Medial Temporal Lobe Damage Impairs Temporal Integration in Episodic Memory

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Abstract

■ Although the role of the medial temporal lobe (MTL) and the hippocampus in episodic memory is well established, there is emerging evidence that these regions play a broader role in cognition, specifically in temporal processing. However, despite strong evidence that the hippocampus plays a critical role in sequential processing, the involvement of the MTL in timing per se is poorly understood. In the present study, we investigated whether patients with MTL damage exhibit differential performance on a temporal distance memory task. Critically, we manipulated context shifts, or boundaries, which have been shown to interfere with associative binding, leading to increases in subjective temporal distance. We predicted that patients with MTL damage would show impaired binding across boundaries and thus fail to show temporal expansion. Consistent with this hypothesis, unilateral patients failed to show a temporal expansion effect, and bilateral patients actually exhibited the reverse effect, suggesting a critical role for the MTL in binding temporal information across boundaries. Furthermore, patients were impaired overall on both the temporal distance memory task and recognition memory, but not on an independent, short-timescale temporal perception task. Interestingly, temporal distance performance could be independently predicted by performance on recognition memory and the short temporal perception task. Together, these data suggest that distinct mnemonic and temporal processes may influence long interval temporal memory and that damage to the MTL may impair the ability to integrate episodic and temporal information in memory. ■

INTRODUCTION

Efficient behavior requires that we simultaneously operate across a wide range of different timescales, supported by distinct neural systems. Although it is fairly well established that cortico-cerebellar and corticostriatal circuits play distinct roles in millisecond and second timescales (Allman, Teki, Griffiths, & Meck, 2014; Teki, Grube, Kumar, & Griffiths, 2011), the mechanisms supporting timing in the multiple seconds to minutes range are less clear. Electrophysiological findings across species suggest that hippocampal neurons can "time" delays in this range (Reddy et al., 2021; Umbach et al., 2020; Eichenbaum, 2014; MacDonald, Lepage, Eden, & Eichenbaum, 2011; Naya & Suzuki, 2011). Thus, one intriguing possibility is that the same hippocampal mechanisms that support episodic memory may also support timing in the time range necessary to encode episodic events.

Although many studies have investigated how medial temporal lobe (MTL) damage including the hippocampus influences performance on timing tasks, the results have been inconsistent. In one early study, the famous amnesic patient H.M. (who had a bilateral MTL resection) was found to reproduce temporal intervals from 1 to 20 sec normally, but severely underestimated intervals between 20 and 300 sec, suggesting that hippocampal timing may only be necessary for long durations (Richards, 1973). In a subsequent study, a different amnesic patient (whose amnesia developed after removal of a cyst near her third ventricle) was found to underestimate durations starting at 5 sec (Williams, Medwedeff, & Haban, 1989). However, Shaw and Aggleton (1994) failed to find an impairment in the 1- to 96-sec range for temporal lobe amnesics (resulting from viral encephalitis) but instead found that patients with Korsakoff's syndrome (a memory disorder associated with damage to many brain regions, including the MTL; Kril & Harper, 2012) showed an impairment. The impairment in Korsakoff's was predicted by a performance on a task thought to rely on the frontal lobe, thus suggesting that frontal—rather than hippocampal—mechanisms may support timing in this range.

Data from patients with unilateral temporal lobe lesions are similarly mixed, with effects varying with the time range and hemisphere of the resection (for a review, see Palombo & Verfaellie, 2017). For example, some studies observed deficits at milliseconds to seconds timescales (Melgire et al., 2005; Perbal, Ehrlé, Samson, Baulac, & Pouthas, 2001), whereas others observed deficits only within the minute range (Palombo, Keane, & Verfaellie, 2016; Noulhiane, Pouthas, Hasboun, Baulac, & Samson, 2007). Rodent work has also produced varied results, demonstrating that hippocampal lesions impair duration discrimination in some cases (Sabariego et al., 2021;

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Jacobs, Allen, Nguyen, & Fortin, 2013; Meck, Church, & Olton, 1984) but not others (Kyd, Pearce, Haselgrove, Amin, & Aggleton, 2008; Dietrich, Allen, & Bunnell, 1997). Thus, the existing data are inconclusive as to whether MTL damage impairs temporal judgments and what the relevant tasks and timescales are.

Intriguingly, however, some of the work in human patients has observed deficits only when the task contains mnemonic demands (i.e., when the to-be-produced duration had to be held in memory; Noulhiane et al., 2007; Melgire et al., 2005), suggesting that the hippocampus may be particularly important for remembering duration. Relatedly, recent work has suggested that the hippocampus is critical for supporting temporal duration judgments in the context of a sequence, whereas duration judgments for single events were not impaired (Palombo et al., 2020). Thus, these data suggest that the hippocampus may play a privileged role in binding temporal information in episodic memory.

This notion converges with neuroimaging studies in healthy participants, which consistently point to a role of the hippocampus in supporting the integration of temporal information in episodic memory (Lee, Thavabalasingam, Alushaj, Çavdaroğlu, & Ito, 2020; Davachi & DuBrow, 2015). For example, the hippocampus is thought to support memory for temporal duration and distance, specifically across contextual shifts, or "boundaries." This is often studied using the Ezzyat–DuBrow–Davachi paradigm, in which boundaries are indicated by changes in image category or visual context (Heusser, Ezzyat, Shiff, & Davachi, 2018; Ezzyat & Davachi, 2014; DuBrow & Davachi, 2013). Behaviorally, this type of context manipulation has been consistently shown to affect memory for temporal order and distance (for recent reviews, see Buonomano, Buzsáki, Davachi, & Nobre, 2023; Yates, Sherman, & Yousif, 2023; Clewett, DuBrow, & Davachi, 2019). For example, memory for the temporal order of events is disrupted across boundaries (DuBrow & Davachi, 2013; Ezzyat & Davachi, 2011; Zwaan, 1996; Zwaan, Langston, & Graesser, 1995). In addition, time is subjectively expanded across boundaries, such that intervals spanning a boundary are rated as having been longer or further apart in time (Ezzyat & Davachi, 2014; Waldum & Sahakyan, 2013; Poynter, 1983; Block & Reed, 1978; Block, 1974). These effects have been linked to the hippocampus: Prior work has shown greater hippocampal pattern stability—as measured by similarity between two trials with an intervening boundary—is related to temporal binding across boundaries. Specifically, hippocampal pattern similarity has been related both to subjective judgments of temporal distance (Ezzyat & Davachi, 2014) and to temporal order memory (DuBrow & Davachi, 2014) across boundaries, suggesting that the hippocampus plays a role in integrating temporal information across event boundaries. Thus, synthesizing across the patient and human neuroimaging results raises the hypothesis that MTL damage might not to lead to a deficit in timing per se, but more specifically to a deficit in integrating temporal information in episodic memory.

In the present study, we tested this hypothesis, asking whether and how MTL damage affects temporal distance judgments at a relatively long timescale. Our primary question was how MTL damage influences behavioral estimates time across context boundaries. Critically, we predicted that patients would show impaired binding across context boundaries, as hippocampal pattern similarity has been related to temporal memory specifically across boundaries (DuBrow & Davachi, 2014; Ezzyat & Davachi, 2014). To this end, we tested patients with MTL damage in a version of the Ezzyat–DuBrow–Davachi paradigm, in which they were presented with a series of faces and objects and subsequently had to judge the temporal distance between two encoded items. We hypothesized that the context switch expansion effect (increases in subjective temporal distance estimates across context boundaries) would be eliminated in patients.

