Behavioral/Cognitive

Maintenance of Procedural Motor Memory across Brief Rest Periods Requires the Hippocampus

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Research on the role of the hippocampus in memory acquisition has generally focused on active learning. But to understand memory, it is at least as important to understand processes that happen offline, during both wake and sleep. In a study of patients with amnesia, we previously demonstrated that although a functional hippocampus is not necessary for the acquisition of procedural motor memory during training session, it is required for its offline consolidation during sleep. Here, we investigated whether an intact hippocampus is also required for the offline consolidation of procedural motor memory while awake. Patients with amnesia due to hippocampal damage ($n = 4$, all male) and demographically matched controls ($n = 10$, 8 males) trained on the finger tapping motor sequence task. Learning was measured as gains in typing speed and was divided into online (during task execution) and offline (during interleaved 30 s breaks) components. Amnesic patients and controls showed comparable total learning, but differed in the pattern of performance improvement. Unlike younger adults, who gain speed across breaks, both groups gained speed only while typing. Only controls retained these gains over the breaks; amnesic patients slowed down and compensated for these losses during subsequent typing. In summary, unlike their peers, whose motor performance remained stable across brief breaks in typing, amnesic patients showed evidence of impaired access to motor procedural memory. We conclude that in addition to being necessary for the offline consolidation of motor memories during sleep, the hippocampus maintains access to motor memory across brief offline periods during wake.

Key words: amnesia; hippocampus; motor learning; offline gains; procedural memory; sharp-wave ripples

Significance Statement

Decades of research have established the hippocampus as the key structure for memory. While this work has generally focused on active learning, it is now clear that to understand memory it is at least as important to understand memory processes that happen offline, during both wake and sleep. In a study of patients with amnesia, we previously demonstrated that although a functional hippocampus is not necessary for the acquisition of procedural motor memory during a training session, it is required for its offline consolidation during sleep. Here, using this same dataset, we show that an intact hippocampus is also required for the offline maintenance of procedural motor learning during brief rest periods while awake.

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Introduction

Decades of research have established the hippocampus as the key structure for the consolidation of declarative memory. While this work has generally focused on active learning, it is now clear that to understand memory it is at least as important to understand consolidation processes that happen offline, during both wake and sleep. In rodents, hippocampal firing during spatial navigation represents ongoing experience. During the wakeful rest and sleep that follow, the hippocampus replays this pattern of firing during sharp-wave ripples (Buzsaki, 2015). Disrupting

hippocampal ripples during either wakeful rest or sleep impairs memory, suggesting that ripple-related replay is necessary for consolidation (Girardeau et al., 2009; Ego-Stengel and Wilson, 2010; Roux et al., 2017). In humans, the consolidation of declarative memory also depends on the hippocampus and presumably memory reactivation during ripples. Procedural memory, in contrast, is classically thought to rely on the striatum (Knowlton et al., 1996; Cavaco et al., 2004). This clear distinction is challenged by evidence that the hippocampus is engaged while learning a procedural motor task (Poldrack and Packard, 2003; Albouy et al., 2013) and that it is required for its offline consolidation over sleep (Schapiro et al., 2019). Specifically, despite intact learning of a procedural motor task during training, patients with dense amnesia due to hippocampal damage failed to show overnight performance improvement (Schapiro et al., 2019). Here, using this same dataset, we investigated whether an intact hippocampus is also required for the offline consolidation of procedural motor learning during brief rest periods while awake. To address this question, we divided motor procedural learning into its online (during active task performance) and offline (during interleaved rest breaks) components.

