Does the Hippocampus Keep Track of Time?

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ABSTRACT: In the present study, we examined the role of the medial temporal lobe (MTL) in prospective time estimation at short and long timescales using a novel behavioral paradigm adapted from rodent work. Amnesic patients with MTL damage and healthy control participants estimated the duration of nature-based video clips that were either short (≤90 s) or long (more than 4 min). Consistent with previous work in rodents, we found that amnesic patients were impaired at making estimations for long, but not for short durations. Critically, these effects were observed in patients who had lesions circumscribed to the hippocampus, suggesting that the pattern observed was not attributable to the involvement of extra-hippocampal structures. That the MTL, and more specifically the hippocampus, is critical for prospective temporal estimation only at long intervals suggests that multiple neurobiological mechanisms support prospective time estimation. © 2015 Wiley Periodicals, Inc.

KEY WORDS: amnesia; time estimation; medial temporal lobes; prospective; lesion

INTRODUCTION

Although it is well accepted that the hippocampus plays a critical role in coding spatial and temporal relations—properties that define episodic memory (Tulving, 1983)—greater empirical focus has been placed on the role of the hippocampus in aspects of space than in aspects of time. However, in recent years, a growing body of evidence indicates a key role for the hippocampus in supporting the retrieval of many elements of time, including duration, recency, and temporal ordering (reviewed in Howard and Eichenbaum, 2013). These aspects of time coding are referred to as "retrospective": They rely on remembered time in hindsight, as in real-world contexts where information about time is incidentally encoded as part of an unfolding experience, but can subsequently be reconstructed. Still, aspects of time coding can also be "prospective," whereby the passing of time is consciously attended to facilitate goal-directed behaviors (MacDonald, 2014; MacDonald et al., 2014). In the laboratory, the distinction between retrospective and prospective time estimation maps onto conditions in which participants, at the outset of the experiment, are naïve or aware, respectively, that they will need to provide estimations of time. By contrast to retrospective judgments of remembered time, the role of the hippocampus in prospective time is less clear as studies have produced mixed findings with respect to prospective time estimations in patients with medial temporal lobe (MTL) lesions (e.g., Shaw and Aggleton, 1994; Perbal et al., 2000, 2001; Noulhiane et al., 2007).

Importantly, recent theoretical proposals have suggested that the role of the hippocampus in prospective time estimation may critically depend on the timescale at which judgments are made (see MacDonald et al., 2014 for discussion): Whereas cortico-striatal networks are thought to support time estimation at shorter timescales, the hippocampus may be more critical for time estimation at longer timescales. In support of this proposal, Jacobs et al. (2013) recently showed that in rodents with hippocampal lesions, temporal discriminations at long timescales (several minutes) are impaired, whereas temporal discriminations of equivalent temporal resolution at short timescales (60–90 s) are unaffected, and even facilitated by hippocampal damage, possibly due to competition between striatal and hippocampal systems (Meck, 2005; Poldrack and Packard, 2003; Lee et al., 2008).

In human studies of prospective time estimation, much of the focus has been on intervals of shorter durations (i.e., milliseconds to <2 min). Consistent with the findings of Jacobs et al. (2013), intact performance following MTL damage has been demonstrated for production[1] of durations measured up to 38 s (Perbal et al., 2000) and 96 s (Shaw and Aggleton, 1994), suggesting that the MTL may not be required for production at shorter durations. And yet, incompatible with this notion, one study demonstrated production deficits as early as 5 s in patients with right (but not left) temporal lobectomy (Perbal et al., 2001). Focusing on time estimation on the order of minutes, Noulhiane et al. (2007) reported that

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[1]Production tasks involve demarcating a target duration (i.e., indicating when a specified time interval has lapsed). Other studies have used reproduction tasks that involve replicating a previously presented interval, but this type of task places heavy demands on initially encoding the to-be-reproduced interval, and thus may not provide a pure metric of time estimation per se.)

TABLE 1.

