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Hippocampal contributions to memory for time: evidence from neuropsychological studies

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Time and space are two critical elements of episodic memory that are supported by the hippocampus. Yet, until recently, there has been much greater focus on the involvement of this structure in spatial than in temporal features of memory. Here we highlight evidence from neuropsychological studies of patients with medial temporal lobe lesions, which have provided evidence that the hippocampus is critical for multiple facets of time, even in tasks that are not typically considered episodic. These studies show that the hippocampus supports memory for first, event duration, second, temporal order, and third, temporally discontiguous experiences. Overall, these findings align with theoretical models suggesting that the hippocampus codes for the temporal context of unfolding events.

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Introduction

Episodic memory refers to the recollection of experiences that are oriented within a specific temporal and spatial context [1]. Extensive research has highlighted the critical role of the medial temporal lobes (MTL) and, more specifically, the hippocampus in episodic memory [2]. Although early neuropsychological studies brought to light that MTL lesions are associated with impairments in memory for both the temporal and spatial features of events, theoretical understanding of the role of the hippocampus in temporal memory has lagged behind that of understanding its role in spatial memory. The last decade has seen a renewed interest in identifying the conditions under which the hippocampus contributes to time, and the neural mechanisms by which it does so. Drawing on both earlier and more recent work on this topic, in this review we highlight how neuropsychological studies of amnesic patients with MTL damage have provided an important test bed for understanding the role of the hippocampus in processing elements of time. These studies provide critical converging evidence for lesion and single-cell recording studies involving non-human animals as well as functional neuroimaging studies in humans (reviewed in [3,4•,5]). Here, we discuss studies examining the effects of MTL lesions on memory for (1) temporal duration, (2) temporal order, and (3) temporally discontiguous events. This work suggests that the hippocampus plays a critical role in many facets of timing, not only in tasks that directly probe aspects of events but also those in which temporal aspects indirectly support performance.

Memory for temporal duration

A number of paradigms have been used to assess memory for the duration of an event or the interval between two events (see Box 1). The cognitive processes involved in these tasks differ markedly. In particular, tasks such as temporal discrimination and reproduction not only require estimation of a temporal duration, they additionally require that a reference-duration be encoded and maintained in working memory. Although some temporal discrimination [6,7] and reproduction [8,9] studies suggest impairment following MTL lesions, the role of the hippocampus in these tasks and its precise contribution is unclear.

Focusing on tasks with demands more narrowly focused on temporal estimation, some evidence suggests that the MTL is not critical for temporal duration judgments on the order of *seconds*: Patients with MTL damage demonstrate normal production of durations up to 38 s [8] and 96 s [10]. Yet, contrary to these findings, one study of epilepsy patients with temporal lobe resection (including both medial and lateral temporal lobe structures), showed production deficits for durations as short as 5 s in patients with right, but not left, lesions [11].

In one of the few studies to examine judgments of temporal duration on the order of *minutes*, patients with left or right temporal lobe resection showed a variable pattern of performance across a range of intervals (between 1 and 8 min) in a production task; they were impaired for some intervals and not for others, with no systematic effect of duration. In a verbal estimation task,

Box 1 Assessment of temporal duration estimation

A variety of tasks assess estimation of temporal duration (see Section 1). These include tasks that require *judgments* about a duration and tasks that require *production* of a duration. Examples of judgment tasks include temporal bisection tasks, which require judging whether a given duration is closer to one of two reference-durations (one shorter and one longer) and verbal labeling tasks, which require estimation of duration in verbal measurement units. Production tasks involve the producing of a given duration from a verbal time label or based on the amount of time that has elapsed (i.e. reproduction). Another production task designed to measure the interval between two events is the peak interval procedure, in which a motor response needs to be emitted at the appropriate time to receive a reward. Although this procedure has been used extensively in the animal literature [60] it is less common in human studies.