Neuroimaging studies show hippocampal activation during the learning of motor procedural tasks (Albouy et al., 2008), but the role of the hippocampus is unclear. Recent work shows that during training on the finger tapping motor sequence task (MST; Walker et al., 2002), healthy young adults improve their performance not online, during active typing, but offline, during the interleaved rest breaks (Bonstrup et al., 2019; Jacobacci et al., 2020). In other words, at the end of a typing trial, participants are no faster than when they began, but when they resume typing after a brief break, they are significantly faster. This phenomenon has been labeled micro-offline gains to distinguish it from the more macroscale of offline learning that occurs over hours of sleep (Bonstrup et al., 2019). There is also neuroimaging evidence of increased hippocampal activity and sequential memory replay during rest breaks that predict the level of micro-offline gains (Jacobacci et al., 2020; Buch et al., 2021). This suggests that the hippocampus is involved in motor memory reactivation during rest breaks, reminiscent of what is seen in rodents after spatial navigation (Foster and Wilson, 2006). But neuroimaging studies cannot answer the question of whether the hippocampus is simply engaged during offline motor learning or contributes to that learning. To address this question, we returned to our data from patients with amnesia and demographically matched controls (Schapiro et al., 2019). Based on the previous literature (Bonstrup et al., 2019; Jacobacci et al., 2020), we hypothesized that, unlike controls, amnesic patients would fail to improve motor performance across rest and would compensate during typing periods to achieve the same amount of total learning (i.e., show a pattern of reduced offline gains and greater online gains compared with healthy controls). Such findings would extend our prior study to show that the hippocampus is necessary for the offline consolidation of motor learning during wake as well as sleep.

Materials and Methods

For detailed descriptions of participants and procedures, see Schapiro et al. (2019). Data will be made available upon reasonable request to the corresponding authors.

Participants

Eight patients with medial temporal lobe lesions and 12 control participants enrolled in the study. Four patients and two controls failed to meet the inclusion criterion of typing a minimum of 10 correct sequences on average over the last three trials of MST training (Schapiro et al., 2019). The low scores in the four excluded patients are more likely to reflect motor slowing than a sequence learning deficit, since they were the slowest of all participants on a warmup task that does not require sequence learning (typing 1, 2, 3, 4 as described below). Whereas the four included patients did not differ from control subjects in warmup task typing speed (average time between key presses: 348 ms patients; 408 ms controls; $t_{(14)} = 0.38$, $p = 0.71$), the excluded patients were much slower (783 ms; $t_{(14)} = 4.97$, $p = 0.0002$). Both excluded controls came close to meeting the typing threshold (8.3 and 9.1 average correct sequences), but only one of the four excluded patients was close (P05, 8.6 vs P06, 3.7; P07, 3.2; P08, 3.1). This patient was asked to return for a second training and test session but again failed to meet threshold, with a score of 9.3. Two of the other excluded patients (P07 and P08) had basal ganglia damage in addition to hippocampal loss: one had extensive volume reduction in the caudate, putamen, and pallidum bilaterally (z's < -2.29 relative to 9 age-matched controls) and the other had volume reduction in the left pallidum ($z = -2.68$). None of the other patients had any evidence of basal ganglia involvement.

The etiology of amnesia and demographic and neuropsychological characteristics of the four included patients are provided in Table 1. The average time postinjury was 17.5 years (range, 3.5–27.3 years). The neuropsychological profiles of each patient indicated severe episodic memory impairment (mean general memory index, 64), with otherwise preserved cognition [mean verbal IQ (VIQ), 110; mean working memory index, 109]. Structural MRI showed that two patients (P02 and P04) had lesions restricted to the hippocampus, and one patient had volume loss extending outside of the hippocampus (P01). The remaining patient (P03) had suffered cardiac arrest and could not be scanned due to medical contraindications. Medial temporal lobe damage was inferred based on etiology and neuropsychological profile.

The 10 included control participants were well matched to the included patients in terms of sex (8/10 vs 4/4 male), handedness (9/10 vs 4/4 right-handed), age (mean: 57.7 vs 58.0), years of education (mean: 14.7 vs 16.8), and VIQ (mean: 112 vs 110).

All participants provided informed consent in accordance with the Institutional Review Board of VA Boston Healthcare System and the Declaration of Helsinki.

Experimental design and statistical analyses

MST warmup. To acclimate older participants to the structure of the MST, they were administered a warmup task at the start of each session. Participants rested the four fingers of their left hand on a button box with buttons labeled 1, 2, 3, and 4. They were instructed to repeatedly type the sequence 1-2-3-4 "as quickly and accurately as possible." The sequence remained on the screen during both typing and rest periods. During 30 s typing periods, the screen remained green, and a dot appeared in a horizontal line on the screen for each button press. After the line reached the right border, the dots disappeared one at a time, from right to left, with each additional button press. After 30 s, the screen turned red, and participants rested for 30 s. A countdown of the number of seconds until the screen turned green was displayed as spelled out numbers. The last three numbers were replaced with tones to alert the participants to get ready to resume typing when the screen turned green again. Participants completed two warmup trials.