Demographic and Neuropsychological Characteristics of Amnesic Patients

				WAIS III		WMS III			Volume loss (%)	
Patients	Etiology	Age	Edu	VIQ	WMI	GM	VD	AD	Hippocampal	Subhippocampal
P01	Anoxia/ischemia	65	12	83	84	52	56	55	N/A	N/A
P02	Anoxia + left temporal lobectomy	51	16	86	84	49	53	52	63%	60%[a]
P03	Anoxia	56	14	90	99	45	53	52	70%	–
P04	CO poisoning	59	14	111	117	59	72	52	22%	–
P05	Cardiac arrest	63	17	134	126	86	78	86	N/A	N/A
P06	Cardiac arrest	65	16	110	92	86	78	83	N/A	N/A
P07	Anoxia/ischemia	47	12	103	95	59	68	55	46%	–
P08	Stroke	50	20	111	99	60	65	58	43%	–

Note: Age, age in years; Edu, education in years; WAIS-III, Wechsler Adult Intelligence Scale-III (Wechsler, 1997a); WMS-III, Wechsler Memory Scale-III (Wechsler, 1997b); VIQ, verbal IQ; WMI, working memory index; GM, general memory; VD, visual delayed; AD, auditory delayed; CO, carbon monoxide; Hippocampal, bilateral hippocampal volume loss; Subhippocampal, bilateral parahippocampal gyrus volume loss.

[a]Volume loss in left anterior parahippocampal gyrus (i.e., entorhinal cortex, medial portion of the temporal pole, and the medial portion of perirhinal cortex; (see Kan et al., 2007 for methodology).

patients with left or right MTL resection were impaired in production of 6- and 8-min intervals, but showed more variable performance for shorter intervals (1–4 min). Critically, several of these studies have involved patients with lesions extending beyond the MTL, thus making it difficult to draw parallels to the rodent findings of Jacobs et al. (2013). Further, no human studies have compared performance for short and long intervals in patients with bilateral MTL lesions.

To elucidate the role of the MTL in prospective time estimation, the present study assessed the performance of amnesic patients with lesions restricted to the MTL at both long and short timescales.[2] To be able to align the human and rodent work, we used a human analogue of the temporal discrimination paradigm used by Jacobs et al. (2013). Following these authors, we predict that amnesic patients with MTL damage will show impaired performance at long durations, but intact or even augmented performance at short durations.

METHOD

Participants

Eight patients with amnesia (three women) participated in the study (see Table 1 for demographic and neuropsychological data). Each patient's neuropsychological profile indicated severe impairment limited to the domain of memory. Etiology of amnesia included ischemia or anoxia (seven patients) and status epilepticus followed by temporal lobectomy (one patient). Four patients (P03, P04, P07, and P08) had lesions restricted to the hippocampus (see Table 1), one patient (P01) had a lesion that included the hippocampus and MTL cortices, and one patient (P02) had a lesion that extended beyond the MTL. Patients' lesions are presented in Figure 1 on MRI or CT. Two patients (P05, P06), who had suffered from cardiac arrest, could not be scanned due to medical contraindications and are thus not included in the figure. MTL pathology for these patients was inferred based on etiology and neuropsychological profile. As shown in Table 1, volumetric data for the hippocampus and MTL cortices were available for five patients (P02, P03, P04, P07, and P08) using methodology reported elsewhere (Kan et al., 2007).

Fourteen healthy control participants (seven women) were matched to the patient group in age (62.6 ± 10.1 yrs), education (15.6 ± 2.1 yrs), and verbal IQ (108.7 ± 14.6), which was assessed with the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997a). All participants provided informed consent in accordance with the VA Boston Healthcare System Institutional Review Board.

Materials and Procedure

To enhance the ecological validity of the prospective time estimation task, participants watched video clips (presented in *Eprime*), which depicted unfolding nature-based scenes. Video clips were obtained from wildlife documentaries and were devoid of human activity, stripped of sound, and segmented into 24 unique video clips (four from each of six documentaries) of varying lengths using *QuickTime Player*. Twelve of the videos comprised the "short" condition ($\leq$90 s; two from each of the six documentaries), and twelve comprised the "long" condition (more than 4 min; two from each of the six documentaries). Participants were asked to make time interval discriminations using forced choice, as described below. Each

[2]Although one of our patients had a lesion that extended beyond the MTL, the remaining patients for whom lesion information was available had lesions restricted to the MTL or the hippocampus (see Method).