A helpful heuristic in tasks that assess temporal duration estimation is the distinction between prospective and retrospective judgments [23,61]. This distinction maps onto conditions in which participants at the outset of the experiment are aware or naïve, respectively, that they will be required to provide estimations of time. Although MacDonald and colleagues [23,61] have suggested that the hippocampus plays a more prominent role in retrospective than in prospective judgments, there are nonetheless conditions under which the hippocampus is critical for prospective time judgments (see Section 1, which discusses prospective time estimation tasks).

there was no impairment for intervals up to 3 min, but there were group differences for intervals between 4 and 8 min, reflecting poor performance in patients with left temporal lobe resections [12]. An important limitation of all these studies, however, is that they involve patients with lesions extending outside of the MTL.

Relevant to this issue, a recent study by Palombo *et al.* [13••] examined judgments of temporal duration in patients with damage mainly restricted to the MTL, including a subset of patients with focal hippocampal lesions. Patients were asked to make forced-choice judgments about the length of time that had elapsed in a nature-based video clip (Figure 1). Patients were impaired at making temporal estimations for durations greater than 4 min, but not for durations less than 90 s, with the hippocampal-only patients demonstrating the same pattern of impaired and spared performance as the full group. This dissociation cannot be accounted for by task difficulty, as performance across conditions was equivalent in the healthy controls. Notably, this study was motivated by rodent work from Jacobs *et al.* [14] in which rats with hippocampal lesions were likewise impaired in making forced-choice judgments of temporal discriminations involving long, but not short, temporal intervals. Thus, although preliminary, this evidence converges on the idea that the hippocampus may be critical for making duration judgments on the order of minutes, but not on the order of seconds.

Intriguingly, non-human animal studies involving single-cell recordings show that the hippocampus has robust signals that represent elapsed time. That is, ensembles of cells in the hippocampus (dubbed 'time' cells) have differential firing patterns depending on how long ago an event occurred [15–17]. Whereas many of these studies examine time-cell patterns on the order of seconds, some work suggests that the hippocampus codes for time even on the order of minutes or longer [18–20].

Although it is still unclear precisely how these time cells are causally linked to cognitive processes, it has been suggested that the existence of time cells allows for the recovery of temporal context (i.e. what and when information) (e.g. [19,21••,22]), which can support inferences about duration. Yet the findings of Palombo *et al.* and Jacobs *et al.* that short duration judgments are intact following hippocampal lesions appear to be at odds with evidence that there are time cells in the hippocampus that code for both short and long durations. This apparent contradiction can be reconciled by the speculation [13••,14,23] that time estimation for intervals in seconds may be accommodated by redundant cortico-striatal timing mechanisms known to be critical for duration judgments within this temporal range [24]. Nonetheless, as discussed below, hippocampal time cells — regardless of duration — may be essential for coding higher-order aspects of temporal mnemonic processing.