MST training and testing. MST training took place during the work day (Monday–Thursday, 9 A.M.–4:30 P.M.) at a time that was convenient for the participant. Postsleep testing occurred 24 ± 2 h later to minimize circadian effects. Before each MST administration, participants filled out a survey asking how well they slept the previous night, the duration of their sleep, and how alert they felt. Training and testing blocks had the same structure as the warmup, with 30 s of typing interleaved with 30 s of rest, but consisted of 12 typing trials. Participants were assigned to one of four sequences in a counterbalanced order: 4-1-3-2-4, 1-4-2-3-1, 3-1-4-2-3, or 2-4-1-3-2. The sequence was continuously displayed both on the screen and on an index card placed next to the keypad. Amnesic patients returned for a second session of training and testing on a different sequence an average of 22 ± 2 weeks later. There

Table 1. Demographic and neuropsychological characteristics of amnesic patients

	Etiology	Age (years)	Edu (years)	WAIS III VIQ	WAIS III WMI	WMS III GMI	WMS III VD	WMS III AD	Years since onset	% VL in bilateral hippocampus	% VL in subhippocampal cortex
P01	Status epilepticus + left temporal lobectomy	53	16	93	94	49	53	52	27.3	63%	60%[a]
P02	Hypoxic-ischemic	61	14	106	115	59	72	52	24.2	22%	—
P03	Hypoxic-ischemic	65	17	131	126	86	78	86	15.0	Unknown	Unknown
P04	Stroke	53	20	111	99	60	65	58	3.5	43%	—

Edu, education; WAIS III, Wechsler Adult Intelligence Scale III (Wechsler, 1997a); WMS III, Wechsler Memory Scale III (Wechsler, 1997b); VIQ, verbal IQ; WMI, working memory index; GMI, general memory index; VD, visual delayed; AD, auditory delayed; VL, volume loss.
[a]VL in left anterior parahippocampal gyrus (i.e., entorhinal cortex, medial portion of the temporal pole, and the medial portion of perirhinal cortex).

is no transfer of learning across MST sequences (Walker et al., 2003) and both sessions were included in the analyses.

The primary outcome measures are total micro-online and micro-offline gains in typing speed during training. Typing speed is quantified as the inverse of the average interval between adjacent key presses within each correctly typed sequence (i.e., key presses per second). Micro-online gains are defined as the difference in typing speed between the first and the last correct sequence of each 30 s trial (Fig. 1; Bonstrup et al., 2019). Micro-offline gains are defined as the difference in typing speed between the last correct sequence of a trial and the first correct sequence of the next trial. Total gains are the sum of micro-offline and micro-online gains and are equal to the difference in typing speed between the first correct sequence of one trial and the first correct sequence of the next. The micro-online gain from the last (12th) typing trial was not included in the calculations as there is no subsequent rest period.

Statistical analyses. We assessed differences in total gains between patients and controls using a mixed effects model with Group (Amnesics, Controls) as a fixed effect, and, to account for correlations between repeated measures, we included Subject as a random effect. To test our hypothesis that the relative contribution of micro-online and micro-offline gains to total gains would differ by group, the gains were summed across trials and analyzed using a mixed effects model with Group, Gains (Online, Offline), and their interaction as fixed effects, and Subject as a random effect. To evaluate the effects of order of sessions in amnesic patients, we added Order (first vs second session) to this model as a fixed effect. Group differences in error rate (mean errors per trial) and survey reports of sleep duration, sleep quality, and alertness were assessed using mixed effects models with Group as a fixed effect and Subject as a random effect.