We additionally asked a secondary, more exploratory question of what role the MTL plays in remembering temporal distance, irrespective of context shifts. For this question, we analyzed the correlation between participants' temporal distance judgments and the true temporal distance between items (collapsing across switch and no switch trials). Beyond assessing the overall effect of MTL damage on participants' temporal distance judgments, we related their performance on this measure to performance on additional tasks. Specifically, in addition to the temporal distance task, we tested recognition memory for the same stimuli and additionally administered a separate short-term scale temporal perception task. We included these tasks to obtain potentially co-varying measures that could be used to assess the extent to which temporal duration judgments can be decomposed into more basic cognitive mechanisms. Specifically, including the recognition memory task allows us to assess the influence of episodic memory on temporal duration judgments; including the shorter-timescale temporal duration task enables us to assess to what extent longer-term temporal memory judgments are a product of more basic perceptual timing abilities.

METHODS

Participants

Patients: 29 anterior temporal lobectomy (ATL) patients and two bilateral MTL patients were recruited through NYU Patient Registry for the Study of Perception, Emotion, & Cognition. They were remunerated $20/hour and compensated for travel expenses. One left ATL patient was excluded from analysis because of below chance performance (false alarm rate > hit rate in the recognition memory phase) likely because of a failure to understand instructions. Thus, 14 right and 14 left ATL patients were included in the present study. All ATL patients had surgical

resections to treat intractable focal epilepsy. The two bilateral patients had focal temporal lobe injury: one resulting from anoxia because of postsurgical complications of general anesthesia and the other because of herpes encephalitis. All individuals in the patient group underwent comprehensive neuropsychological examinations as part of recruitment to obtain objective evidence of cognitive impairment consistent with lesion localization.

Matched control participants: 37 control participants were recruited through NYU Patient Registry for the Study of Perception, Emotion, & Cognition and from the broader community to match the patients in terms of mean age and education. They were remunerated $20/hour to match the patient rate. One control participant was excluded from the analysis because of chance performance on the temporal distance task (a Spearman correlation between the true temporal distances and remembered temporal distances that was not reliably above what would be expected from random responding). Thus, 36 mean age and education-matched control participants were included in the present study.

Young control cohort: 20 young adult participants (mean age = 19.7) were recruited from New York University and the broader community and were remunerated $10/hour. We collected data from this cohort, in addition to the age and education-matched controls, to validate our effects in an age range in which these effects were previously established (Ezzyat & Davachi, 2014; DuBrow & Davachi, 2013). Because the goal of collecting this sample was to replicate our effects in this specific iteration of the task, these participants only completed the temporal distance task (not the temporal perception tasks).

For all groups, informed consent was obtained in a manner approved by the University Committee on Activities Involving Human Subjects. Demographic information for patients and controls is reported in Table 1, including neuropsychological measures for patient groups.

Procedure

Participants came in for a single session consisting of three tasks (with the exception of one bilateral participant, who came in for an additional brief session on a separate day to complete a modified version of the temporal perception task; see below). Patient participants were often involved in multiple research studies and/or neuropsychological testing in the same day. The first task was the temporal perception task, for which participants completed one block that took approximately 5–10 min. Next, participants performed the temporal distance task, for which there were 12 study-test rounds (each of which lasted approximately 4–5 min total). They first performed eight rounds, then performed a second longer temporal perception task, and finally completed the four rounds of the temporal distance task. The session was set up with this break in the temporal distance task to reduce fatigue. The second temporal perception task (which aimed to provide a complementary, albeit slightly longer [10–30 sec] metric of short-timescale temporal perception and was modeled off of Liverence & Scholl, 2012) is not reported, as the effect of our manipulation was not reliable in control groups and many participants were found to doze off or otherwise disengage during the task.

Temporal Perception Task

In the temporal perception task (similar to Sherman, DuBrow, Winawer, & Davachi, 2023), participants judged the duration that a square appeared on a computer screen. Squares were presented in green, blue, or yellow on a gray background, and durations ranged between 500 msec and 5 sec in 500-msec increments. For half of the trials, the color stayed the same for the entire duration ("continuous"), and for the other half of the trials, the color switched ("boundary"; see Figure 1, bottom). The color–condition–duration combinations were counterbalanced, and the order of presentation was pseudorandomized such that condition–duration combinations were not repeated back-to-back and no single condition or duration appeared in a row more than 4 times. Immediately following the square, a black line appeared on the screen bounded by .5 sec and 5 sec and participants were instructed to use the mouse to click the location on the line that corresponded to their estimated duration. Importantly, participants were instructed not to count during the presentation of the square but instead to use their best

Table 1. Demographic Information for Patients and Matched Control Participants

	N	*Age*	*Sex*	*Education*	*FSIQ*	*PRI*	*VCI*
Right ATL	14	38.7 ± 11.7	9 F, 5 M	15.6 ± 2.1	100.6 ± 12.4	102.4 ± 13.8	98.6 ± 9.7
Left ATL	14	43.1 ± 11.2	8 F, 6 M	16.0 ± 2.1	109.9 ± 12.7	104.4 ± 13.5	114.4 ± 13.1
Bilateral 1	1	76	M	17	118	107	127
Bilateral 2	1	43	F	16	105	102	114
Matched controls	36	41.5 ± 10.7	22 F, 13 M	16.3 ± 2.0	–	–	–

Age, education, and neuropsychological measures are represented as means ± standard deviation. Age and education are both reported in years. FSIQ = Full Scale Intelligence Quotient; PRI = Perceptual Reasoning Index; VCI = Verbal Comprehension Index.

