The Human Medial Temporal Lobe Is Necessary for Remembering Durations within a Sequence of Events but Not Durations of Individual Events

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Abstract

■ Recent interest in the role of the hippocampus in temporal aspects of cognition has been fueled, in part, by the observation of "time" cells in the rodent hippocampus—that is, cells that have differential firing patterns depending on how long ago an event occurred. Such cells are thought to provide an internal representation of elapsed time. Yet, the hippocampus is not needed for processing temporal duration information per se, at least on the order of seconds, as evidenced by intact duration judgments in rodents and humans with hippocampal damage. Rather, it has been proposed that the hippocampus may be essential for coding higher order aspects of temporal mnemonic processing, such as those needed to temporally organize a sequence of events that form an episode. To examine whether (1) the hippocampus uses duration information in the service of establishing temporal relations among events and (2) its role in memory for duration is unique to sequences, we tested amnesic patients with medial-temporal lobe damage (including the hippocampus). We hypothesized that medial-temporal lobe damage should impair the ability to remember sequential duration information but leave intact judgments about duration devoid of a sequential demand. We found that amnesics were impaired in making judgments about durations within a sequence but not in judging single durations. This impairment was not due to higher cognitive load associated with duration judgments about sequences. In convergence with rodent and human fMRI work, these findings shed light on how time coding in the hippocampus may contribute to temporal cognition. ■

INTRODUCTION

The role of the hippocampus in processing temporal and spatial features of events is well documented (Howard & Eichenbaum, 2015). Historically, there has been much greater focus on the involvement of this structure in processing spatial features (O'Keefe & Nadel, 1978), but recently, there has been a surge of interest in the role of the hippocampus in temporal aspects of cognition. This interest has been fueled, in part, by the observation of "time" cells in the rodent hippocampus—that is, cells that have differential firing patterns (as measured through single-cell recordings) depending on how long ago an event occurred (Mau et al., 2018; MacDonald, Carrow, Place, & Eichenbaum, 2013; MacDonald, Lepage, Eden, & Eichenbaum, 2011; Pastalkova, Itskov, Amarasingham, & Buzsaki, 2008). Such cells are thought to provide an internal representation of elapsed time.

In light of the existence of time cells, it is puzzling that the hippocampus is not needed for processing temporal duration information per se. That is, damage to this structure, both in humans and rodents, leaves intact the ability to estimate time elapsed, at least on the order of seconds (e.g., Palombo, Keane, & Verfaellie, 2016; Jacobs, Allen, Nguyen, & Fortin, 2013). Rather, it has been proposed that the hippocampus may be essential for coding higher-order aspects of temporal mnemonic processing, such as those needed to temporally organize a sequence of events that form an episode (see Palombo & Verfaellie, 2017; Eichenbaum, 2013). Indeed, the hippocampus has been implicated in varied aspects of sequential processing, such as judging temporal order, recency, or distance of events within an episode (e.g., Palombo, Di Lascio, Howard, & Verfaellie, 2019; Ezzyat & Davachi, 2014; Hsieh, Gruber, Jenkins, & Ranganath, 2014; Fortin, Agster, & Eichenbaum, 2002; Mayes et al., 2001).

Does the hippocampus also use temporal duration information in the service of establishing temporal relationships among events? Rodent work involving time cells suggests that this is indeed the case: Neurons in the hippocampus fire in a temporally ordered manner to "bridge the gap" between two successive events (MacDonald et al., 2011). Recent human fMRI work examining both univariate (Barnett, O'Neil, Watson, & Lee, 2014) and multivariate (Thavabalasingam, O'Neil, & Lee, 2018) patterns of activity

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in this region likewise suggest that the hippocampus is sensitive to temporal duration information of events that comprise a sequence (on the order of seconds). However, both animal and human work illuminate that, although the hippocampus represents temporal information of this nature, it is not unique in doing so: Time cells have been demonstrated outside the hippocampus (e.g., Tiganj, Cromer, Roy, Miller, & Howard, 2018; Mello, Soares, & Paton, 2015), and human fMRI work shows that extrahippocampal regions are sensitive to sequential temporal duration information (Barnett et al., 2014).

An important question, then, is whether the hippocampus is necessary for processing temporal durations within an event sequence. Furthermore, is its role "unique" to sequences? If so, damage to this structure should impair the ability to process sequential temporal duration information, whereas it should leave intact judgments about individual durations. Across two experiments, we tested this hypothesis for the first time in a group of amnesic patients with medial temporal lobe (MTL) damage.

EXPERIMENT 1

Participants

The VA Boston Healthcare System institutional review board approved all experimental procedures for the Boston participants, and the University of Toronto institutional review board approved all experimental procedures for the Toronto participants. All participants provided informed consent.

Patients

Eight patients (P1–P8) with amnesia (two female patients) secondary to MTL damage participated (see Table 1 for demographic and neuropsychological data). Seven of these patients were recruited through the Memory Disorders Research Center at VA Boston Healthcare System, whereas the eighth patient (P8) was recruited through the University of Toronto.

Each patient's neuropsychological profile indicated severe impairment that was limited to the domain of memory. Etiology of amnesia included hypoxic-ischemic injury secondary to either cardiac or respiratory arrest ($n = 4$), stroke ($n = 1$), encephalitis ($n = 2$), and status epilepticus followed by left temporal lobectomy ($n = 1$). MTL lesions for seven of the eight patients are presented in Figure 1, either on MRI or CT images. P5, who had suffered from cardiac arrest, could not be scanned because of medical contraindications and is thus not included in the figure. MTL pathology for this patient was inferred based on etiology and neuropsychological profile.