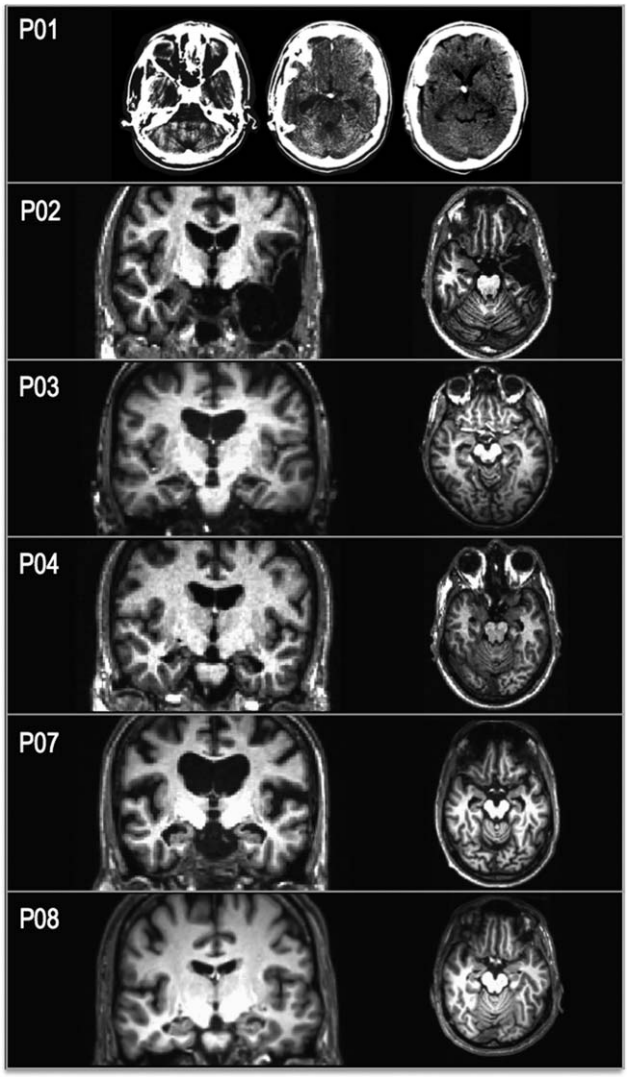

FIGURE 1. Structural CT and MRI scans, which depict medial temporal lobe (MTL) lesions for six of the eight amnesic patients (see Method). The left side of the brain is displayed on the right side of the image. CT slices show lesion location for P01 in the axial plane. T1-weighted MRI images depict lesions for P02, P03, P04, P07, and P08 in the coronal and axial plane.

video was paired with two forced-choice response options, one the accurate duration and the other differing by a mean log value of 0.26 (range 0.25–0.27; short condition: 45 s vs. 1 min 20 s, 50 s vs. 1 min 30 s, 40 s vs. 1 min 15 s; long condition: 4 min 5 s vs. 7 min 20 s, 4 min 15 s vs. 7 min 40 s, 4 min 10 s vs. 7 min 50 s) roughly in accordance with Jacobs et al., 2013. Critically, the mean log temporal differences were identical for the short and long temporal conditions.

There were a total of 24 trials (12 short and 12 long duration) divided between two experimental sessions to avoid fatigue. The experimental sessions were separated by at least 5 days. Groups did not differ in the number of days between sessions ($P = 0.41$). Each session included six short-duration and six long-duration trials. Within each session, each pair of response options was used twice, once with the correct answer being the shorter duration, and once with the correct answer being the longer duration. Across the two instances of a given response option pair, the videos were entirely non-overlapping (i.e., came from different documentaries). Presentation of stimuli was quasi-random, such that videos from the same documentary never appeared in succession, and the two instances of a response option pair never appeared in succession. There were two randomized lists, which were assigned equally often to participants in each group.