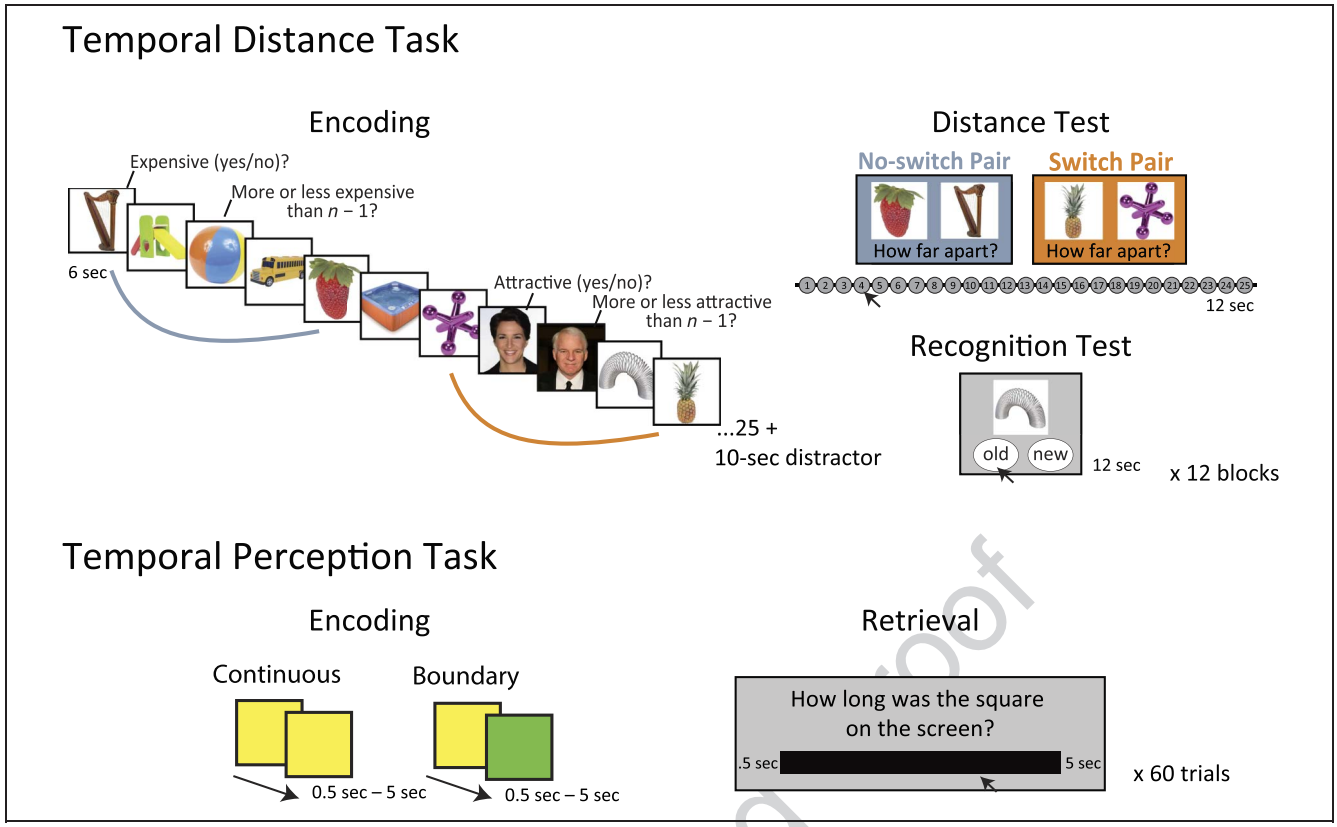

Figure 1. Schematic of behavioral tasks. Top: During encoding, participants were presented with lists of 25 images and made 1-back category-specific judgments. Following a short distractor task, participants were presented with 10 pairs of images and were instructed to indicate the distance between them. The main conditions of interest were no-switch (blue), which came from sequences of same-category items, and switch (orange), which came from sequences that had intervening context boundaries. Following the distance test, participants made old/new judgments on four old and four new images to assess recognition memory. Bottom: Participants were presented with colored squares for between .5 sec and 5 sec. On half the trials, the color of the square switched halfway through the duration. At the offset of the square, the participant was prompted to rate how long the square was presented, regardless of color. For both tasks, participants responded using the mouse.

intuitive estimation of duration. Debriefing questionnaires suggested that compliance with this instruction was high. The response period was self-paced with a maximum response time of 12 sec, and participants performed 60 trials of this task. If a participant failed to respond within the 12-sec window, their response was recorded as their mouse position at the time. We included this small subset of trials in analyses, but note that all patterns replicate when excluding these trials.

For the two bilateral patients, brief instructions were repeated before every trial. One bilateral patient used only the .5- to 1-sec range of the number line during his first testing session; in a subsequent session, we performed a free response version of the task in which he responded out loud rather than on the number line, and we report those data here.

Note that although we included the continuous and boundary conditions to be analogous to the context switch effect in the temporal distance task, our primary goal in including this task was to assess temporal perception (irrespective of boundaries) and relate this short-timescale temporal perception task to performance in the temporal distance task. Thus, we do not report any analyses analyzing the switch effects in this task.

Temporal Distance Task

In the temporal distance task (modeled off DuBrow & Davachi, 2013, 2014), participants were instructed to judge the distance between pairs of images presented in lists of 25. Stimuli consisted of color images of celebrity faces and nameable objects (see DuBrow & Davachi, 2013) and were randomly assigned for each participant. Each study-test round consisted of an encoding phase, a temporal distance memory task, and a recognition memory task.

During the encoding phase, participants were presented with a series of 25 images with their corresponding label. Participants were instructed to make a category-specific 1-back judgment on each image—a relative attractiveness judgment for faces and a relative expensiveness judgment for objects, comparing each with the prior same-category item. For the first image of each category train, they were instead instructed to make an absolute (yes/no) attractive or expensive judgment. This task was chosen to be engaging and encourage associative processing. Practice trials were repeated until the participants understood the task. During encoding, participants had up to 6 sec to view each image and make a response with

the mouse. The image remained on the screen for the full 6 sec, regardless of when participants made their response. Each encoding trial was separated by a 0.5-sec intertrial interval. Immediately after the encoding phase, participants performed an odd/even task (during which they judged whether a digit 1–9 was odd or even) for 10 sec as a brief distractor.

Next, during the temporal distance memory task, 10 pairs of images from the preceding list were shown and participants were instructed to estimate how far apart they were in terms of how many images were spanned during encoding. Participants were tested on five trial types: neighbors, no-switch, switch, long, and across-category, which primarily varied in their true temporal distance. "Neighbors" were pairs of neighboring items and were always from the same category; thus, the correct answer would be 1. The main conditions of interest were the "no-switch" and "switch trials." Both of these were lag four pairs (i.e., pairs that had three intervening items), and the presented pairs were always from the same category (faces or objects). Critically, however, these two conditions differed in whether there was a category switch within the intervening four items during encoding. Specifically, on "no-switch" trials, if the presented pairs were two objects, those two objects, during encoding, contained all objects in between their presentations. In other words, they were drawn from a same-category train during encoding. By contrast, on "switch" trials, if both stimuli were objects, for example, during encoding, there was an intervening category switch within the three intervening items (see Figure 1, top). In addition to these no-switch/switch pairs and neighboring items, we included "long" trials, in which same-category items presented across seven to nine intervening images were tested. Finally, "across-category" trials were included, which were pairs from the ends of the list (Lag 23) and were composed of different categories (i.e., the pair would consist of a face and an object, whereas all other pair types were composed of the same category items). Including these different trial types enabled us to sample a range of true temporal distances and assess overall temporal memory performance. The no-switch and switch conditions were matched for a serial position across lists, and the other distance conditions were matched according to their mean serial position within list fifths. Each pair type (neighbors, no-switch, switch, long, and across-category) was tested twice per round, and the order of test trials was randomized. Participants responded with a mouse by clicking on the location on the number line corresponding to the distance between the images. This retrieval phase was self-paced with a 12-sec upper limit. As with the temporal perception task, if a participant failed to respond within the 12-sec window, their response was recorded as their mouse position at the time. We included these trials in analyses, but note that all patterns replicate when excluding these trials.

Lastly, participants performed a recognition memory test. For each round, eight images were shown, in which four were from the immediately preceding list ("old") and four were novel foils ("new"). To clarify the task for the bilateral patients, the "old" and "new" prompts instead read "seen" and "not seen," respectively; furthermore, bilateral patients were reminded of the instruction immediately prior to each recognition phase. The face and object categories were equally represented. Furthermore, half of the old images were boundary items and half were preboundary items (items immediately preceding a boundary). Critically, none of the images presented in the recognition memory test had been presented as a pair in the temporal distance memory task; thus, participants could not use their memory of the presented images in the temporal distance task to guide their decision. Again, participants used the mouse to respond in a self-paced manner with a 12-sec upper limit. Between rounds, participants were encouraged to take a short break.

MRI Methods

Structural MRIs were acquired from each of our patient participants post-operatively on either a 1.5- or 3-T Siemens scanner. Segmentation of MTL subregions (hippocampus, parahippocampal cortex, perirhinal cortex, and entorhinal cortex) was performed manually on high-resolution T1 magnetization prepared rapid gradient echo images for both hemispheres. The boundaries between subregions were based on published landmarks (Frankó et al., 2014; Ding & Van Hoesen, 2010; Pruessner et al., 2002; Goncharova, Dickerson, Stoub, & deToledo-Morrell, 2001).