As shown in Table 1, volumetric data for the hippocampus and MTL cortices were available for a subset of patients (P2, P3, P4, P7), using methodology reported elsewhere (see Kan, Giovanello, Schnyer, Makris, & Verfaellie, 2007). This revealed that three patients (P3, P4, P7) had normal parahippocampal gyrus volume as a whole but showed significant volume loss of the hippocampus (see Table 1). However, given the involvement of the entorhinal cortex in temporal memory, we also examined volume of this region in these three patients, using

Table 1. Demographic and Neuropsychological Information for Patients

					WAIS III		*WMS III*			*Volume Loss (%)*	
Experiment	*Patient*	*Etiology*	*Age*	*Edu*	*VIQ*	*WMI*	*GM*	*VD*	*AD*	*Hippocampal*	*Subhippocampal*
1 and 2	P1	Hypoxic-ischemic	67	12	88	75	52	56	55	N/A	N/A
1 and 2	P2	Status epilepticus + left temporal lobectomy	54	16	93	94	49	53	52	63	60[a]
1	P3	Hypoxic-ischemic	59	14	84	84	45	53	52	70[b]	–
1 and 2	P4	Hypoxic-ischemic	61	14	106	115	59	72	52	22	–
1 and 2	P5	Hypoxic-ischemic	65	17	131	126	86	78	86	N/A	N/A
1 and 2	P6	Encephalitis	75	13	99	104	49	56	58	N/A	N/A
1 and 2	P7	Stroke	53	20	111	99	60	65	58	43	–
1 and 2	P8	Encephalitis	67	17	117[c]	–	74[d]	–	–	N/A	N/A

Age = age in years (at the time of Experiment 1); Edu = education in years; WAIS-III = Wechsler Adult Intelligence Scale–Third Edition; WMS-III = Wechsler Memory Scale–Third Edition; VIQ = verbal intelligence quotient; WMI = working memory index; GM = general memory; VD = visual delayed; AD = auditory delayed; N/A = not available.

[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).

[b]Patient has significant left entorhinal cortex volume loss (see main text).

[c]Verbal comprehension index (Wechsler, 2011).

[d]WMS-Revised (see Ryan et al., 2016).

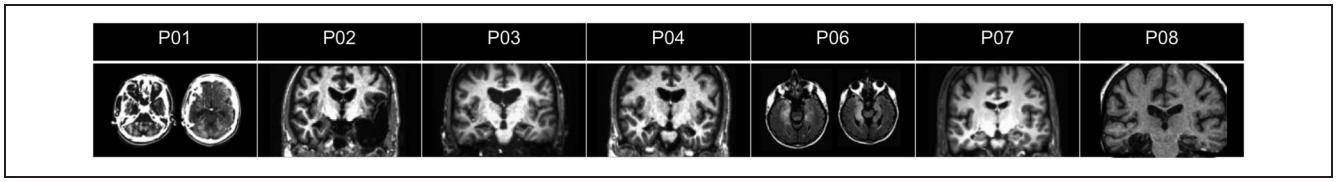

Figure 1. Structural MRI and CT scans depicting MTL lesions for seven of the eight amnesic participants. The left side of the brain is displayed on the right side of the image. CT slices show lesion location for P1 in the axial plane. T1-weighted MRI images depict lesions for P2, P3, P4, P7 and P8 in the coronal plane. T2 flair MRI images depict lesion locations for P6 in the axial plane. (The image for P08 was modified from Kwan, Kurczek, & Rosenbaum, 2016, with permission.)

an automated pipeline, namely, FreeSurfer 6, which has been employed in amnesic patients in prior work (Baker et al., 2016; Sheldon, Romero, & Moscovitch, 2013). As in prior work, patient data were compared with age-matched controls (n = 9). All volumes were normalized by estimated total intracranial volume. No significant volume loss was observed for entorhinal cortex in either hemisphere for P4 (left z = 1.16, right: z = 0.34) or P7 (left: z = 0.07, right: z = 0.04). For P3, significant volume loss was observed for the left entorhinal cortex (z = −2.27) but not the right entorhinal cortex (z = 0.32). Two other patients (P2 and P8) also had lesions that included the hippocampus and MTL cortices, but their damage extended into lateral temporal neocortex (see Figure 1; also see Ryan et al., 2016; Rosenbaum et al., 2008, for P8's full lesion profile). P1 had damage that included the hippocampus and MTL cortices (as per CT scan). For P6, clinical MRI was acquired but only in the acute phase of the encephalitis, with no visible lesions observed on T1-weighted images. However, T2 flair images demonstrated bilateral hyperintensities in the hippocampus and MTL cortices. Notably, a ninth amnesic patient from the Boston group was excluded before analyses after completing one session of the experiment because of excessive drowsiness during multiple testing attempts. P5 was retested on the sequence condition of Experiment 1 at a later date because he told the experimenter he had counted time.

Healthy Controls

Whereas 14 of the healthy controls were recruited through the Memory Disorders Research Center at VA Boston Healthcare System, two controls were recruited through the University of Toronto. The 14 healthy control participants (four women) from Boston were matched to the Boston patient group in age (61.0 years, SD = 9.1 years), education (14.9 years, SD = 2.5 years), and verbal IQ (109.7, SD = 16.2), which was assessed with the Wechsler Adult Intelligence Scale–Third Edition (Wechsler, 1997). Likewise, the two controls from Toronto (one woman) were matched to the Toronto patient in age (67.0 years, SD = 4.2 years), education (14.5 years, SD = 3.5 years), and verbal comprehension index (116.0, SD = 21.2), which was assessed with the Wechsler Abbreviated Test of Intelligence–Second Edition (Wechsler, 2011). Seven control participants were excluded (and replaced) from Experiment 1 before data analysis for the following reasons: counting time (n = 3), drowsiness (n = 1), difficulty understanding the instructions (n = 2), and for not returning to complete the second session (n = 1).