Figure 2 provides a schematic of the design. Prior to the first trial, participants were shown an "Instruction" screen and were verbally instructed: "I am going to show you some video clips. Please pay attention to the videos because I will be asking you some questions about the content and the duration of the video. In other words I will ask you about what you saw and how long the video lasted. Please do not count time; it is important that you simply pay attention to the video but do not deliberately count time." Prior to each subsequent trial, participants were reminded of the instructions. Participants next saw a cue screen ("The video will begin shortly") for 2,000 ms, followed by the video onset. To additionally remind participants of the task instructions, participants saw a reminder cue ("You will be asked about the content and duration of the video"), which remained on the screen for the entire duration of the video. Additional reminder cues included a visual image of a clock and a fast audible rhythmic ticking sound (approximately five ticks per sec). This ticking sound was also used to circumvent participants' ability to count time subvocally. Next, participants were given a forced choice probe ("How long was the video?") and the accompanying response options were presented on the screen (see Fig. 2). Across trials, the placement of response options was counterbalanced such that the "correct" answer appeared equally often on each side of the screen, as did the longer duration. Participants were given as much time as they needed to make a response.

Following a 100 msec blank inter-stimulus interval (ISI) screen, participants were probed for the content of the video with one forced choice probe displayed on the screen (e.g., "was there a polar bear?"; "did one of the eagles get injured?"; "did the parrots share food?") and accompanied by response options (yes vs. no; yes always on the left). The correct answer was "yes" for half of the trials. The purpose of this "memory" probe was to ensure that participants were paying attention to the video.

Finally, following a 100 ms blank ISI screen, participants were probed about the length of provided durations. The words "Which time is longer?" were displayed on the screen and accompanied by two choices (see Fig. 2), which were counterbalanced across trials such that the correct answer appeared equally often on the left and right sides of the screen. Participants were given as much time as they needed to make a response. This "math" question was intended to interfere with memory for the durations presented in the preceding time estimation judgment probe so that information from preceding trials would not influence performance on subsequent trials.