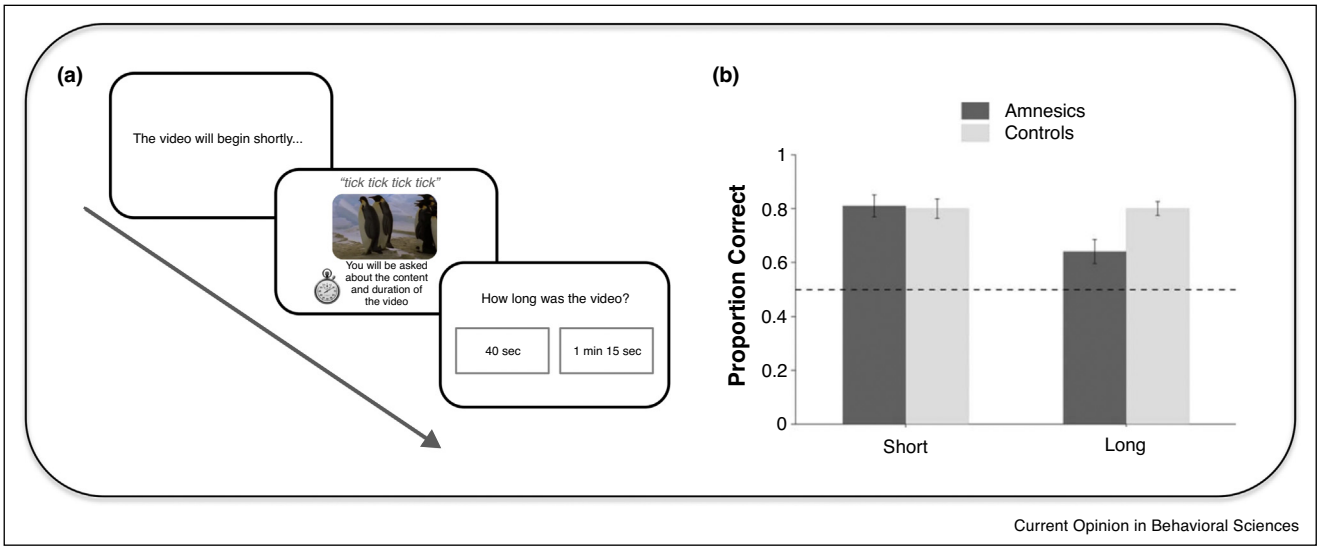
Memory for temporal order

Patients with damage to the MTL are impaired on a range of temporal-order tasks, including those involving recency, sequencing, or list discrimination ([25–29] but see [30]). Although concomitant item recognition deficits have been observed in some studies, temporal-order deficits remain when item recognition is deliberately matched to healthy controls by varying exposure duration (e.g. [28,29]).

Studies assessing the role of the MTL in memory for temporal order typically require explicit judgments about the order of stimuli, but more recent evidence suggests that the MTL is also involved when memory for temporal order is assessed implicitly. Schapiro and colleagues [31] used a paradigm involving the incidental encoding of sequences with embedded temporal regularities and examined subsequent recognition memory for intact (targets) versus recombined (foil) sequences in a patient with an MTL lesion and healthy controls (Figure 2).[1] Unlike controls, the patient was unable to discriminate target from foil sequences, despite her ability to recognize constituent target items above chance.

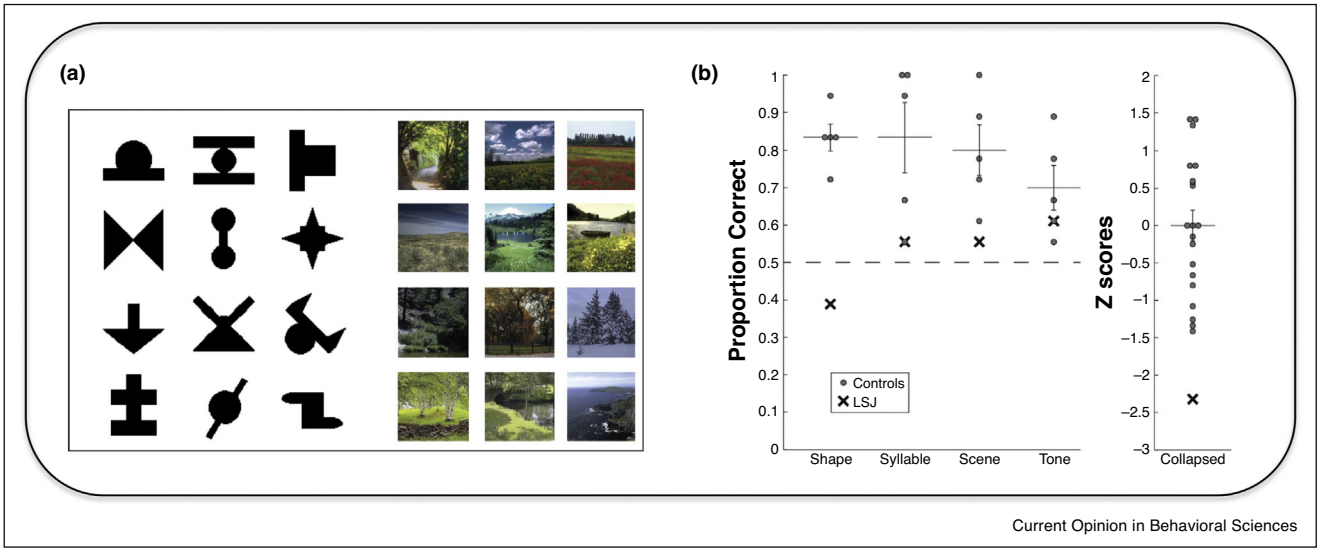
[1] Although a subset of control participants had some level of awareness of the temporal regularities imposed in the task, there were no significant differences in performance between participants with and without awareness.