Results

Amnesic and control groups showed significant improvement over MST training (total gains: $F_{(1,16)} = 58.34$, $p < 0.001$; controls: $t_{(9)} = 4.82$, $p < 0.001$; amnesics: $t_{(7)} = 6.77$, $p < 0.001$) and did not differ in total gains in speed ($F_{(1,16)} = 0.10$, $p = 0.75$; Fig. 2). We note that four of the eight patients enrolled were excluded from analyses for failing to meet the motor criterion, raising the question of whether they could learn a motor sequence. The two excluded patients with basal ganglia damage showed no evidence of learning (total gains; P07, 0.05 key presses/s; P08, −0.49; see Extended Data Fig. 3-1 for data from each enrolled participant). They had the lowest total gains of any participant and were >2 standard deviations below the mean of the included patients (1.31 ± 0.55). The additional basal ganglia volume reduction may account for their motor deficits and possible lack of learning. When the data for the other two excluded patients are included (P05: Session 1, 0.77; Session 2, 1.03; P06: 0.50), amnesic patients still showed significant learning ($t_{(10)} = 7.15$, $p < 0.001$) and did not differ from controls in this regard ($F_{(1,19)} = 0.02$, $p = 0.88$). This supports our prior conclusion that an intact hippocampus is not required to learn the MST (Schapiro et al., 2019).

In contrast to the young healthy subjects of prior studies who learned primarily offline (Bonstrup et al., 2019; Jacobacci et al., 2020), in both groups of the present study, almost all of the improvement occurred online. However, the patterns of improvement differed significantly by group (Group × Gains interaction: $F_{(1,32)} = 5.28$, $p = 0.03$). Whereas controls retained their gains in typing speed over the rest breaks (i.e., showed no offline change; $t_{(9)} = 0.01$, $p = 0.99$), amnesic patients showed a trend to lose speed ($t_{(7)} = -2.27$, $p = 0.058$) and showed a corresponding increase in micro-online gains (Figs. 2, 3*A*; Extended Data Fig. 3-1).

Overall, amnesic patients showed a 3.8-fold increase in performance during online periods compared with controls (Fig. 2*B*), averaging 0.41 versus 0.11 key presses/s per trial ($F_{(1,16)} = 2.05$, $p = 0.17$) suggesting that hippocampal lesions might have led to enhanced online learning. Yet total gains (offline + online) were remarkably similar between groups (amnesics, 0.12 key presses/s per trial; controls, 0.11; $F_{(1,16)} = 0.10$, $p = 0.75$), reflecting the fact that during offline periods amnesic patients showed an average decrease in performance of 0.29 key presses/s between the end of one trial and the start of the next, compared with essentially no change for controls (average, 0.002 key presses/s per trial increase; $F_{(1,16)} = 2.09$, $p = 0.17$). (The lack of significance of these group differences likely results from the small sample sizes.) We then performed permutation analyses to test whether the learning curves for offline and online gains differed by group (Fig. 2*B*). The slopes of the 11 training trials for each group were estimated using linear regression (Extended Data Fig. 2-1). We then randomly permuted the group labels and estimated the slopes 10,000 times to create a null distribution of group differences. Consistent with our a priori hypotheses, amnesic patients showed steeper offline losses ($p = 0.038$) and compensated during online periods with steeper online gains ($p = 0.040$) based on one-tailed tests.

This pattern of greater offline losses followed by greater online gains in amnesic patients suggests that their enhanced online learning reflects a recovery of the losses from the previous offline period. To test this hypothesis, we correlated online gains in each trial of each subject with their losses during the previous offline rest period. Significant correlations were found for all amnesic patients in at least one of the two sessions (all p's ≤ 0.008) and for 5 of the 10 controls ($p < 0.05$; Table 2). Using a linear mixed effect model with Block (Training, Test), Group and the interaction of Offline gains by Group as fixed effects, and Subject as a random effect to predict Online gains, the correlation was significant ($F_{(1,352)} = 229.15$, $p < 0.001$) and did not differ by group ($F_{(1,352)} = 0.88$, $p = 0.35$).