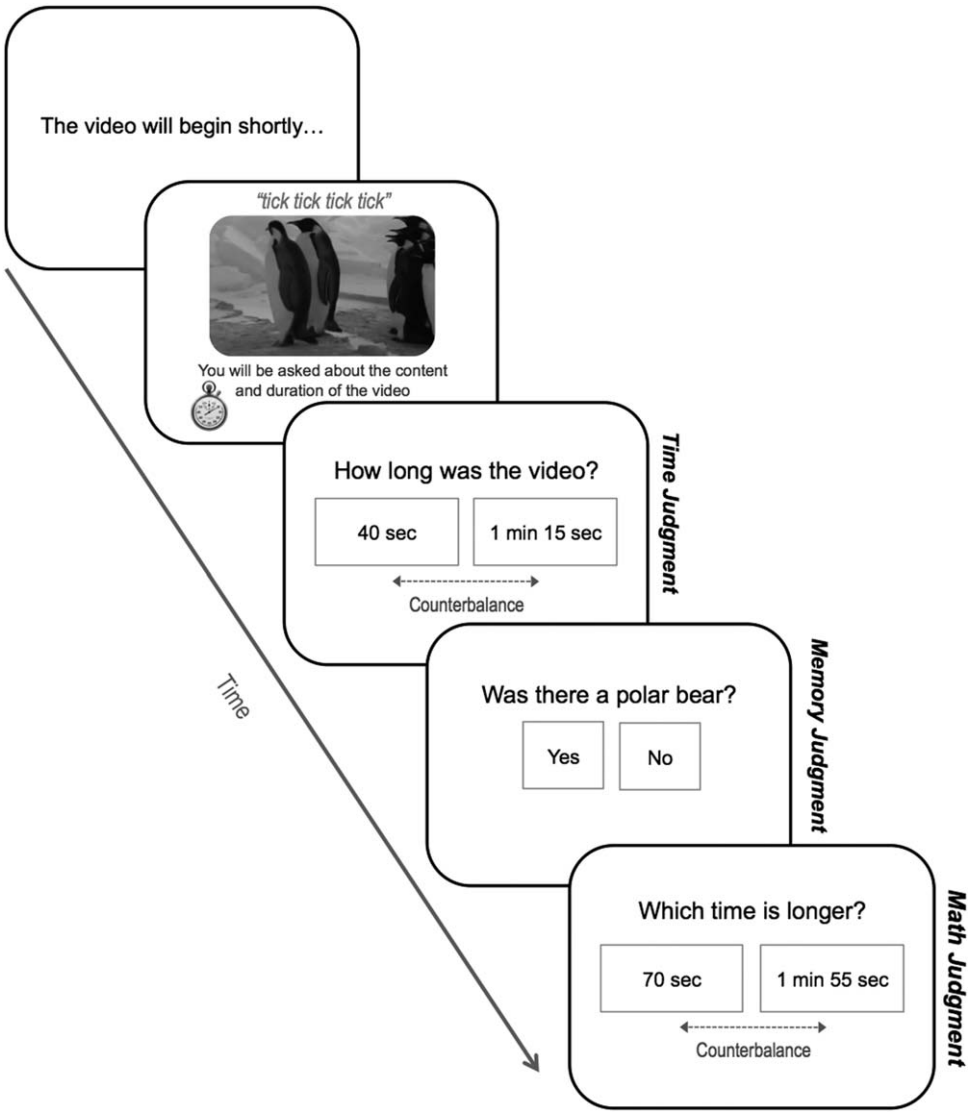

FIGURE 2. Trial overview for the experiment.

All responses were read aloud and keyed in by the experimenter. At the end of the task, participants were asked whether they counted time during the task. All subjects responded "no" to this question with the exception of one patient (P04) who noted "sort of" keeping track of 10-s intervals, despite being told repeatedly not to do so during the experiment. However, exclusion of this patient did not change the pattern of results observed. As such this patient was included in all analyses.

RESULTS

Time Estimation

The dependent measure was proportion correct on the time estimation probes (Fig. 3). A two-way mixed factorial ANOVA with group (amnesic patients, healthy controls) as a between-subjects factor and temporal condition (short, long) as a within-subjects factor revealed a significant main effect of temporal condition ($F_{1,\ 20} = 5.91$, $P = 0.025$, $\eta^2 = 0.23$), a marginally significant main effect of group ($F_{1,\ 20} = 3.92$, $P = 0.06$, $\eta^2 = 0.16$) and a significant group by condition interaction ($F_{1,\ 20} = 4.74$, $P = 0.04$, $\eta^2 = 0.19$). Follow-up t tests revealed no significant group difference in the short temporal condition ($t_{20} = 0.10$, $P = 0.92$, Cohen's $d = 0.05$), but impaired performance in the amnesic group in the long temporal condition ($t_{20} = -3.21$, $P = 0.004$, Cohen's $d = -1.36$). Paired-sample t tests revealed worse performance in the long relative to short temporal condition in amnesic patients ($t_7 = 2.51$, $P = 0.04$; 0.64 versus 0.81). By contrast, control participants demonstrated equivalent performance in the long and short temporal conditions ($t_{13} = 0.23$, $P = 0.82$) and performed below ceiling in both conditions (0.80 in both

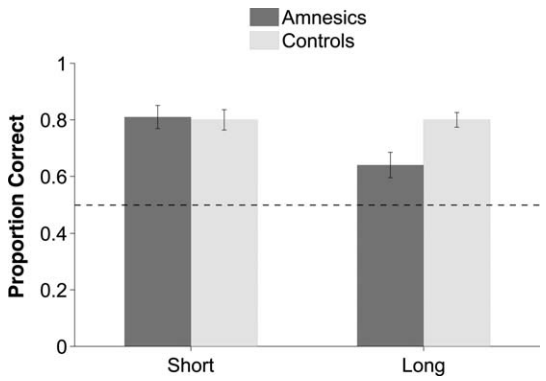

FIGURE 3. Mean time estimation performance for amnesic patients and healthy controls. Chance equals 50% as noted with a dashed horizontal line. Error bars indicate SEM.