Figure 1



Memory for temporal duration in amnesia. **(a)** Amnesic patients with medial temporal lobe lesions and healthy controls made forced-choice judgments about the length of time that had elapsed in a video clip depicting a nature documentary. A ticking clock sound played simultaneously during the video to denote passing time. **(b)** Patients were significantly impaired at making temporal estimations for durations longer than 4 min ('long' condition), but not for durations less than 90 s ('short' condition).
Source: Adapted from Palombo, Keane, and Verfaellie [13••] with permission.

Figure 2



Memory for temporal order in amnesia. **(a)** An amnesic patient (patient LSJ) with medial temporal lobe damage and healthy controls made forced-choice judgments about the familiarity of triads of visual (shapes and scenes) and auditory (syllables and tones; not shown) stimuli. At study, participants viewed a continuous stream of stimuli that contained sequential regularities. At test, stimuli were presented either in the same sequential order in which they had previously been presented (i.e. targets) or were recombined (i.e. foils). **(b)** Unlike healthy controls, patient LSJ was unable to discriminate intact from foil sequences across all stimulus types. Chance is denoted with a dashed line. The right-sided graph depicts performance as *z* scores and collapsed across all versions of the task. Patient LSJ fell 2.32 standard deviations below the mean of the healthy controls.
Source: Adapted from Schapiro, Gregory, Landau, McCloskey, and Turk-Browne [31] with permission.

Allowing for greater neuroanatomical specificity than the foregoing studies, two single-case studies of patients with damage restricted to the hippocampus have demonstrated impaired temporal order in the context of normal recognition memory performance [32,33]. For example, Mayes *et al.* [33] showed a deficit for temporal order in a hippocampal-only patient across a range of tasks. Notably, the patient was impaired at judging the order of words in sequentially presented word pairs, even though word-pair recognition was normal and the tasks were of equivalent difficulty in controls. This finding suggests that distinct mechanisms are involved in item-order and item-item associative binding. A dissociation between spared recognition and impaired temporal order has also been observed in hippocampal-lesioned rodents (e.g. [34]). Moreover, within the autobiographical domain, Dede *et al.* [35•] recently showed that whereas healthy controls tended to recall events from a staged walk in the correct chronological order, patients with mainly hippocampal lesions described the walk in a manner that was unrelated to the order of events. These findings align well with neuroimaging studies that have shown hippocampal activation during both the successful encoding [36] and successful retrieval [37,38] of temporal-order information.

A critical next step is to determine mechanistically how the hippocampus organizes temporal information. One compelling idea that has received considerable traction suggests that hippocampal time cells encode a temporal context (referenced above) that gradually evolves over time and allows for experiences to be bound to appropriate moments (e.g. [19,21••,22]). Originally used to explain contiguity effects in free recall [39], such a temporal context mechanism can potentially account for the coding of a variety of temporal relationships among stimuli. Consistent with this notion, several neuroimaging studies have demonstrated that hippocampal activity patterns are sensitive to changes in temporal context (e.g. [40,41]), and that hippocampal pattern similarity is predictive of temporal memory judgments [40,42].