RESULTS

Recognition Memory

We first assessed recognition memory by computing a corrected recognition score, calculated by subtracting the proportion of "old" responses to novel foils (false alarm rate) from the proportion of "old" responses to presented images (hit rate). Note that this corrected recognition metric is used when referring to recognition memory in all subsequent analyses. Assessing recognition memory across groups via a Kruskal–Wallis test (to account for the non-normality of the recognition memory data), we observed a significant main effect of group, $H(3) = 13.16$, $p = .004$. We ran follow-up Mann–Whitney–Wilcoxon U tests to assess pairwise differences. Control participants showed better recognition memory compared with right ATLs (control: $M = .962$, $SD = .046$; right ATL: $M = .917$, $SD = .064$; control vs. right ATL: $W = 135$, $p = .010$) and bilateral patients ($M = .677$, $SD = .221$; $W = 0$, $p = .016$), but a marginal difference from left ATLs ($M = .939$, $SD = .050$; control vs. left ATL: $W = 171$, $p = .075$). There was no difference between right and left ATLs ($W = 76.5$, $p = .329$), but ATLs (collapsed) performed significantly better than bilateral patients ($W = 53.5$, $p = .036$).

Context Switch Effect in Temporal Distance

The main measure of interest was the switch versus no-switch distance responses across groups. Average temporal distance responses for the switch and no-switch conditions are shown in Figure 2A. In the young cohort, switch pairs were rated as significantly further apart compared with no-switch pairs, $t(19) = 4.47$, $p < .001$, confirming that the context switch manipulation was effective in this task.

The average differences between switch and no-switch responses by patient group are shown in Figure 2B. To assess whether the switch effect differed as a function of group, we ran a linear model, predicting the switch effect as a function of age, recognition memory (corrected recognition: hit rate minus false alarm rate; to control for the influence of cue image recognition on distance judgments), and patient group. To increase power, we collapsed across right and left ATL patients into a single ATL group (this was validated by post hoc analyses that demonstrated no difference in the switch effect between right and left ATL groups; $t(26) = 0.19$, $p = .849$), such that the three patient groups were control, ATL, and bilateral. Note that these three patient groups were used for all subsequent models.

Importantly, we found that adding group as a factor in addition to the age and recognition memory predictors significantly improved the model, $F(2, 61) = 3.28$, $p = .045$. There was no significant difference between the ATL group and controls, $t(61) = -1.23$, $p = .222$, whereas the bilateral group was significantly different from both controls, $t(61) = -2.51$, $p = .015$, and the ATL group, $t(61) = 2.26$, $p = .027$ (Figure 2C). Neither age nor recognition memory emerged as significant predictors of the switch effect, age: $t(61) = -0.98$, $p = .330$; recognition: $t(61) = -1.44$, $p = .154$. Finally, we tested for a linear trend, as we expected there to be a graded effect across groups. Thus, we assigned a value of 1 to the control

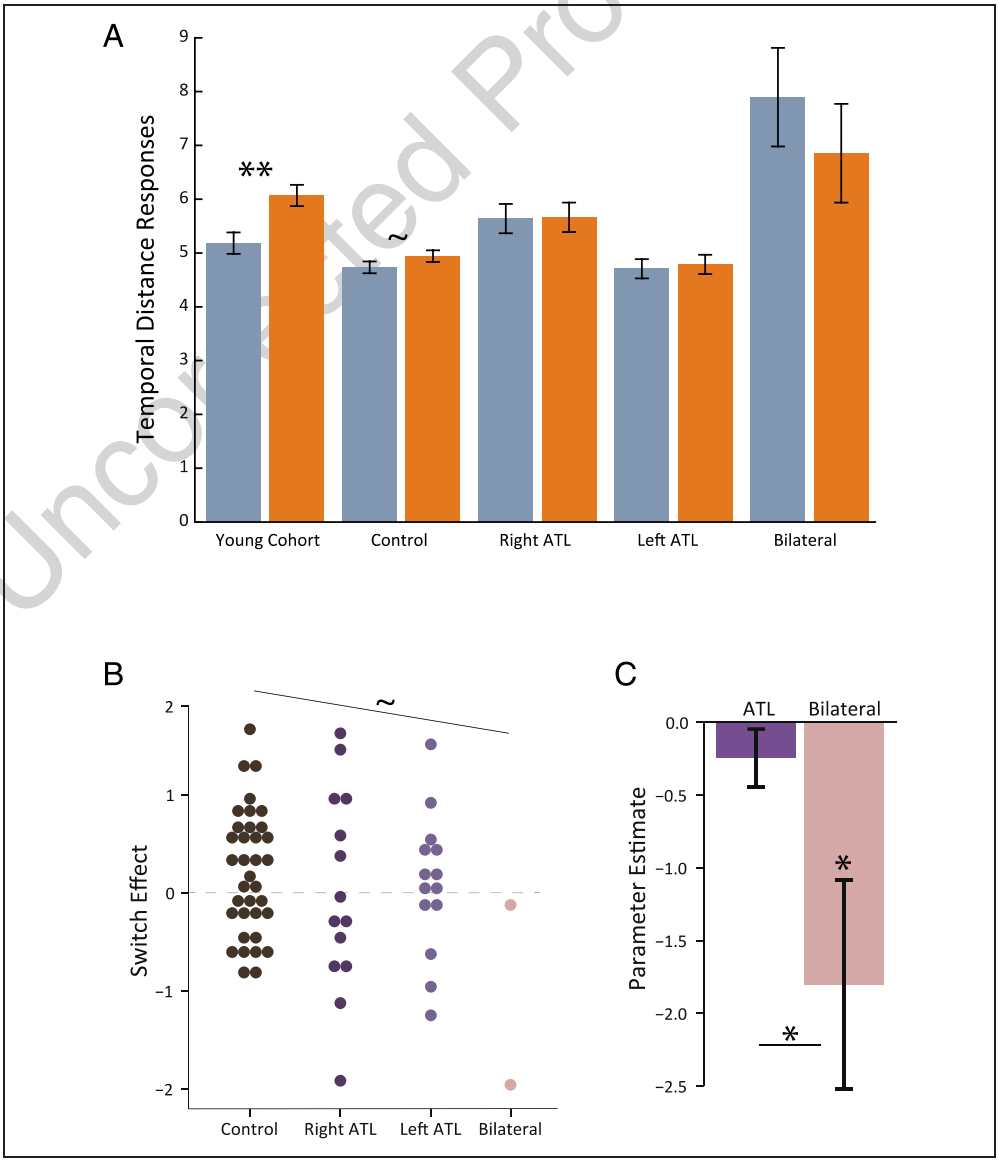

Figure 2. Switch effect in temporal distance by group. (A) Average raw responses on for the no-switch (blue) and switch conditions for each group. Error bars indicate within-participant standard error of the mean. (B) Subtraction of no-switch from switch responses for each group. Responses above 0 indicate switch expansion, and responses below 0 indicate switch compression. The linear trend was tested collapsing the right and left ATL groups. (C) The effect of group on the switch effect controlling for age and recognition memory. Parameter estimates and standard error are in reference to the control group. $^{**}p < .005$; $^{*}p < .05$, $\sim p < .10$.

group, 2 to the ATL group, and 3 to the bilateral group. This linear model resulted in a marginal effect of group, $F(1, 64) = 3.06, p = .085$.

