this flower). When searching for a specific memory, executive attentional processes are required. As such, retrieval can be impaired when participants simultaneously perform a second task that taxes attentional resources [60]. Notably, the executive processes, such as cognitive flexibility and working memory, which support controlled retrieval are thought to be optimal when acetylcholine levels in the cortex are high, yet reactivating a memory is thought to be supported by low acetylcholine levels, even in the cortex [6].

A critical question, therefore, is how the brain engages strategic processes to guide memory search *while* reactivating a targeted memory? Endogenous shifts in tonic acetylcholine are too slow to support rapid switching between attentional search and reactivation. One solution could lie in rapid phasic responses that change across milliseconds. As observed when detecting an externally presented target [10], phasic responses could be evoked in response to (i.e., after) reactivating a target memory. The resulting increase in gain could enhance target memory representation, while suppressing weaker associates. Alternatively, neural oscillations, such as gamma and theta, may support rapid shifts in retrieval states [6]. Some early support for this comes from recent work showing an association between acetylcholine release with hippocampal theta [70] and cortical theta-gamma coupling [71]. Moreover, basal forebrain cholinergic neurons discharge at a rate that is highly correlated with cortical gamma and theta power [72]. This has led to the speculation that acetylcholine modulates cortical gamma and theta activity. Although the function of frontal theta is unclear, some evidence suggests that theta may separate encoding and retrieval operations in time. In particular, memory encoding and retrieval appear to be optimal at different phases of the theta cycle [73], allowing rapid switching between memory operations during high cholinergic innervation. Moreover, in one theory [74], higher inhibition in one phase of theta enables the strongest representations to be activated, whereas lower inhibition enables activation of competing memories. While this model has been used to explain retrieval-induced forgetting [74], it can be extended to understand strategic retrieval; low inhibition could reactivate a particular cue's many associates, with irrelevant ones pruned away during high inhibition phases (Box 2).

**Box 2 Open Questions**

- How coordinated is acetylcholine release across neocortical and hippocampal targets? While some findings show coordination between mPFC and hippocampal levels [68•] there are demonstrations of both coordinated and independent release across PFC, parietal, and occipital regions [75,76], indicating targeted release is possible and common.
- What (if any) 'online' benefits are conferred by sustained attentional lapses, and are they related to low acetylcholine states? Does spontaneous retrieval flourish during these periods, or are they only beneficial for 'offline' processes, like consolidation?
- What are the neural dynamics of memory search? We speculate that rapid alternation between brain states that support memory reactivation and controlled processing or inhibition could be key.
- Prior knowledge can facilitate new memory formation [77] and retrieval can facilitate rapid memory consolidation [78]; under what circumstances do the processes underlying distinct memory phases interact synergistically versus competitively?

## Conclusion

Can a deeper understanding of neuromodulation shed light on why, what, and when we remember? We see the contributions of this approach to be threefold. First, the multiple timescales (tonic shifts versus phasic signals) over which neurotransmitters like acetylcholine fluctuate identify biologically grounded time-windows relevant for memory. In just one example, fluctuations of hippocampal modulation across seconds [34•] inspired the discovery of highly specific memory biases in the seconds following novelty detection [79–82]. This framework could be extended to recast well-documented mnemonic fluctuations across longer acetylcholine-related timescales, such as time of day [83]. Second, considering neural mechanisms at the neurochemical rather than brain structural level may shed light on the interdependence of cognitive concepts like memory and attention. These mechanisms may reduce ambiguity in their definitions and neural mappings by reconceptualizing them in terms of constituent neural processes, such as gain, plasticity, and feed-forward versus recurrent transmission. Lastly, neuromodulation adds adaptive dynamics to the brain. Rather than cognition arising in response to stimuli, it becomes the interaction between stimuli and ongoing brain states — states which may be optimized based on recent outcomes, learned associations, context, goals, and more. Thus, incorporating the neuromodulatory lens extends beyond the mechanistic level to illuminate what memory is really for.

## Conflict of interest statement

Nothing declared.

## CRediT authorship contribution statement

**Alexandra L Decker:** Conceptualization, Writing - original draft, Writing - review & editing, Funding acquisition. **Katherine Duncan:** Conceptualization, Writing - original draft, Writing - review & editing, Funding acquisition.

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