Experimental Design: Procedure

There were three conditions, one sequence condition and two single-duration control conditions (described below). Participants performed the task in two sessions, such that the sequence condition was completed on a separate day than the two control conditions; the order of sessions, as well as the order of the control conditions within session, was counterbalanced across participants. An exception to this prescription was made for the Toronto patient (because of the patient's limited availability); this patient was tested in one session, with the order of control 2, sequence, control 1. Accordingly, the two healthy controls tested in Toronto were also tested with this modified prescription.

In the experimental condition (the sequence condition), participants judged the timing of a sequence of spinning pinwheels (see Figure 2). Specifically, participants saw a set of two pinwheels that would spin in succession (study sequence), with the side (left vs. right) of the initial spinning pinwheel counterbalanced across trials to reduce anticipatory effects. After an ISI of 2250 msec (depicting a crosshair), the two pinwheels appeared again and spun in the same order (test sequence). Participants were asked to judge whether the timing of the test sequence was the same or different from that of the study sequence. On "same" trials, the timing of the test sequence was identical to that of the study sequence, whereas on "different" trials, the timing of one of the pinwheels in the test sequence was different from that of the study sequence. The side of the divergent pinwheel was counterbalanced across trials. Additionally, we counterbalanced on different trials, whether the duration of the divergent pinwheel at test was shorter or longer than at study. That is, on half of the different trials, the divergent pinwheel was longer at test, and on the other half of such trials, it was shorter at test.

In both of the control conditions, participants made same versus different judgments about the timing of a single spinning pinwheel duration; here, participants also

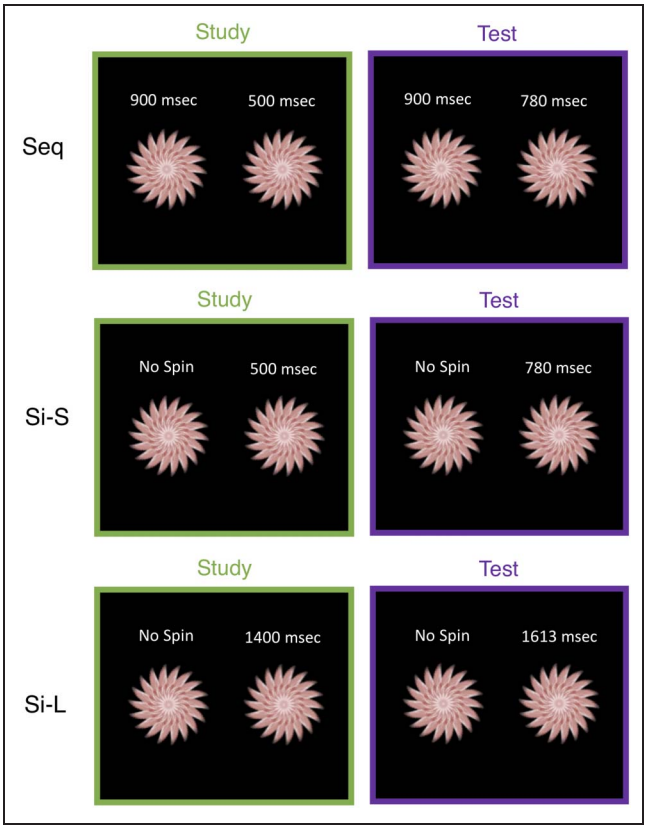

Figure 2. Schematic of the sequence (Seq), single short (Si-S), and single long (Si-L) conditions in Experiment 1.

saw two pinwheels (hence, equating visual load to that of the sequence condition; see Figure 2) but this time, only one of the pinwheels spun (while the other remained still). To reduce anticipatory effects, the side (left vs. right) of the spinning pinwheel was counterbalanced. After the ISI (also depicting a crosshair for 2250 msec), participants again saw two pinwheels and the pinwheel that spun at study spun again. On "same" trials, the timing of the spinning pinwheel at test was identical to the timing of the spinning pinwheel at study, whereas on "different" trials, the timing of the spinning pinwheel at test was different from the timing of the spinning pinwheel at study. For the latter trials, we counterbalanced whether the longer duration appeared in the study versus test phase.

The two control conditions differed as follows: In the first control condition, on each trial, the duration of the spinning pinwheel matched the duration of one of the spinning pinwheels in the sequence condition, thus allowing direct comparison of duration judgments about pinwheels embedded in a sequence and individual pinwheels of similar duration. The second control condition was implemented to control for overall trial duration in the sequence condition, which rules out the possibility that an impairment in the sequence relative to the single duration condition in amnesic patients is simply because sequence trials are longer overall in duration. Accordingly, in this control condition, on each trial, the duration of the spinning pinwheel matched the duration of the sum of both of the spinning pinwheels for a given trial in the sequence condition. These control conditions are referred to as single "short" (Si-S) and single "long" (Si-L), respectively, as shown in Figure 2.

The experiment was run using E-Prime (Version 2.0). In all conditions, participants performed seven practice trials before beginning the task. Participants had an unlimited amount of time to make their response, which was keyed in by the experimenter. Participants were explicitly told not to count time and to instead attend to the pinwheels passively as though watching TV. Participants were reminded of the instructions every five trials. All participants were offered a short break halfway through the task. After completion of the task, participants were debriefed regarding whether they counted time.