Examining the switch effects within each patient group provided further evidence for this graded effect. In age and education matched controls, the switch effect (switch to no-switch trials) was marginally significant, $M = 0.206$, $SD = 0.644$; $t(35) = 1.92, p = .063$; $d = 0.320$. However, right and left ATL patients showed no significant difference between switch and no-switch, right ATL: $M = 0.024$, $SD = 1.02$; $t(13) = 0.09, p = .932$; $d = 0.023$; left ATL: $M = 0.088$, $SD = 0.717$; $t(13) = 0.46, p = .653$; $d = 0.122$. Bilateral patients also did not show a significant switch effect, $M = -1.04$, $SD = 1.30$; $t(1) = -1.14, p = .459$; $d = -0.804$. It is important to note the very small sample size for bilateral patients ($n = 2$), yet both bilateral patients showed a negative switch effect.

In addition to examining the switch effect for both categories of stimuli, we were also interested in whether objects or faces showed a stronger switch effect. Thus, we split the switch effect by category in the young cohort. We found a highly significant effect for object pairs, $t(19) = 3.61, p = .002$, and a nonsignificant effect for faces, $t(19) = 1.69, p = .107$, although the difference between them did not reach significance, $t(19) = 1.61, p = .124$. Because sensitivity to the manipulation was more robust for object pairs (where faces constitute the context switch), we examined the switch effect for object pairs in patients and controls.

For the linear model controlling for age and recognition, the addition of group marginally improved the model, $F(2, 61) = 3.12, p = .051$. Again, neither age nor recognition memory emerged as significant predictors of the switch effect, age: $t(61) = -0.71, p = .482$; recognition: $t(61) = -0.88, p = .380$. In this object-only case, the ATL group significantly differed from controls, $t(61) = -2.16, p = .035$, although the difference between controls and bilaterals did not reach significance, $t(61) = -1.62, p = .110$, nor did the difference between ATLs and bilaterals, $t(61) = 1.02, p = .312$. However, we did find a significant linear trend across groups in the switch effect for object pairs, control > ATL > bilateral, $F(1, 64) = 5.97, p = .017$. Examining this effect separately in each patient group, we found that control participants showed a significant switch effect for object pairs, $t(35) = 2.22, p = .033$, that was not significant in any patient group, $t(13) = 0.33, p = .748$; left ATL: $t(13) = 0.95, p = .359$; bilaterals: $t(1) = 1.33, p = .410$.

Temporal Distance Performance

To assess performance on the temporal distance task irrespective of context switches, we computed the Spearman rank correlation of distance responses for neighbors, Lag 4 pairs (switch and no-switch collapsed), long pairs (Lags 7–9), and across-category pairs (Lag 23). Thus, only the relative ordering of these conditions influenced the correlation, making this measure robust to biases in the absolute use of the number line. Average performance by group is shown in Figure 3A (left). All included participants exhibited above-chance performance, as computed by comparing each participant's rank correlation with a null distribution of correlation values computed by shuffling the correspondence between the true and judged temporal distances. We first ran a linear model predicting performance as a function of group. There was a significant effect of group such that controls showed better performance than right and left ATLs collapsed, $t(62) = 2.16, p = .035$; no difference between right and left ATL, $t(26) = 0.46, p = .648$, and there was a significant linear trend across groups, control > ATL > bilateral, $F(1, 64) = 11.56, p = .001$. However, when adding covariates for age and recognition memory, the effect of group became nonsignificant, $t(62) = -1.50, p = .138$ (Figure 3A, right), and adding group as a factor did not improve the model, $F(2, 61) = 1.16, p = .321$. On the other hand, recognition memory significantly predicted performance, $t(61) = 2.89, p = .005$, and age had a marginally negative relationship with performance, $t(61) = -1.97, p = .053$.

Temporal Perception

Performance on the temporal perception task, as with the temporal distance task, was calculated using a Spearman rank correlation insensitive to bias in number line use. Average performance by group is shown in Figure 3B (left). All participants exhibited above-chance performance, as computed by comparing each participant's rank correlation with a null distribution of correlation values computed by shuffling the correspondence between the true and judged temporal durations. When controlling for age and recognition, neither ATLs nor bilaterals showed a significant difference from controls, ATL: $t(61) = 1.52, p = .133$; bilateral: $t(61) = 1.02, p = .314$ (Figure 3B, right), and adding group as a factor did not improve the model fit, $F(2, 61) = 1.34, p = .270$. The only significant factor was a negative effect for age in predicting temporal perception performance, $t(61) = -2.38, p = .020$.

Relationship between Memory and Perception Measures

We next asked whether performance on the temporal distance task (irrespective of context switches; i.e., the rank correlation of distance responses for neighbors, Lag 4 pairs, long pairs, and across-category pairs) and the temporal perception task were related. Using a linear model, we found that performance on the temporal perception task significantly predicted performance on the temporal distance task, $F(1, 64) = 5.43, p = .023$. Next, we reran the model controlling for age and recognition memory and found that performance on the temporal perception task