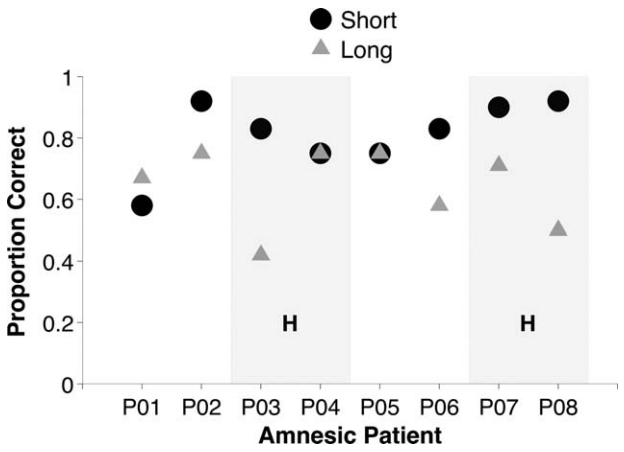

FIGURE 4. Performance of individual amnesic patients on the time estimation task. H = patients with lesions restricted to the hippocampus.

conditions). To determine whether hippocampal damage alone was sufficient to produce the observed pattern, we reanalyzed the data, including only those patients ($n = 4$) with volumetrically confirmed damage restricted to the hippocampus. Critically, the interaction between group and condition remained significant ($F_{1,\ 16} = 7.25$, $P = 0.016$, $\eta^2 = 0.31$). The follow up t tests also revealed a similar pattern of results: no significant group difference in the short temporal condition ($t_{16} = .65$, $P = 0.53$, Cohen's $d = 0.42$) and impaired performance in the amnesic group in the long temporal condition ($t_{16} = -3.19$, $P = 0.006$, Cohen's $d = -1.52$). Figure 4 shows the performance of individual amnesic patients.

To determine if time estimation performance in the short- and long-duration conditions involved similar cognitive demands, we performed correlational analyses in each group. We found no significant association between short and long-duration performance in either patients ($P = 0.60$) or controls ($P = 0.56$). For exploratory purposes, we also computed correlations between time estimation performance in the short condition and working memory scores on the WAIS-III (i.e., digit span forward, digit span backward, arithmetic; Wechsler, 1997a). We observed no significant correlations in either group (all Ps > 0.22). We also computed correlations between time estimation performance in the long condition and episodic memory measures, which were available for patients only (i.e., WMS-III face recognition; Wechsler, 1997b); We observed a moderate correlation for immediate memory, which however was not significant in this small sample ($r = 0.61$, $P = 0.109$). The correlation with delayed memory was not significant ($r = 0.30$, $P = 0.47$).

Memory Performance

The dependent measure was proportion correct on the memory probes. A two-way mixed factorial ANOVA with group (amnesic patients, healthy controls) as a between-subjects factor and temporal condition (short, long) as a within-subjects factor revealed a significant main effect of temporal condition ($F_{1,\ 20} = 41.64$, $P < 0.0001$, $\eta^2 = 0.68$) but no main effect of group ($F_{1,\ 20} = 0.79$, $P = 0.39$, $\eta^2 = 0.04$) and no group by condition interaction ($F_{1,\ 20} = 0.30$, $P = 0.59$, $\eta^2 = 0.02$). The main effect of temporal condition indicated that both the amnesic and the control group showed better memory for the content of the long videos (0.84 and 0.89, respectively) than for the short videos (0.68 and 0.71, respectively). When we included in our analysis only patients with damage restricted to the hippocampus, the pattern of findings was similar. Notably, reduced performance in the short condition in both groups was, in part, driven by poor performance for two items, which were excessively challenging ("Was there a sunset?", 0.18; "Was there a truck?", 0.36), whereas performance for all other items was numerically above chance. When these two items were removed from the analysis, memory performance in the short condition increased to 0.75 and 0.81 for amnesic patients and controls, respectively. However, removal of these items did not change the overall pattern of results.

Math Performance

For consistency, we separated the math interference task into those trials that followed short versus those that followed long videos. A two-way mixed factorial ANOVA with group (amnesic patients, healthy controls) as a between-subjects factor and temporal condition (short, long) as a within-subjects factor revealed no main effect of temporal condition ($F_{1,\ 20} = 1.34$, $P = 0.26$, $\eta^2 = 0.06$), no main effect of group ($F_{1,\ 20} = 2.01$, $P = 0.16$, $\eta^2 = 0.10$), and no group by condition interaction ($F_{1,\ 20} = .64$, $P = 0.43$, $\eta^2 = 0.03$). Amnesic and control participants performed well on the math interference following both long (0.90 and 0.95, respectively) and short (0.93 and 0.96, respectively) videos. Similar results were observed when we restricted the analysis to patients with damage circumscribed to the hippocampus.