Experimental Design: Trial Structure

In each condition, there were 40 "different" and 20 "same" trials. In the sequence condition, trials were constructed such that "initial" pinwheel pairs spun for durations of (A) 500, (B) 600, (C) 700, (D) 800, or (E) 900 msec with each duration paired with every other duration four times. "Different" trials were created at four levels of difficulty, using Weber's Law of Just Noticeable Differences, where $K = \Delta I/I$. Here, I represents the initial stimulus duration (i.e., A–E) and ΔI represents the difference threshold. In this condition, K levels varied between 0.56 and 0.92 in increments of 0.12. To illustrate, for the duration 500 msec and a K value of 0.56, the difference threshold between two pinwheels across the study and test phases was 280 msec (thus, 500 and 780 msec were the durations presented). Same trials were constructed by choosing five trials at random from each K level used in the different trial construction (and included both "initial" and longer values that resulted from the Weber's law formula to ensure that the overall trial durations were matched between the trial types).

The same logic was used to construct trials for the control conditions, except that, in the single duration ("long") condition, we started with the summed duration of the two pinwheels (e.g., 500 + 600) and then computed I. Moreover, the K values for the control conditions were determined via piloting to match the sequence condition in terms of "difficulty," yielding K values of 0.43–0.64 with increments of 0.07 for the Si-S condition and K values of 0.50–0.89 with increments of 0.13 for the Si-L condition.

Data Analyses

All statistical analyses were performed using SPSS. Figures depicting results were created using MATLAB. We first examined group effects in accuracy for "different" and "same" trials separately, followed by analysis of

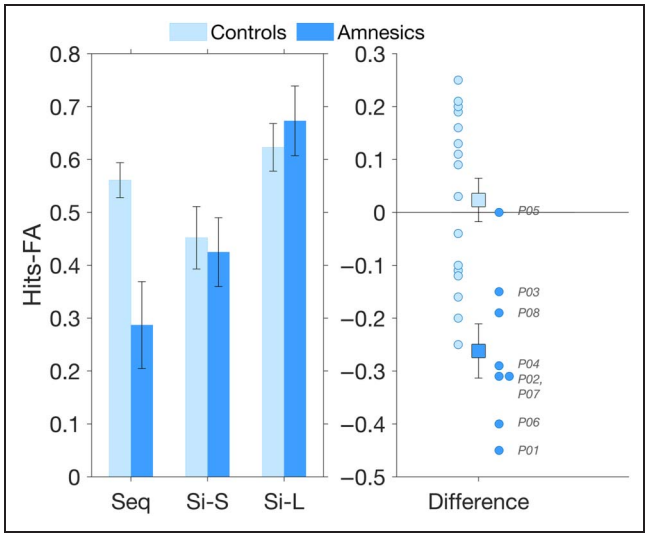

Figure 3. Results of Experiment 1. Left: Results of Experiment 1 for the sequence (Seq), single short (Si-S), and single long (Si-L) conditions for hits minus false alarms (FA). Right: A difference score reflecting performance in the sequence condition minus the average of the two control conditions is shown, with individual participants plotted.

hits minus false alarms (defined as correct different minus incorrect same trials). Follow-up *t* tests were performed when necessary.

Results

For different trials, a mixed ANOVA with factors of Group (control, amnesic), Condition (sequence, Si-S, Si-L), and *K* (difficulty) level (K1, K2, K3, K4) showed a main effect of Group, $F(1, 22) = 9.93, p = .005, \eta^2 = .31$; a main effect of Condition, $F(2, 44) = 50.43, p < .001, \eta^2 = .70$; and a Group × Condition interaction, $F(2, 44) = 10.03, p < .001, \eta^2 = .31$. There was also a main effect of *K*, $F(3, 66) = 56.38, p < .001, \eta^2 = .72$, with performance decreasing overall as a function of greater difficulty. However, because *K* did not significantly interact with any other variable (all *p*s > .39), we collapsed across *K* for subsequent analyses, and *K* will not be discussed further. For same trials, a mixed ANOVA with factors of Group (control, amnesic) and Condition (sequence, Si-S, Si-L) showed no main effect of Group, $F(1, 22) = 1.29, p = .27, \eta^2 = .06$; no main effect of Condition, $F(2, 44) = 0.12, p = .89, \eta^2 = .005$; and no interaction of Group × Condition, $F(2, 44) = 1.21, p = .31, \eta^2 = .05$. Hence, there was no greater tendency for patients to false alarm on this task. Critically, a mixed ANOVA on hits minus false alarm scores with factors of Group (control, amnesic) and Condition (sequence, Si-S, Si-L) showed, as expected, an interaction of Group × Condition, $F(2, 44) = 9.10, p < .001, \eta^2 = .29$, with no main effect of Group, $F(1, 22) = 1.46, p = .24, \eta^2 = .06$, and a main effect of Condition, $F(2, 44) = 20.06, p < .001, \eta^2 = .48$ (as shown in Figure 3, left). Follow-up analyses showed that, whereas patients performed significantly worse than controls in the sequence condition ($Mean_{Control} = 0.56$ (0.13); $Mean_{Patient} = 0.29$ (0.23); $t(22) = -3.73, p = .001$, Cohen's $d = 1.46$), they performed as well as controls for the Si-S ($Mean_{Control} = 0.45$ (0.24), $Mean_{Patient} = 0.43$ (0.18); $t(22) = -0.28, p = .78$, Cohen's $d = 0.13$) and Si-L ($Mean_{Control} = 0.62$ (0.18), $Mean_{Patient} = 0.67$ (0.19); $t(22) = 0.63, p = .53$, Cohen's $d = 0.27$) control conditions. For display purposes (see Figure 3, right), we computed a difference score between the sequence condition and the average of the two control conditions. (An ancillary ANOVA comparing performance in the two control conditions showed that there was no significant interaction between Group and Condition, justifying the decision to collapse across the two.) Data for each individual participant are shown.[1] We also repeated the analyses using a signal detection approach based on recommendations of Kaplan, Macmillan, and Creelman (1978) for the calculation of d' in same/different designs. This analysis revealed a similar pattern to hits minus false alarms (an interaction between Group × Condition, $F(2, 44) = 5.84, p = .006, \eta^2 = .21$, with no main effect of Group, $F(1, 22) = 0.84, p = .37, \eta^2 = .04$, and a main effect of Condition, $F(2, 44) = 13.00, p < .001, \eta^2 = .37$). Follow-up analyses showed that, whereas patients performed significantly worse than controls in the sequence condition, $t(22) = -2.99, p = .007$, Cohen's $d = 1.13$, they performed as well as controls for the Si-S, $t(22) = 0.09, p = .93$, Cohen's $d = 0.04$, and Si-L, $t(22) = 0.49, p = .63$, Cohen's $d = 0.21$, control conditions. The d' scores are reported in Table 2.