Howard and colleagues [19] have further suggested that the recovery of temporal information involves a 'jump back in time' mechanism. At the neural level, a jump back is instantiated through co-activation of hippocampal cells that overlap in time. A given ensemble of cells remains activated — in a gradually evolving fashion — in response to a stimulus such that its firing temporally overlaps with another ensemble of cells' firing in response to a different stimulus. As a result, recovery of a given stimulus can lead to the retrieval of the context (and related stimulus information) that preceded it, thereby providing access to temporal-order information. Several recent studies provide supportive evidence for the involvement of hippocampal cells in encoding temporal-order information (reviewed in [21••], also see [43•]).

Memory for temporally discontiguous events

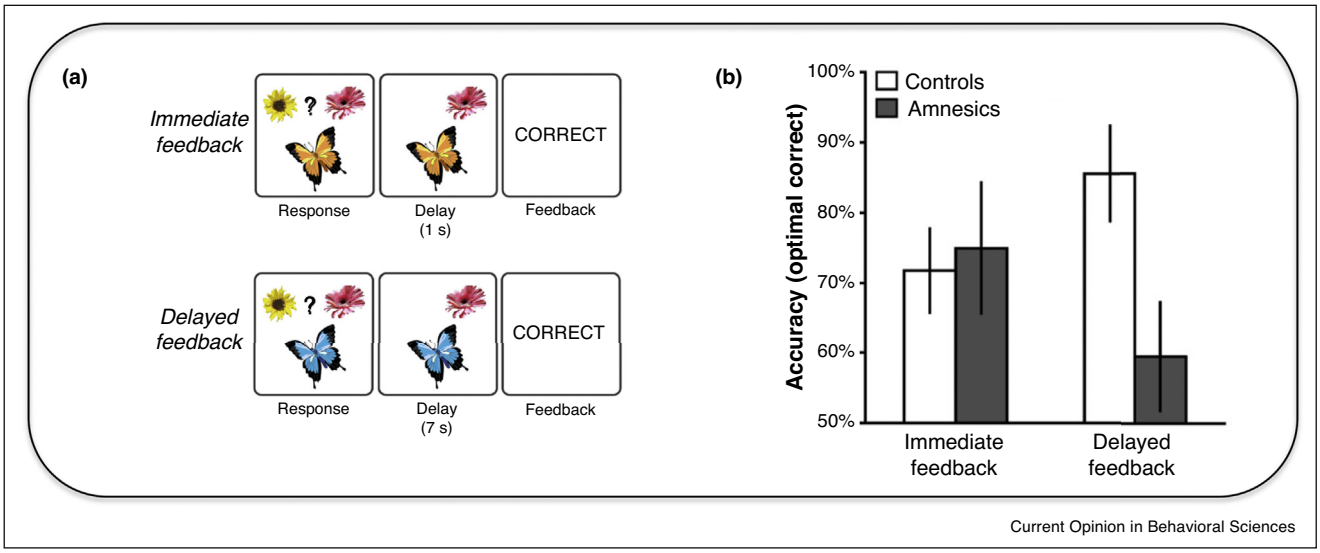
In addition to its involvement in temporal order, the hippocampus also plays a role in memory for temporally discontiguous events, as demonstrated by studies involving conditioning. Specifically, the temporal separation of a conditioned stimulus (CS) and an unconditioned stimulus (US) by a short temporal interval, denoted as 'trace' conditioning, severely impairs learning in patients with MTL damage. Yet, patients are typically not impaired when the CS and US overlap in time, as in 'delay' conditioning ([44–47], but see [48,49]). Though this observation has come mainly from across-study comparisons, spared delay but impaired trace conditioning has also been demonstrated within the same study [50]. Again, a limitation of these studies is that the patients have varying lesion profiles within and outside the MTL, although the findings are consistent with animal work involving lesions limited to the hippocampus [51–53] as well as fMRI studies (see e.g. [54]).