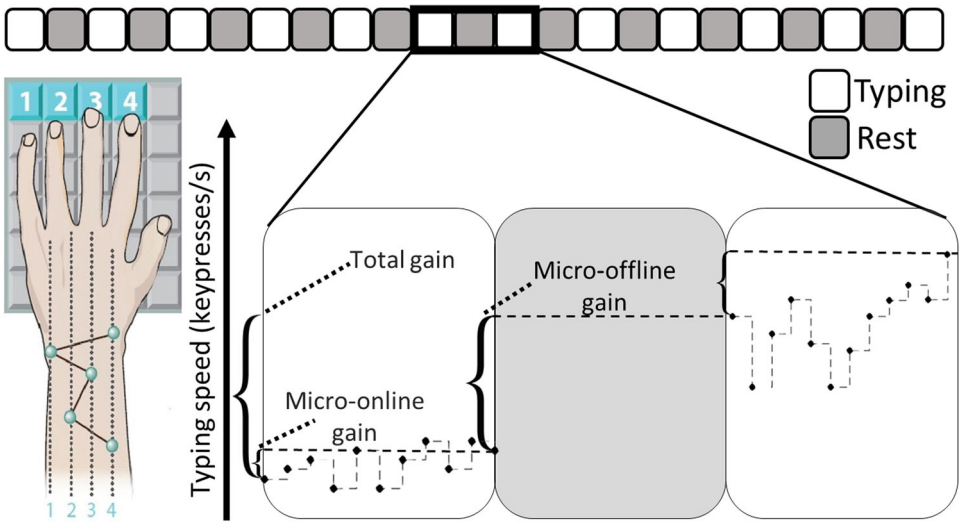

Figure 1. Schematic of total, micro-offline, and micro-online gains. The MST requires participants to repeatedly type a five-digit sequence (e.g., 4-1-3-2-4) on a numerically labeled button box, "as quickly and accurately as possible" for 12 30 s trials separated by 30 s rest periods. Typing speed was calculated as the inverse of the average interval between adjacent keypress within each correctly typed sequence (i.e., key presses per second). For each trial, we calculated micro-online gains as the change in speed from the first to the last sequence of each trial and the micro-offline gains as the change in speed from the last sequence of each trial to the first sequence of the next trial. Total gain is the sum of micro-online and -offline gains across trials.