Next, we examined whether the impairment in the sequence condition in amnesia was affected by the position of the divergent pinwheel at test. That is, we asked whether amnesic patients were any worse in their performance when it was the second pinwheel that was divergent (vs. the first pinwheel) in the test phase. We used a mixed ANOVA with factors of Group (amnesic, control) and Position (Pin 1, Pin 2) to examine performance on different trials in the sequence condition. There was a main effect of Group, $F(1, 22) = 18.78, p < .001, \eta^2 = .46$; no effect of Position, $F(1, 22) = 0.07, p = .80, \eta^2 = .003$; or Group × Position interaction, $F(1, 22) = 0.63, p = .44, \eta^2 = .03$. That is, neither patients nor controls performed worse when the second pin diverged. Thus, the impairment in amnesic patients in the sequence

Table 2. d' Scores

	Experiment 1			*Experiment 2*
	Seq	*Si-S*	*Si-L*	*Si-HL*
Controls	3.03 (0.67)	2.48 (1.34)	3.39 (0.91)	2.44 (1.40)
Amnesics	1.77 (1.42)	2.53 (0.95)	3.59 (1.00)	2.71 (2.07)

Means and *SD*s (in parentheses) are shown. Seq = Sequence; Si-S = single short; Si-L = single long; Si-HL = single high load.

condition was not simply due to the need to maintain two items in memory at test.

Finally, to examine whether the impairment was present in patients with lesions restricted to the hippocampus we employed a Bayesian approach for case studies (Crawford & Garthwaite, 2007) to examine the performance of each individual hippocampal patient in comparison to the control mean. Using the authors' program *DiffBayes.exe* (which compares the difference between two means for the single case to the control group using Bayesian inferential methods), we inputted the sequence condition and the average of the two control conditions. This analysis showed that P4 and P7 had a significantly larger difference between the two conditions than controls, with 4.3% (Bayesian 95% upper limit, one-tailed = 12.1%) and 3.3% (Bayesian 95% upper limit, one-tailed = 9.9%) of control individuals expected to exhibit a greater difference than P4 and P7, respectively.

EXPERIMENT 2

Experiment 1 showed that, whereas amnesic patients were impaired in judging the duration of a sequence, they were not impaired in judging the duration of a single item, as shown by their intact performance in the Si-S and Si-L conditions. As the control conditions were matched to the sequence condition in visual as well as in temporal load (at single duration and overall trial duration levels, respectively), the impairment in the sequence condition cannot be explained by these factors per se. Moreover, ancillary analyses of the sequence condition suggested that the impairment in this condition was not impacted by the number of test items to be considered before a response was possible, as the impairment was equally present when it was the first test pin that was divergent compared with when the second test pin was divergent. Notably, given that such trials only required one comparison to yield a correct response, they were also matched to the control trials in which only a single comparison was required.

Nonetheless, even on the sequence trials in which it was the first test pin that was divergent, the number of items kept in mind was not matched with that in the control conditions (three items in those sequence trials vs. two items in the control conditions). Thus, Experiment 1 leaves open the possibility that the impairment in the sequence condition was due to the greater overall item load associated with that condition. To rule out this possibility in Experiment 2, we created a condition that posed no demands on remembering a sequence but involved three pinwheels: Participants saw only a single spinning pinwheel at study, whereas two pinwheels spun at test and they were asked to judge whether the duration of the studied pinwheel matched that of either test pinwheel (see Figure 4, top). We hypothesized that amnesic patients would perform as well as healthy controls in Experiment 2.