Mechanistically, the observed deficit in trace conditioning following hippocampal damage has been interpreted as a 'bridging the gap' impairment, wherein the hippocampus is required to overcome stimulus discontinuity between the CS and US [55]. By contrast, such bridging is not required when the CS and US overlap in time, as in delay conditioning. A similar bridging mechanism has been postulated to account for a study of instrumental learning [56], which showed that patients with MTL damage are impaired in learning stimulus-response-outcome associations when feedback is delayed by several seconds but perform normally when feedback is provided immediately (Figure 3). Akin to the aforementioned interpretation of trace conditioning impairments, the authors suggested that the hippocampus might be necessary to bind the appropriate cue-related response to the outcome over a delay, thereby resolving temporal discontiguity (see also [57] for corresponding findings of hippocampal activation in normal subjects during delayed feedback learning).

The findings from trace conditioning and delayed feedback learning can be interpreted in two distinct ways. On the one hand, they can be taken as evidence that the role of the hippocampus in temporal processing is not limited to episodic memory tasks. On the other hand, it is possible that when tasks require bridging of a temporal gap, hippocampally based episodic mechanisms involved in encoding temporal context are mandatorily recruited. Also debated is the link between awareness and such putative episodic mechanisms [50].

The notion that the hippocampus bridges temporal gaps can accommodate the above findings but is not sufficient to explain the observation that in some human (e.g. [44]) as well as non-human animal (e.g. [51]) trace-conditioning studies, conditioned responses are emitted, but are poorly

Figure 3



Memory for temporally discontiguous events in amnesia. **(a)** Amnesic patients with medial temporal lobe lesions and healthy controls made forced-choice judgments in a probabilistic feedback-based learning task with interleaved immediate (1 s) and delayed (7 s) feedback. At study, participants learned via trial and error which flower a given butterfly preferred, with different butterfly stimuli used for each condition. **(b)** Performance during a critical test phase revealed that patients were impaired at learning in the delayed feedback condition but not in the immediate feedback condition.
Source: Adapted from Foerde, Race, Verfaellie, and Shohamy [56] with permission.

timed. Moreover, even in some rodent delay-conditioning studies that use a longer CS, ill-timed conditioned responses have been documented (e.g. [58]). Such findings may be better understood with reference to the notion that the hippocampus 'jumps back in time' (discussed above). Specifically, a *jump back* is thought to provide information about how long ago the CS occurred so that an appropriately timed conditioned response can ensue ([21••,22], also see [59] for a different view). In other words, the hippocampus does not just serve as a bridge over a delay, but provides a contextual representation of when the CS was first presented. Notably, although this model may provide a more parsimonious account of alterations in the timing of conditioned responses observed in both trace and delay conditioning under certain conditions, it does not explain why hippocampal lesions leave unaffected the timing of responses when shorter-duration delays are employed.

Conclusions and future directions

The last few years have seen a resurgence of interest in the study of memory for time and the involvement of the hippocampus. The findings discussed here broadly align with theoretical models suggesting that the hippocampus supports the temporal context of unfolding events, although a number of unanswered questions remain. Moving forward, additional human lesion studies, especially those involving patients with focal lesions, will help resolve some of these issues. In particular, such studies can help to distinguish conditions in which the human hippocampus is *involved* from conditions in which the hippocampus is *critical* for aspects of temporal processing. Relatedly, the examination of various aspects of time within the same group of patients will elucidate relationships among distinct forms of memory for temporal information. Illustrating this point, Shaw and colleagues [10,27] showed that deficits in temporal order in MTL patients were *not* driven by a more basic impairment in duration memory, suggesting that different aspects of time memory are dissociable. Complementary to this idea, cross-domain comparisons (e.g. space, time, and potentially other contextual features) in patients can address whether time should be given 'special' status as a feature of hippocampal functioning or whether it is but one facet of context information to which the hippocampus is sensitive.

Finally, although we focused our review on hippocampal contributions to memory for time, it will be important to determine how the hippocampus interacts with other brain regions (e.g. cortico-striatal circuits) that have been strongly implicated in processing of temporal information [24].

Conflict of interest statement

Nothing declared.

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