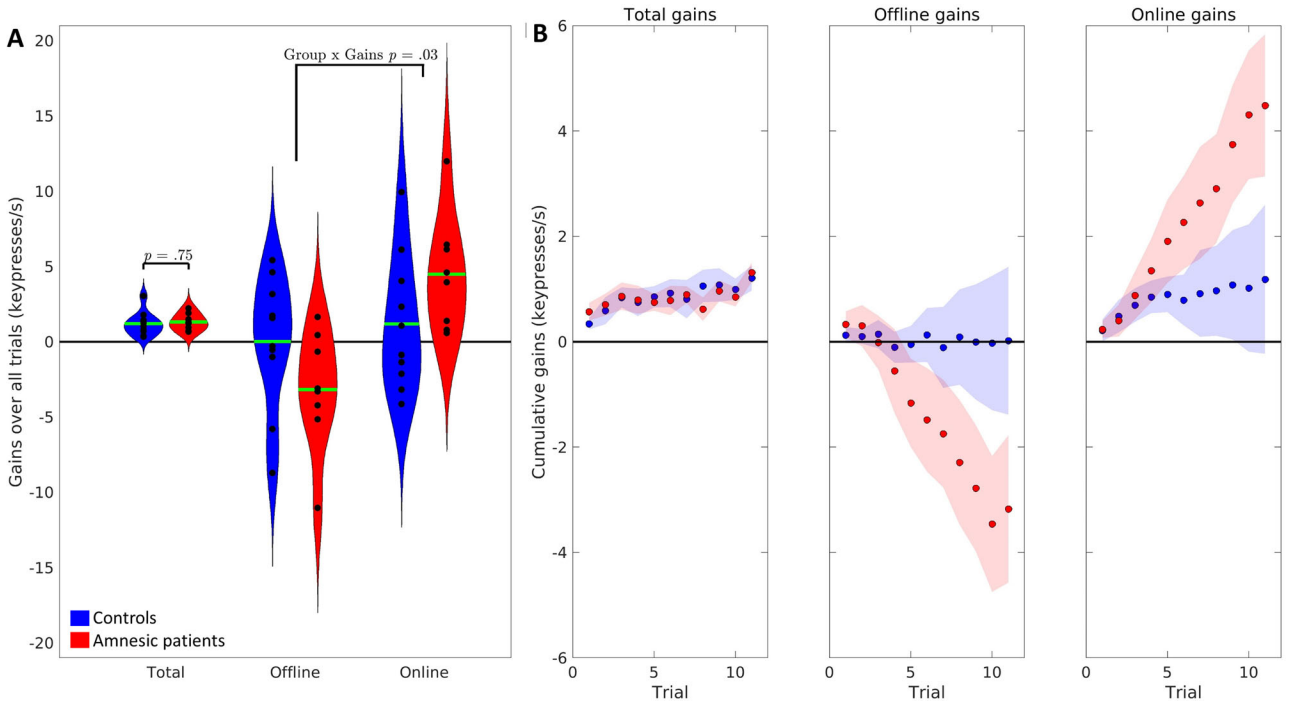

Figure 2. Micro-offline and micro-online gains in speed by group. ***A***, Data points in the violin plots depict the sums of total, micro-offline, and micro-online gains over all trials for each subject. Mean gains per group are shown as green horizontal lines. ***B***, Cumulative sums of total, micro-offline, and micro-online gains per trial for each group. Shaded areas depict the standard errors of the mean for each group. See Extended Data Figure 2-1 for slopes of cumulative micro-offline and micro-online gains by group.

We also compared groups on the latency to the first correct button press for each trial. At the start of each trial, amnesic patients took significantly longer to begin typing (controls, 711 ± 490 ms; amnesics, 1,257 ± 363 ms; $t_{(16)} = 2.62$, $p = 0.02$), raising the possibility that amnesic patients had more difficulty re-establishing the task set. Their latency to begin typing the first digit of a trial, however, did not correlate with the speed of typing that sequence (within-subject correlations all nonsignificant). This suggests that this loss of set did not carry over into impaired typing of the first sequence of the trial.

Control analyses

Our results were similar when we substituted the fastest sequence for the final sequence of the trial in the calculation of gains (Group × Gains interaction: $F_{(1,32)} = 4.79$, $p = 0.04$). The pattern of offline and online gains was the same during the test block, 24 h later (Fig. 3*B*; Group × Gains interaction: $F_{(1,32)} = 4.54$, $p = 0.04$). The groups did not differ in error rate during training ($F_{(1,16)} = 1.13$, $p = 0.30$; controls, 0.88 ± 0.58; amnesics, 1.26 ± 0.79) or testing ($F_{(1,16)} = 0.08$, $p = 0.78$; controls, 1.48 ± 1.24; amnesics, 1.29 ± 0.96), indicating that speed–accuracy trade-offs