DISCUSSION

We investigated prospective time estimation in a group of amnesic patients with MTL damage and healthy controls using

a novel behavioral paradigm that was adapted from rodent work (Jacobs et al., 2013). We found that although patients performed similarly to controls when asked to make temporal discriminations at short intervals ($\leq$90 s), they were significantly impaired at making such judgments at long intervals (more than 4 min). Critically, these effects were observed even when our analysis was restricted to patients who had lesions circumscribed to the hippocampus, suggesting that the pattern observed was not attributable to the involvement of extrahippocampal structures. The results of the present study align with previous research in rodents with hippocampal lesions (Jacobs et al., 2013) that also observed a deficit for long, but not short, temporal intervals using very similar temporal discriminations. Together, these results suggest that the MTL, and more specifically the hippocampus, is critical for prospective temporal estimation only for long intervals, i.e., at least several minutes, and is not required for shorter durations.

The lack of correlation between short and long interval duration, taken together with the selective role of the MTL in long duration estimation, suggests that the short and long interval estimations pose different cognitive demands. Psychological models of prospective time estimation suggest that prospective interval timing requires three elements: a clock (which includes an internal pacemaker and an accumulator), a store of "reference" memories, and a decision (Church, 1984; also see Wittmann, 2009 for review). The onset of an event is accompanied by the opening of a "gate" that permits the accumulation of pulses generated by an internal pacemaker into a temporary accumulator. At the decision phase, the accumulated contents are compared to information stored in a reference memory to indicate how much time has passed. This reference memory is thought to contain vast distributions of stored accumulator values. That our patients were able to make accurate time judgments at short intervals suggests that they have intact judgments (decision stage) and memorial representations of time (reference memory), in accordance with the notion that reference memory is supported by well-established semantic or procedural memories (Perbal et al., 2001). Still, an additional memory demand may stem from the clock mechanism itself: Given the proposed transient nature of the accumulator, it is possible that deficits become apparent at longer intervals because the to-be-estimated intervals exceed the short-term memory capacity of the accumulator and must instead be instantiated within long-term memory. If so, time estimation deficits following MTL damage would be expected whenever durations exceed the capacity of the accumulator. Consistent with this notion, we observed a moderate correlation between performance in the long duration condition and a task of episodic memory, although this correlation did not reach significance in this small patient sample. Yet, we observed no evidence for an association between performance in the short duration condition and tasks of working memory. Such a correlation would be expected on the assumption that the accumulator bears resemblance to "classic" conceptualizations of short-term memory capacity, although this idea is speculative. It should also be noted that, with the exception of Digit Span Forward, the working memory tasks we examined may be more sensitive to central executive demands than to the ability to keep information in mind per se. As such, the relationship between short duration judgments and aspects of working memory remains to be elucidated.

Other models focus less on the involvement of a transient accumulator. For instance, the beat frequency model (e.g., see Matell and Meck, 2000) postulates that time is coded via coincidence detectors (located in the striatum) that receive input from temporally oscillating cortical neurons with different periodic properties that phase "reset" at the onset of a to-be-timed signal. Based on the specific pattern of inputted oscillations at some specified end point (e.g., an environmental change), time duration is computed by comparing the pattern across the inputted neurons to one that is stored in memory (i.e., coincidence detection; Matell and Meck, 2000). Intriguingly, this model also suggests a connection between interval timing and working memory, in that both may rely on similar oscillatory mechanisms that involve the striatum (Gu et al., 2015). Hence, to the extent that the accumulator and striatal beat models implicate working memory in interval timing, they can accommodate the observed dissociation between spared short- and impaired long-term time estimation in our patients. Extrapolating from this idea, there may be two distinct timing mechanisms: a striatal mechanism that supports time estimation at shorter intervals (and may involve working memory) and an MTL mechanism that supports time estimation at longer intervals.