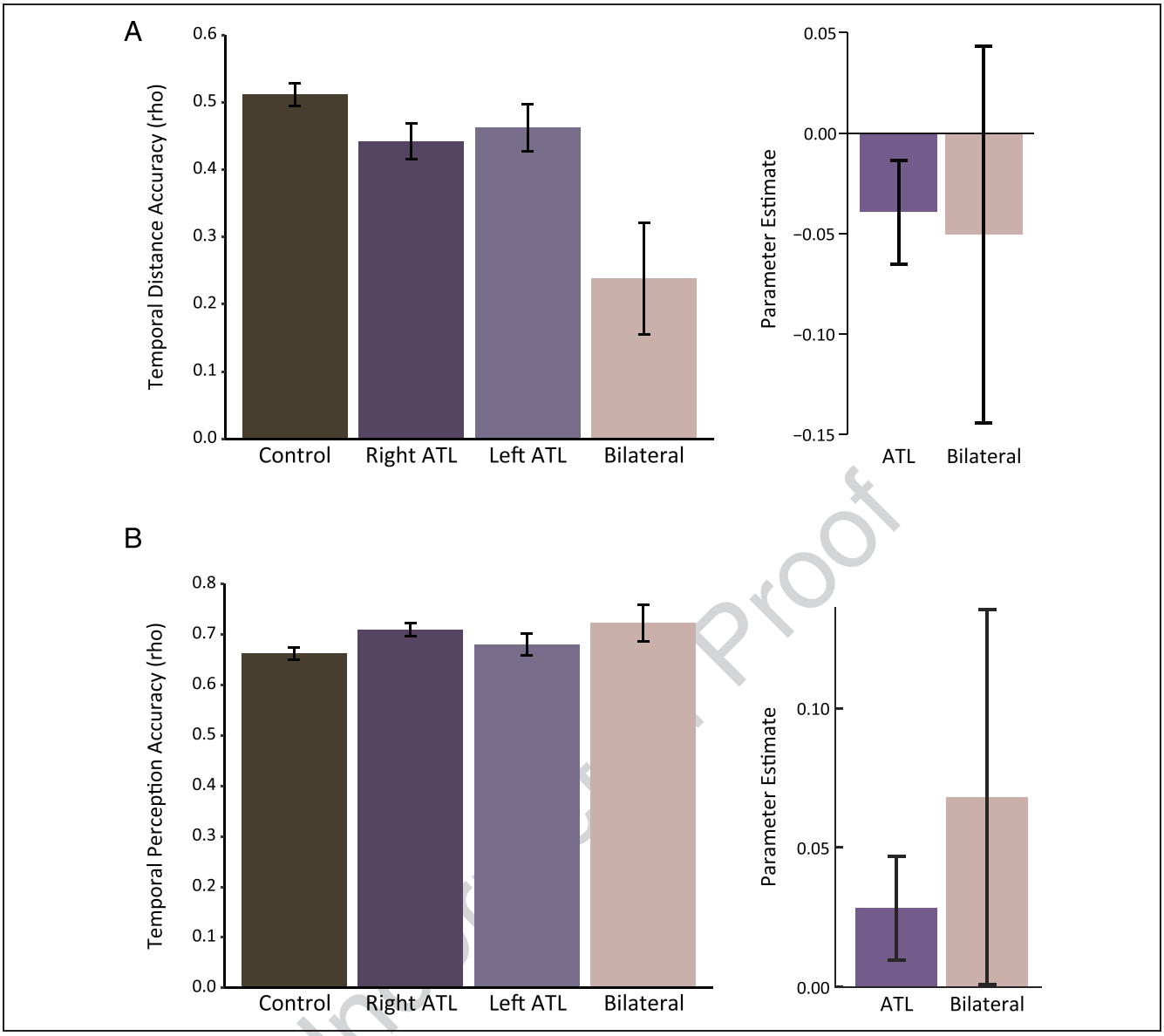

Figure 3. Performance measures by group. (A) Left: Accuracy on the temporal distance task as measured by rank correlation between the true distance and behavioral responses by group. Statistical comparisons are not shown, as they do not hold after controlling for age and recognition memory. Right: Effect of group on temporal distance performance controlling for age and recognition memory. Estimates are in reference to the control group. (B) Left: Accuracy on the temporal perception task as measured by rank correlation between the true duration and behavioral responses by group. Right: Effect of group on temporal distance performance controlling for age and recognition memory. Error bars indicate standard error of the mean.

significantly improved the model fit, $F(1, 62) = 7.52, p = .008$. Interestingly, both temporal perception performance and recognition memory were highly significant factors in the model, recognition: $t(62) = 4.99, p < .001$; temporal perception: $t(62) = 2.74, p = .008$, and the addition of recognition memory as a factor also significantly improved the model, $F(1, 62) = 24.89, p < .001$. We did not find interactions with group in these effects, recognition by group: $t(59) = -0.10, p = .922$; temporal perception performance by group: $t(59) = 0.81, p = .424$, nor did the addition of interactions with group as factors significantly improve the model fit, $F(3, 62) = 1.86, p = .146$. However, although both recognition memory and temporal perception performance significantly predicted temporal distance performance in the patients, recognition: $t(26) = 3.87, p < .001$; temporal perception performance: $t(26) = 2.67, p = .013$, these effects were nonsignificant or marginal in the control group alone, recognition: $t(32) = 1.59, p = .122$; temporal perception performance: $t(26) = 1.96, p = .061$. Figure 4 shows the relationship between recognition memory and temporal distance performance (left), the relationship between temporal perception performance and temporal distance performance (middle) and the lack of a relationship between recognition memory and temporal perception performance (right) excluding the bilateral patients for

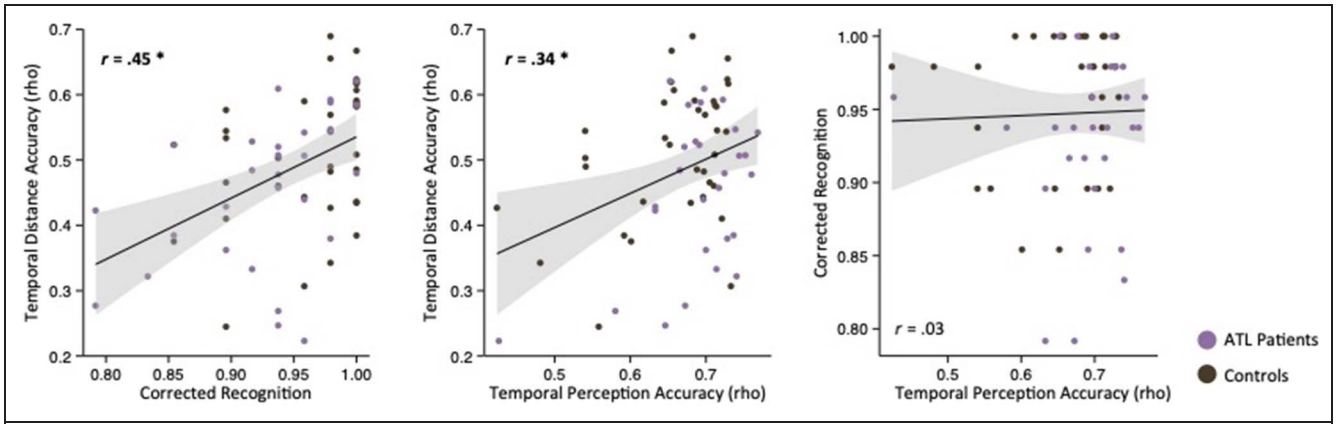

Figure 4. Recognition memory and temporal perception independently contribute to temporal memory performance. Scatter plots show the relationship between recognition memory and temporal distance performance (left), the relationship between temporal perception and temporal distance performance (middle), and the lack of a relationship between temporal perception and recognition memory (right).

visualization (factors remain significant without bilateral patients; recognition: $t(60) = 3.87, p < .001$; temporal perception performance: $t(60) = 2.60, p = .012$. Together, these results indicate that recognition memory and temporal duration perception each independently predict temporal distance memory, suggesting that they may correspond to separable component processes contributing to the temporal distance judgments.