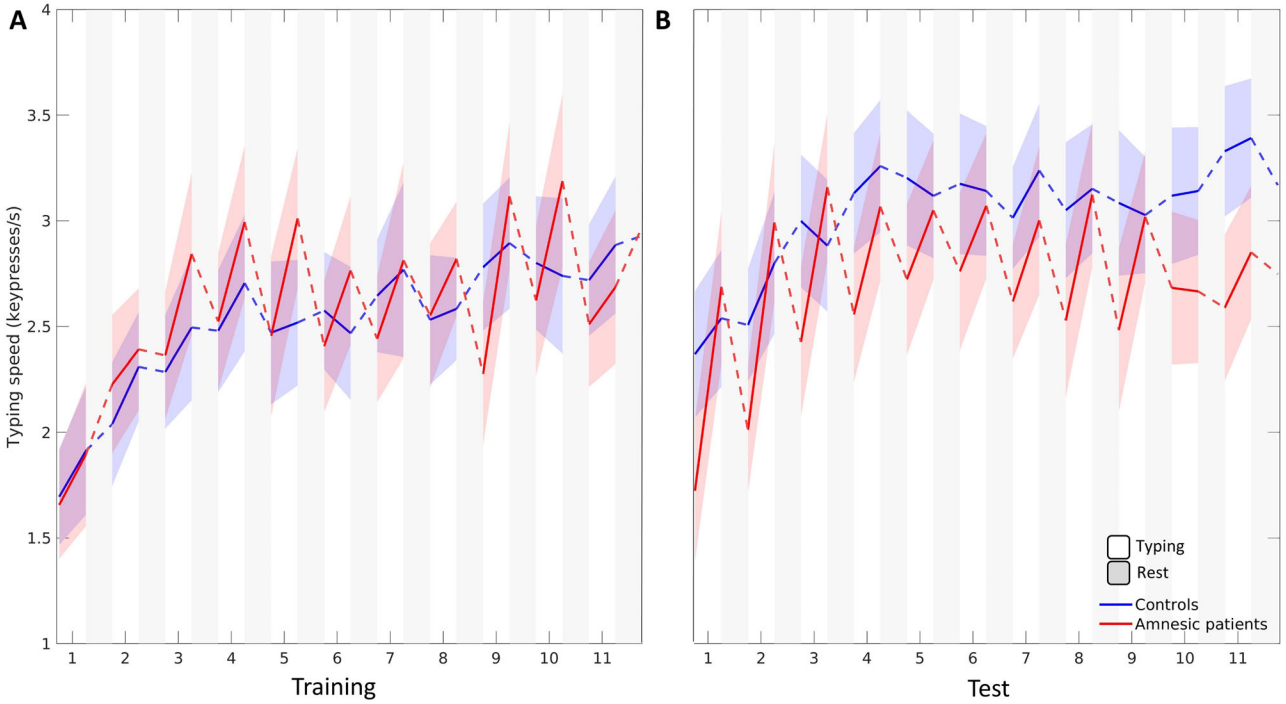

Figure 3. Changes in speed by trial in the training and testing blocks. Typing speed at the beginning and end of each trial per group during the (***A***) training and (***B***) test blocks. Solid lines depict online gains in speed and dashed lines depict offline gains. Shaded areas depict the standard errors of the mean typing speed for each group. See Extended Data Figure 3-1 for data from each enrolled participant.

Table 2. Correlations of online gains for each trial with offline gains of the previous trial by subject and session

Subject	Group	Session	*r*	*p*
P01	Amnesia	1	−0.41	0.07
		2	−0.60	0.005*
P02	Amnesia	1	−0.42	0.06
		2	−0.57	0.008*
P03	Amnesia	1	−0.74	<0.001*
		2	−0.80	<0.001*
P04	Amnesia	1	−0.38	0.10
		2	−0.68	<0.001*
01	Control	1	−0.44	0.054
02	Control	1	−0.48	0.03*
03	Control	1	−0.008	0.98
04	Control	1	−0.42	0.07
05	Control	1	−0.37	0.14
06	Control	1	−0.57	0.009*
07	Control	1	−0.41	0.07
08	Control	1	−0.59	0.006*
09	Control	1	−0.49	0.03*
10	Control	1	−0.53	0.02*

Values with asterisks are significant at $p < 0.05$.

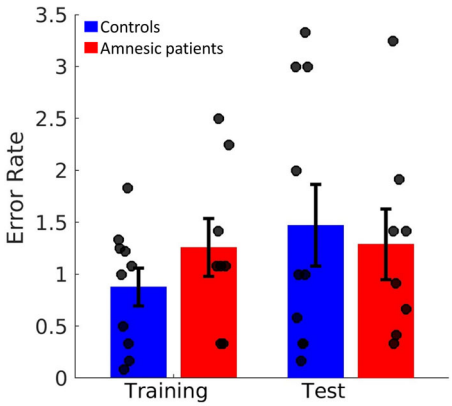

Figure 4. Error rate by group. Bar graphs of mean error rate (errors per trial) for each group with standard error bars. Black dots represent individual data points.

are unlikely to account for group differences (Fig. 4). Nor are group differences in sleep or alertness likely to account for the results. At the training visits, controls and patients reported similar sleep duration (controls, 7.2 ± 1.1 h; patients, 8.0 ± 1.5 h; $F_{(1,16)} = 0.98$, $p = 0.34$) and sleep quality (1 = slept very poorly to 7 = very well; controls, 5.6 ± 1.1; patients, 5.3 ± 0.3; $F_{(1,16)} = 0.27$, $p = 0.61$) the previous night. They also reported a similar level of alertness at the start of training (1 = may fall asleep to 7 = wide awake; controls, 6.2 ± 0.8; patients, 6.1 ± 0.9; $F_{(1,16)} = 0.03$, $p = 0.87$). Amnesic patients had two sessions. When added to our model, there was no effect of Order (first vs second session; $F_{(1,31)} = 0.02$, $p = 0.90$), and it did not change our main result (Group × Gains: $F_{(1,31)} = 5.12$, $p = 0.03$).