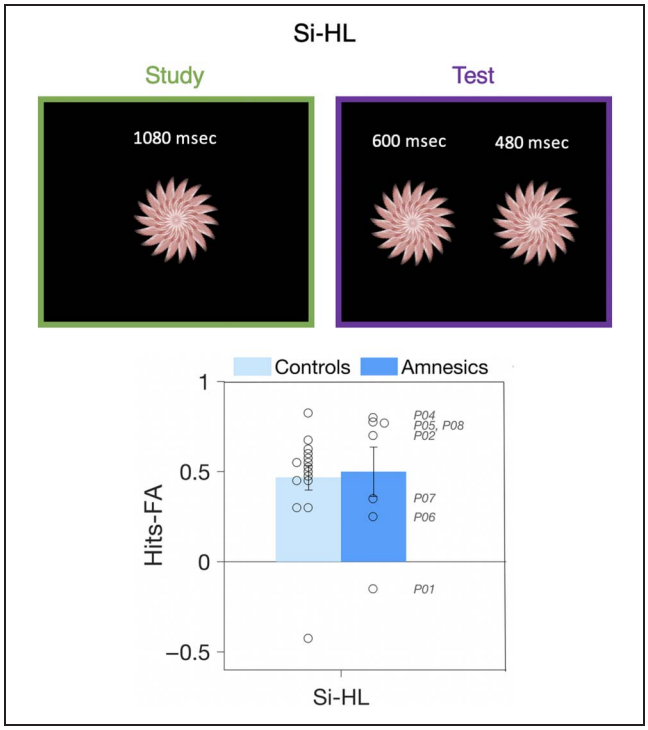

Figure 4. Schematic and results for Experiment 2. Top: Schematic of the single high load (Si-HL) condition in Experiment 2. Bottom: Results for the Si-HL condition for hits minus false alarms (FA).

Notably, of critical interest are trials in which the second test pinwheel matches the study pinwheel, as accurate performance on such trials requires that three items be maintained in memory.

Participants

Patients

Seven of the eight patients from Experiment 1 participated in Experiment 2 (see Table 1). P1 was retested because it was unclear whether she understood the instructions, and P5 was retested because he counted time the first time he was tested.

Healthy Controls

For Experiment 2, a group of 14 healthy control participants (six women) were recruited through the Memory Disorders Research Center at VA Boston Healthcare System and matched to the Boston patient group in age (59.0 years, *SD* = 7.6 years), education (14.4 years, *SD* = 2.3 years), and verbal IQ (109.4, *SD* = 19.4). Two controls (one woman) were recruited from the University of Toronto and matched the Toronto patient in age (67.0 years, *SD* = 3.5), education (14.5 years, *SD* = 3.5), and verbal comprehension index (116.0, *SD* = 21.2). Of the 16 controls, five had also participated in Experiment 1 (three from Boston and two from Toronto).

Experimental Design: Procedure and Trial Structure

The stimuli and general procedures used were very similar to the sequence condition in Experiment 1, with differences noted below. At study, participants saw only a single spinning pinwheel, whereas at test they saw two pinwheels, each of which spun in turn. Participants were asked to judge whether the duration of either of the two test pinwheels matched the study pinwheel. To reduce anticipatory effects, the side (left vs. right) of the pinwheel to spin first at test was counterbalanced. Moreover, for different trials, we also counterbalanced whether the longer duration appeared at study versus at test.

In this experiment, different trials involved two test pinwheels that diverged from the study pinwheel. To compute the duration of one of the test pinwheels, the same *K* values were used as in the sequence condition of Experiment 1 (determined through piloting to match difficulty to the sequence condition). The second different pinwheel was either 20–25% longer or shorter than the first (i.e., it was always easier). Same trials entailed that one of the test pinwheels was identical to the study pinwheel and were constructed by choosing five trials from each *K* level, with the duration of the second pinwheel 20–25% longer or shorter. After completion of the task, participants were debriefed regarding whether they counted time.

Data Analyses

All statistical analyses were performed using SPSS. Figures depicting results were created using MATLAB. As in Experiment 1, we examined "different" and "same" trials separately and then examined hits minus false alarms (correctly identified different trials minus incorrectly rejected same trials). Follow-up *t* tests were performed when necessary.

Results

For different trials, a mixed ANOVA with factors of Group (control, amnesic) and *K* level (K1, K2, K3, K4) showed no main effect of Group, $F(1, 21) = 0.04$, $p = .85$ $\eta = .002$; no significant interaction between Group and *K*, $F(3, 63) = 2.59$, $p = .06$, $\eta = .11$; and a main effect of *K*, with performance decreasing overall as a function of difficulty, $F(3, 63) = 18.86$, $p < .001$, $\eta = .47$. For same trials, an independent samples *t* test (control, amnesic) showed no significant difference between groups ($\text{Mean}_{\text{Control}} = 0.79$ (0.14), $\text{Mean}_{\text{Patient}} = 0.84$ (0.23); $t(21) = 0.63$, $p = .54$, Cohen's $d = 0.26$). An independent samples *t* test (control, amnesic) examining hits minus false alarms showed no significant difference between groups ($\text{Mean}_{\text{Control}} = 0.47$ (0.27), $\text{Mean}_{\text{Patient}} = 0.50$ (0.36); $t(21) = 0.25$, $p = .81$, Cohen's $d = 0.11$; see Figure 4, bottom). Analysis of d' scores yielded similar results, $t(21) = 0.37$, $p = .72$, Cohen's $d = 0.15$ (see Table 2). Notably, when we only considered trials on which the second pin matched (thus requiring that three items be kept in mind), we again found no impairment in the amnesic group ($\text{Mean}_{\text{Control}} = 0.73$ (0.16), $\text{Mean}_{\text{Patient}} = 0.81$ (0.24); $t(21) = 0.99$, $p = .34$, Cohen's $d = 0.41$). Considering also the pin order analysis from Experiment 1, these analyses suggest that patients do not have trouble processing a load of three spinning pinwheels; it is only when this occurs in the context of a sequence that patients are impaired. To directly compare performance for first pin divergent trials from Experiment 1 and second pin match trials from Experiment 2, we computed patient *z* scores for each and compared them using a paired *t* test. As one patient did not participate in Experiment 2, this analysis was based on the remaining seven patients. Patients performed significantly worse in Experiment 1 (Mean $z = -1.90$ (1.48)) versus Experiment 2 (Mean $z = 0.53$ (1.53)), $t(21) = -4.83$, $p = .003$.