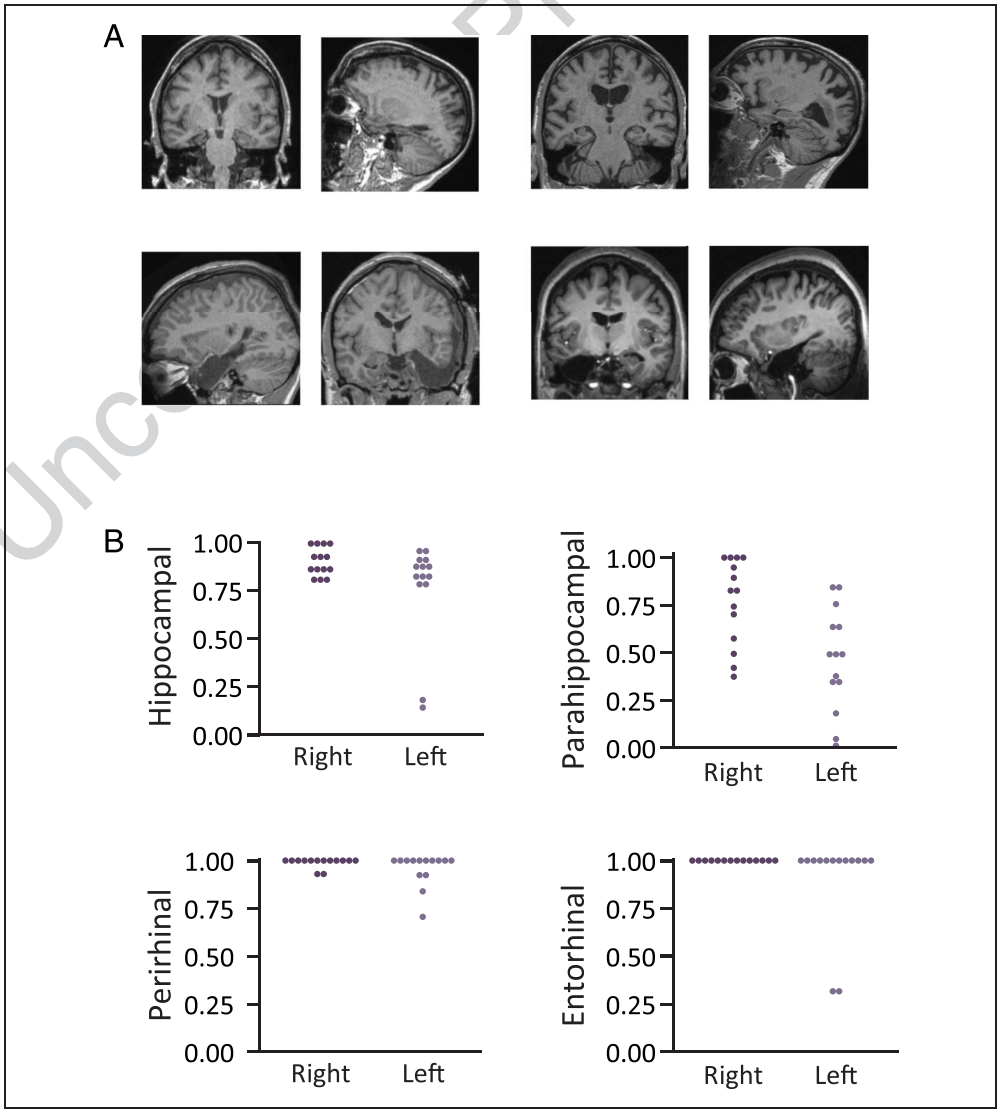

Figure 5. MTL lesion data. (A) Structural MRIs of two bilateral patients (top) and representative right and left ATL patients (bottom, respectively). (B) Proportion unilateral volume loss in each MTL subregion for the right and left ATL patients estimated by taking 1 minus the ratio of remaining tissue in the lesioned hemisphere to that of the intact hemisphere.

Table 2. Volumetric Data for All Patients

	Right Hipp	*Left Hipp*	*Right PHC*	*Left PHC*	*Right PRC*	*Left PRC*	*Right EC*	*Left EC*
Right ATL	338.6 ± 264.0	3238.4 ± 466.0	592.4 ± 582.9	2753.8 ± 565.7	43.6 ± 112.1	2265.4 ± 668.0	0 ± 0	789.1 ± 156.8
Left ATL	3296.1 ± 504.3	818.0 ± 988.4	2255.6 ± 444.1	1239 ± 680.3	2195.9 ± 646.3	111.0 ± 240.9	821.7 ± 231.9	52 ± 135.4
Bilateral 1	2340	1177	1454	420	1044	0	435	0
Bilateral 2	1817	2040	1818	2111	1396	1225	688	707

All values are reported in mm^3 and are represented as means ± standard deviation. Hipp = hippocampus; PHC = parahippocampal cortex; PRC = perirhinal cortex; EC = entorhinal cortex.

Volumetry

Structural MRIs for the bilateral patients and representative right and left ATL patients are shown in Figure 5A. We calculated volumetry by summing the voxels labeled within any given MTL subregion. Table 2 shows the raw volume measures in cubic millimeters for each MTL subregion by group. In addition, for the ATL patients, we computed the proportion of unilateral volume loss by taking one minus the ratio of the lesioned hemisphere volume to that of the intact hemisphere for each subregion (Figure 5B). More loss was evident in the right ATLs than the left, hippocampus: $t(26) = 1.90, p = .069$; parahippocampal cortex: $t(26) = 3.28, p = .003$. This is consistent with more conservative surgery of the left hemisphere because of left language dominance. However, there were also two left patients with relatively focal resections. One had a specialized resection because of a developmental lesion. The other had an amygdalaectomy because of focal epileptic discharges from the amygdala. Excluding those patients reduced the difference between right and left ATL patients, although it remained significant for parahippocampus, hippocampus: $t(24) = 1.38, p = .179$; parahippocampal cortex: $t(24) = 2.77, p = .011$.

To investigate whether the extent of MTL damage correlated with any of our dependent measures of interest, we reran the multiple regressions on the ATL patients with volumetric predictors controlling for age. We included hippocampal and parahippocampal volume loss (1-lesioned/intact, described above), but not perirhinal or entorhinal, as there was not enough variance in those measures across patients. Neither hippocampal nor parahippocampal loss predicted the switch effect nor performance on either task. The only evidence of a relationship with behavior was a marginal effect for recognition memory such that remaining hippocampal volume positively correlated with recognition memory performance, $t(25) = -1.74, p = .094$. However, this marginal effect did not hold when excluding the two patients with minimal MTL damage, $t(23) = -0.96, p = .348$, as they both had high recognition memory scores.

DISCUSSION

In the present study, we investigated how damage to the MTL influences different forms of temporal memory. First, by using a context change manipulation, we tested how temporal distance memory was affected by context switches. We found modest evidence that MTL damage caused a blunting of the characteristic context switch effect, compared with matched controls. Second, we assessed how MTL damage influenced temporal memory irrespective of context shifts. Relating both recognition memory and performance on a shorter-timescale temporal perception task for short duration stimuli revealed distinct influences of these factors on temporal memory, across both patients and controls. Although we interpret these findings with caution, given relatively small sample sizes in the patient groups and some variable effects in the control group, these findings provide an important causal bridge with prior, correlational work examining hippocampal contributions to temporal memory. Specifically, taken together, these results suggest that MTL damage may not affect timing mechanisms per se but rather the interaction between timing and memory systems that support temporal judgments at longer timescales.

MTL Damage and the "Switch Expansion" Effect

Our primary analysis focused on whether the switch expansion effect in temporal distance memory was modulated by MTL damage. The switch effect is characterized by consistently longer temporal distance ratings for items that occurred across a context shift and has been found in numerous studies (Clewett, Gasser, & Davachi, 2020; Ezzyat & Davachi, 2014; Waldum & Sahakyan, 2013; Poynter, 1983; Block, 1974). Here, we replicated this effect in a young cohort and found a marginally significant effect in our older control cohort. However, we failed to find this effect in ATL patients and surprisingly found the reverse effect in our bilateral patients. That said, we caution interpretation of the reversed effect in bilateral patients, as we only collected data from two bilateral patients (one of whom had damage resulting from encephalitis, which likely led to extra-MTL damage as well).

To understand the typical switch expansion effect, it is important to note that there is no difference between the switch and no-switch conditions at retrieval; rather, the only difference is whether there is an intervening context switch during encoding. Thus, the switch expansion effect must be driven by the association between the intervening context and the probe items; a failure to bind sequences of items across context shifts might therefore result in a reduced switch expansion effect. This interpretation is consistent with prior neuroimaging data, which has shown that hippocampal pattern similarity across context changes—a proxy for temporal binding—is associated with temporal memory measures (DuBrow & Davachi, 2014; Ezzyat & Davachi, 2014). Hippocampal damage, therefore, is likely to impair associative binding, which may be particularly important for temporal memory across context shifts. Indeed, we find that the ATL patients show no switch effect and the bilateral patients ($n = 2$) show switch compression, consistent with the view that hippocampal damage impairs associative binding, particularly across changing contexts. An alternative explanation for the reduction of the switch expansion effect—and reversal in the bilateral patients—could be that the context-switch items "drop out" of the memory representation. To the extent that these items may be used to infer temporal distance (Block, 1974; Ornstein, 1969), a failure to encode or remember the intervening items may eliminate or reverse the effect. That said, we note that we did not find a relationship between recognition memory and the switch expansion effect.