Alternatively, it is possible that the MTL codes timing irrespective of duration, but that additional timing mechanisms, such as those supported by the striatum, also support timing at short intervals, and thus "rescue" performance following MTL damage during prospective time coding. In support of redundant timing mechanisms, striking overlap in temporal coding has been observed across hippocampal, striatal, and medial prefrontal neurons for shorter intervals (MacDonald et al., 2011; Adler et al., 2013; Kim et al., 2013).

The notion that the hippocampus supports timing regardless of duration can be accommodated by a recent computational model that suggests that the hippocampus codes for the history of events via a conjunctive representation of temporal context (i.e., what and when). This view is motivated by two important properties of hippocampal cells: (1) they differentially fire depending on how long ago an event occurred; (2) they have different temporal receptive windows, i.e., cells that fire later in time respond to a broader range of time intervals (MacDonald et al., 2011; Mankin et al., 2012; Eichenbaum, 2014; Howard and Eichenbaum, 2014). Whereas this model has been proposed specifically to account for hippocampal involvement on a range of retrospective time tasks regardless of duration, we propose that this coding of conjunctive representations of "what" and "when" can equally support prospective aspects of time estimation (regardless of duration).

Although our proposal suggests the existence of redundant mechanisms in the service of interval timing over short

timescales, intriguingly, the findings of Jacobs et al., (2013) suggest a competitive dynamic between hippocampal and striatal memory systems: In their study, hippocampal-lesioned rats performed significantly better than control rats at short delays. The authors suggest that damage to the hippocampus releases the striatum to exert greater control over this type of behavior (Poldrack and Packard, 2003; Meck, 2005; Lee et al., 2008). Notably, in contrast to their study, we did not observe this "facilitation" effect as patients and controls performed equivalently in the short interval condition. However, it is possible that the competition observed in their study is related to the learning demands of their task, as other evidence suggests competition between different learning processes supported by the hippocampus and striatum (Wimmer et al., 2014).

In interpreting the present results, it is important to consider the caveat that prospective time judgments are unlikely to be driven solely by prospective information per se. That is, although participants are told from the outset that they will be required to estimate time (by definition a prospective time task), it is still possible that retrospective (i.e., memory retrieval-based) information may also aid performance. For example, participants may have used memorial information about the number of salient events or other details that came to mind for each video in order to extract duration information, particularly for longer duration videos. If such a strategy was employed, these retrospective cues would likely be more accessible to controls than to patients as their recovery would rely heavily on hippocampal-based retrieval processes. Of relevance to this issue, it is noteworthy that memory for the content of the videos was not significantly correlated with accuracy of time estimation in either group for either condition (all $Ps > 0.61$), arguing against the contribution of retrospective memorial information to support time estimation performance in either group, although a larger sample size may reveal such an association.

Still, it remains an open question as to what strategies may have influenced time estimation performance and whether these may have differed across groups. Notably, patients performed as well as controls on the memory probes. Here we raise the possibility that this null difference in memory performance may actually reflect an attentional trade-off in the task, whereby control participants gave more attentional priority to the passing of time (even if they did not explicitly count time per se), whereas patients gave attentional priority to the content of the video clips. This type of trade off may have resulted in equal memory performance, in which a group difference would otherwise be expected. Moreover, if patients were indeed allocating relatively more attentional resources to the content information of the videos at the expense of tracking time, this may have lead to more guessing, as they would have insufficient prospective information to compute an accurate time judgment, particularly for long duration judgments. Although we found no evidence for the use of different strategies across groups, our debriefing question may not have been sensitive to differences in attentional strategies across groups.

In summary, the present study provides compelling evidence that the hippocampus is necessary for computing time elapsed on the order of minutes but not on the order of seconds. Given these findings, it remains important to incorporate the hippocampus into existing computational and neuroanatomical models of prospective timing that have predominantly focused on striatal contributions. The notion that there are multiple biological mechanisms that have evolved in the brain to process time information is in accordance with the sensitivity of goal-directed behavior to various scales of time in the real world.

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