Notably, this pattern of results rules out an additional possible interpretation of the results of Experiment 1, namely, that the impairment in amnesia is simply due to longer study-to-test delay in the sequence condition compared with the control condition (i.e., in the sequence condition, the delay period between a study and test item always includes another intervening spinning pinwheel, whereas this was not the case in the control condition). By contrast, the trials used in the abovementioned comparison have an equivalent temporal delay (i.e., both involve an intervening pinwheel), yet patients perform normally in Experiment 2 and are impaired in Experiment 1. This suggests that differential decay is unlikely to be the source of patients' impairment in the sequence condition.

The above results did not change when we excluded one outlier control participant who performed considerably worse than all other participants (see Figure 4). A similar Bayesian approach to that employed in Experiment 1, except for a single condition (SingleBayes.exe; see Crawford & Garthwaite, 2007), suggested that the two patients with lesions limited to the hippocampus (P4 and P7) were within normal limits for hits minus false alarms. Specifically, this analysis showed that 87.6% and 34.2% of controls, respectively, fall below P4 and P7 (Bayesian 95% lower limit, one-tailed = 74.9% and 19.8%, respectively).

DISCUSSION

In this study, we explored the role of the human hippocampus in memory for temporal duration. Specifically, we asked whether the hippocampus uses duration information in the service of establishing temporal relationships among events, that is, in encoding and remembering a sequence, and whether its role in memory for duration is unique to sequences. We found that amnesic patients with MTL damage (including the hippocampus) were impaired in making memory judgments about durations within a sequence but not in making judgments about single durations (judgments that were equally, if

not more, challenging than sequence judgments in healthy controls; Experiment 1). We additionally demonstrated that this impairment was not due to the higher item load associated with duration judgments about a sequence (Experiment 2).

A wealth of recent evidence shows that the hippocampus contains "time cells"—cells that have differential firing patterns depending on how long ago an event occurred (on the order of seconds or longer). These firing patterns are not readily attributable to other factors, such as active movement or spatial location information (see, e.g., Mau et al., 2018; MacDonald et al., 2011, 2013; Pastalkova et al., 2008). Yet, lesion research has shown that the hippocampus is not critical for processing temporal duration information: Damage to this structure, both in humans and rodents, leaves intact the ability to estimate time elapsed, at least on the order of seconds (e.g., Palombo et al., 2016; Jacobs et al., 2013; also see Palombo & Verfaellie, 2017, for a review of the literature). Our data may help to reconcile these seemingly contradictory findings by suggesting that, whereas the hippocampus codes for elapsed time (likely through connections with other cortical and subcortical structures that show similar time cell patterns; Tiganj et al., 2018; Teki, Gu, & Meck, 2017; Barnett et al., 2014; Jin, Fujii, & Graybiel, 2009), it does so in the service of supporting higher order aspects of cognition, namely, for sequential processing (Palombo & Verfaellie, 2017), or as Buzsáki and Tingley (2018) state, the hippocampus is a "sequence generator." That is, the hippocampus uses duration information (coded by time cells) to represent the temporal relationships between successive microevents that form a sequence. Specifically, encoding of a sequence requires binding of the end of the first microevent with the beginning of the second microevent to form a holistic, unified representation of an unfolding event. This notion is in accordance with the broader theoretical framework that suggests that the hippocampus is critical for binding elements of an experience together (Olsen, Moses, Riggs, & Ryan, 2012; Eichenbaum, 2001) as well as temporal context models that postulate that slowly drifting contextual representations in the hippocampus support the linking of items within an unfolding event (Palombo et al., 2019; Folkerts, Rutishauser, & Howard, 2018; Howard & Eichenbaum, 2015; Kahana, Howard, & Polyn, 2008; Howard, Fotedar, Datey, & Hasselmo, 2005).

Our findings dovetail with recent functional neuroimaging studies demonstrating sensitivity of the hippocampus to changes in temporal duration of events that comprise a sequence, both at short (seconds; Thavabalasingam et al., 2018; Barnett et al., 2014) and at long (24 hr) retention intervals (Thavabalasingam, O'Neil, Tay, Nestor, & Lee, 2019). In one such study, Thavabalasingam et al. (2018) showed significant reduction in hippocampal voxel pattern similarity when the temporal durations within a sequence of images (namely, the empty intervals between images) were altered between study and test at very short retention intervals (also see animal work by MacDonald et al., 2011). Although we used a different experimental approach (i.e., we manipulated the duration of the events themselves, not the empty intervening intervals; also see Barnett et al., 2014), this study extends this work by highlighting the necessity of the hippocampus to representing sequential duration information and the selective nature of its contribution to the temporal processing of sequences of durations, as opposed to individual durations per se.

Notably, encoding a sequence by definition entails encoding multiple items, and this raises the question of whether the impairment in sequential processing is due to the higher mnemonic load during encoding. In our view, encoding a sequence and the higher load of encoding multiple items are intrinsically linked because a sequence by necessity involves multiple items. Moreover, one cannot eliminate the possibility that whenever multiple items are presented successively, they are coded as a sequence, even in tasks that pose no explicit demands on sequential processing.