Although ATL patients did not show a significant difference in the switch effect relative to the control group overall, the category-specific analysis did reveal a significant difference between controls and the ATL patients for object stimuli. If anterior hippocampal damage specifically impairs face binding, we might have predicted this result. Although a large body of neuroimaging work suggests that hippocampal binding is content-general (LaRocque et al., 2013; Staresina, Duncan, & Davachi, 2011; Preston et al., 2010; Diana, Yonelinas, & Ranganath, 2007; Davachi, 2006), there is evidence that hippocampal content sensitivity varies along the anterior–posterior axis (Robin, Rai, Valli, & Olsen, 2019; Liang, Wagner, & Preston, 2013), with faces preferentially represented in anterior MTL regions (see also Inhoff et al., 2019). Rather than content specificity, another possible explanation for the null effect collapsed across categories is that hippocampal stability in posterior hippocampus specifically (which is relatively preserved in anterior temporal lobectomies) may support temporal memory. Indeed, Ezzyat and Davachi (2014) found that left posterior hippocampus was the only region to show similarity across context shifts that related to temporal distance memory. This is also consistent with the view that posterior hippocampus represents fine-grained positional information compared with more global, gist-level information in anterior hippocampus (see Poppenk, Evensmoen, Moscovitch, & Nadel, 2013, for a review).

Separable Contributions of Episodic Memory and Temporal Perception on Temporal Distance Memory

Irrespective of the switch expansion effect, patients in our study also exhibited worse temporal distance memory overall when compared with controls. However, this differential effect by group did not remain after controlling for recognition memory, suggesting that recognition memory has a strong influence on temporal distance memory in this task. This relationship was not unique to MTL patients, but also emerged when collapsing across all participants. On the one hand, this relationship may be because of the use of object and face stimuli as cues to make the temporal distance judgment. That is, if the stimuli are not recognized, the temporal distance judgment is likely to be at chance. However, recognition memory was extremely high in this task, even for ATL patients, making it unlikely that the patients did not recognize the cues. Thus, another possibility is that small variations in performance on the recognition memory test may be correlated with episodic memory more generally, which may play an important role in temporal distance judgments from memory.

Interestingly, across all participants, performance on the short-timescale temporal perception task also (independent from recognition memory) contributed to performance on the temporal distance task. Such an effect may be surprising given the distinct timescales of the two tasks: The short-timescale temporal perception task measured duration judgments of 0.5–5 sec, whereas in the temporal distance memory task, the range of tested durations spanned ~6.5–150 sec. This finding also leads to open questions about what range(s) of temporal perception might predict longer-timescale temporal memory. In other words, if we had included a temporal perception task testing durations up to minutes, might we have seen a stronger correlation with temporal memory?

Taken together, this suggests that at least two dissociable cognitive processes may be playing a role in temporal distance judgments—perception of time past as measured in the temporal perception task and episodic memory as measure by recognition memory. Indeed, these may map on to distinct neural mechanisms, as recognition memory, but not temporal perception, was impaired by MTL damage in the present study. This is consistent with theories of short duration estimation and interval timing implicating striatal and dlPFC mechanisms (Meck, Penney, & Pouthas, 2008; Buhusi & Meck, 2005). Furthermore, this potential dissociation between neural systems supporting episodic temporal memory and pure temporal duration perception may help reconcile prior patient data showing mixed results for MTL contributions to timing tasks.

Palombo and colleagues (Palombo et al., 2016) investigated hippocampal contributions to duration judgments on short and long timescales, extending the work of Jacobs and colleagues (Jacobs et al., 2013) to humans. As with the rodent data, hippocampal damage impaired duration discrimination for long but not short durations. The interpretation is that although striatal mechanisms can support time estimation at short timescales, the hippocampus is necessary for time estimation at longer intervals (see also Noulhiane et al., 2007). However, an alternative possibility is that temporal duration may be computed in the striatum, whereas the role of the hippocampus could be limited to episodic retrieval, which is required more in the long compared with the short duration discriminations. This would be consistent with the internal clock models that posit distinct processes for calculating duration versus remembering the reference (Matell & Meck, 2004; Matell & Meck, 2000). Although Palombo and colleagues report a nonsignificant, although trending, relationship between an episodic memory measure and long duration discrimination performance, the analysis was underpowered with only eight patients. Thus, an important area for future research will be in investigating the relationship between long temporal estimation an episodic memory measures, ideally using the same stimuli over the same delay to assess whether a single mechanism could account for both effects.

Finally, we note that it may be surprising that we did not find an effect of MTL lesions on performance in the temporal perception task, given our recent findings that hippocampal pattern similarity tracks duration judgments in a similar task (Sherman et al., 2023). Reconciling the current

findings with the prior fMRI finding suggests that although the (intact) hippocampus may support these short timescale duration judgments, compensatory mechanisms may be at play to support temporal perception in the absence of the hippocampus. Perhaps consistent with this idea, it may be interesting to note that although no significant differences were found between groups in the temporal perception task, all patient groups showed numerically better performance than controls. It has been proposed that competition between hippocampal and striatal timing systems may result in enhanced performance on short duration discriminations following hippocampal damage, based on this finding in rodents (Jacobs et al., 2013). Thus, our results may provide some very preliminary support for competition between MTL and striatal timing systems. However, it is also important to note that patients may also be more motivated, in general, than control participants, as they are involved in the study because of their neurological history.

Conclusion

By assessing memory for temporal duration in patients with MTL damage, this study revealed insights into how the MTL supports temporal memory. First, we found that patients with MTL damage exhibited no "switch expansion" effect in memory, suggesting a critical role for the MTL in binding across context shifts in support of memory. This finding converges with prior patient work (Palombo et al., 2020) and broader proposals (Lee et al., 2020), suggesting that the MTL may be particularly critical for encoding time in the context of episodic sequences (see also Bellmund, Polti, & Doeller, 2020). Second, across all participants, we found that temporal distance memory was distinctly predicted by (i) recognition memory for the stimuli from the temporal distance task and (ii) performance on an independent, short-timescale temporal perception task. This finding suggests that memory for time is not a single process, but instead is multifaceted, dually supported by the mechanisms of perception and memory. Thus, our findings suggest that the MTL may not play a role in supporting timing per se, but instead may support the integration of episodic memories with temporal information to support memory for time.

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Data Availability Statement

This article was originally prepared by the first author, Sarah DuBrow, before she tragically passed away in February 2022. Because all of the authors have moved institutions since the original data collection, we were not able to recover all of the raw data that were the basis of Sarah's original analyses. With the data we were able to recover (complete raw data for 18 patients and partial data for 11 patients, as well as participant-level means for many of the key measures), we were able to qualitatively replicate all results. Anyone interested in accessing the available data can do so by contacting the corresponding author.

Author Contributions

Sarah DuBrow: Conceptualization; Formal analysis; Investigation; Methodology; Software; Visualization; Writing—Original draft. Brynn E. Sherman: Formal analysis; Investigation; Validation; Writing—Review & editing. Michael R. Meager: Project administration; Supervision; Writing—Review & editing. Lila Davachi: Conceptualization; Funding acquisition; Project administration; Supervision; Writing—Review & editing.

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Diversity in Citation Practices

Retrospective analysis of the citations in every article published in this journal from 2010 to 2021 reveals a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience* (*JoCN*) during this period were M(an)/M = .407, W(oman)/M = .32, M/W = .115, and W/W = .159, the comparable proportions for the articles that these authorship teams cited were M/M = .549, W/M = .257, M/W = .109, and W/W = .085 (Postle and Fulvio, *JoCN*, 34:1, pp. 1–3). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article's gender citation balance. The authors of this paper report its proportions of citations by gender category to be: M/M = .38; W/M = .1; M/W = .2; W/W = .32.

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