Our data suggest that the hippocampus is sensitive to temporal duration structure, but they do not speak to the nature of the hippocampal representation that supports such temporal processing. Is temporal information maintained independently or in combination with other forms of information such as object information? Relevant to this question is recent imaging work examining pattern similarity within the hippocampus. In the aforementioned study by Thavabalasingam et al. (2018), changes in hippocampal activity patterns were observed when only temporal information was manipulated. It is unclear, however, whether these activity changes reflected alterations solely to temporal representation or to higher level representation of sequence information. More recently, Thavabalasingam et al. (2019) showed that hippocampal activation patterns represented the combination of event content (which comprised images of scenes) and temporal duration structure (the empty intervals between scene images) in a sequence but did not represent temporal structure in isolation. One possible explanation for this pattern of results is that hippocampal activity patterns best reflect the highest level of binding (also see Ranganath & Hsieh, 2016, for similar discussion).

More broadly, that we observed hippocampal involvement in a time frame considered to be within STM is at odds with a classic memory systems view (see, e.g., Squire, Stark, & Clark, 2004) and fits with other recent data suggesting that this structure is also involved in multiple cognitive processes, including STM and perception, particularly in tasks with a binding or conjunctive demand (Koen, Borders, Petzold, & Yonelinas, 2017; Yonelinas, 2013; Lee, Yeung, & Barense, 2012; Olsen et al., 2012). Indeed, the observation that patients performed well even when we controlled for overall trial duration suggests that the impairment in amnesia is specific to sequential processing and not a general STM deficit per se.

Although our work focused on sequential processing in the context of temporal duration, our findings align with a growing body of evidence that suggests that the

hippocampus is important for processing other types of sequence information, such as temporal order information. This includes older lesion data showing impairments in judgments of order but not item memory following damage to the hippocampus in humans and animals (reviewed in Palombo & Verfaellie, 2017) and more recent neuroimaging evidence of patterns of univariate and multivariate hippocampal activation that predict ordinal information (Clewett, DuBrow, & Davachi, 2019; Lieberman, Kyle, Schedlbauer, Stokes, & Ekstrom, 2017; Jenkins & Ranganath, 2010, 2016; Ranganath & Hsieh, 2016; Schapiro, Turk-Browne, Norman, & Botvinick, 2016; Davachi & DuBrow, 2015; DuBrow & Davachi, 2014; Ezzyat & Davachi, 2011, 2014; Hsieh et al., 2014; Kumaran & Maguire, 2006). It is unknown whether the coding of order information involves similar hippocampal mechanisms to that of sequential duration coding; for example, it is possible that time cell firing patterns can be used to reconstruct order information (Allen, Salz, McKenzie, & Fortin, 2016), but there may be mechanisms other than temporal coding at play as well (e.g., see Mayes et al., 1989; Huppert & Piercy, 1978).

Other recent work, both in humans and animals (Bellmund, Deuker, & Doeller, 2019a, 2019b; Montchal, Reagh, & Yassa, 2019; Thavabalasingam et al., 2019; Tsao et al., 2018; Teki et al., 2017) highlights the importance of the entorhinal cortex, particularly the lateral portion (but see Robinson et al., 2017), in coding temporal information during events. Our data cannot speak to the putative contributions of the hippocampus versus entorhinal cortex to temporal sequential processing in this study, as many of our patients have damage to both structures, although the fact that a selective impairment in the sequence condition was also present in the patients with damage restricted to the hippocampus suggests that not only entorhinal cortex but also the hippocampus is critical for processing the duration of temporal sequences. Given that the entorhinal region is the primary gateway for cortical input to the hippocampus, it is possible that the entorhinal cortex feeds the hippocampus with critical timing information from other parts of the brain (Robinson et al., 2017).

An alternative interpretation of the observed sequence impairment in amnesia is that it reflects a spatial deficit. Although the task was designed to be devoid of overt spatial demands (spatial position is not diagnostic in the sequence condition as it is always congruent between study and test), is it possible that participants nonetheless attempted to perform the task using a spatial strategy by mapping durations to relative pinwheel location ("left" vs. "right" as opposed to "first" vs. "second") and that this placed patients at a disadvantage? Although impairments in spatial STM have been documented in MTL patients, these are usually under conditions of high precision and/or memory load. Notably, with set size and spatial resolution analogous to those in this study, patients have been shown to perform normally (Kolarik, Baer, Shahlaie, Yonelinas, & Ekstrom, 2018; Koen et al., 2017; Jeneson, Mauldin, & Squire, 2010). Thus, it is unlikely that errors in binding of duration to location at this course of a resolution would account for the present deficit. However, this is an important consideration for follow-up research.

Although gaps in our understanding of hippocampal contributions to temporal processing remain, our findings shed new light on the critical role of the human hippocampus in coding durations within a sequence. By using carefully controlled experimental tasks, we are able to provide clear insight into the conditions in which the human hippocampus is involved in memory for temporal durations and therefore speak to potential mechanisms that are relevant to the temporal processing of memories as they are constructed from our continuous experience.

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Note

1. Although we sought to match performance of the control participants in the control conditions to the sequence condition (see the Methods section), simple effects within this group showed that performance was lower in the Si-S control condition, $t(15) = -2.10, p = .053$, relative to the sequence condition, although this difference was only marginally significant; the Si-L control condition did not significantly differ from the sequence condition, $t(15) = 1.38, p = .19$. In the context of interpreting the amnesia impairment, the marginal difference in the healthy controls between the sequence and Si-S conditions is not problematic as amnesics were impaired in the easier (sequence) condition but not in the more difficult (control) condition.

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