Unlike young adults, healthy older participants did not show improvement in motor performance across wakeful rest. To ensure that this was not due to differences in task timing, since some previous studies of young participants used shorter (e.g., 10 s) typing and rest epochs (Bonstrup et al., 2019, 2020), we compared our older control participants to a sample of young participants performing the same task from a previous study (for methodological details, see Mylonas et al., 2020). We matched the age of the sample from Bonstrup et al. (2019; mean ± SEM age, 26.6 ± 0.9) by including all healthy participants aged 35 or younger ($n = 22$; 16 male; age, 27.2 ± 0.7) and compared groups on total gains using a linear model with Group

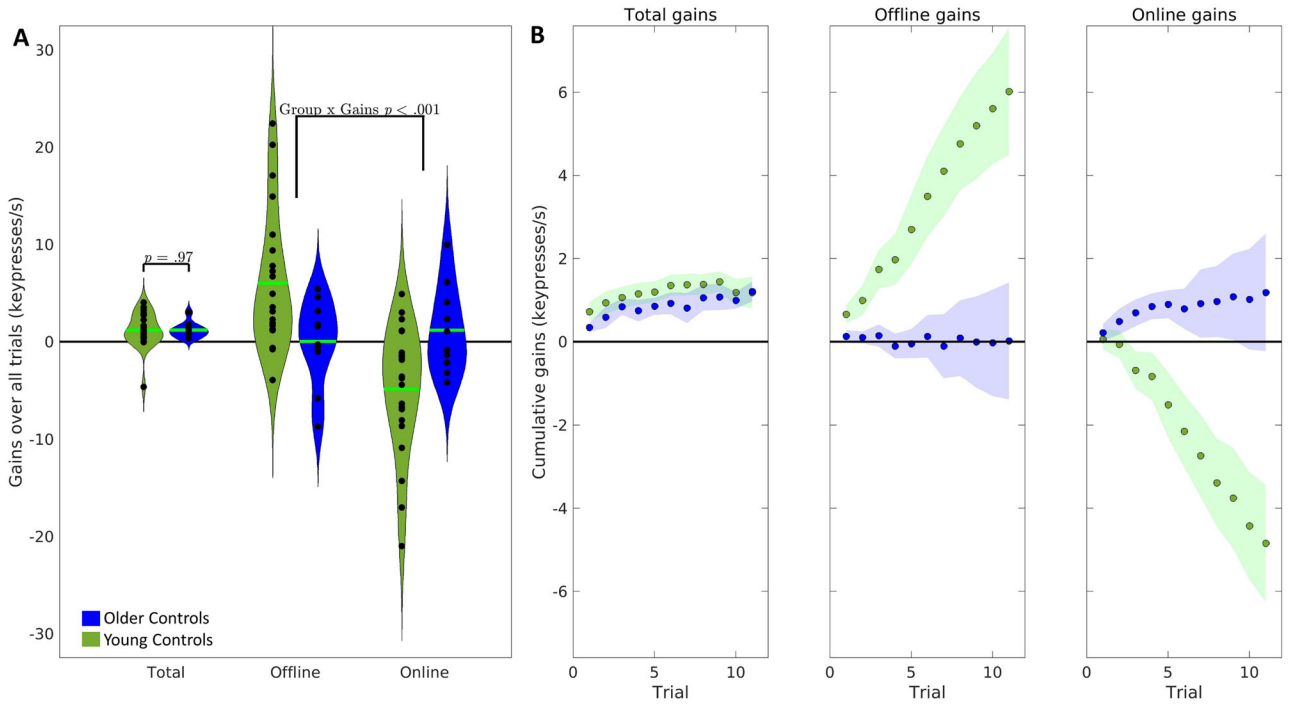

Figure 5. Micro-offline and micro-online gains in speed by group for healthy young and older adults. ***A***, Data points in the violin plots depict the sums of total, micro-offline, and micro-online gains over all trials for each subject. Mean gains per group are shown as green horizontal lines. ***B***, Cumulative sums of total, micro-offline, and micro-online gains per trial for each group. Shaded areas depict the standard errors of the mean for each group.

(Young, Older) as a fixed effect. To assess whether their patterns of learning differed, we used a linear model with Group, Gains (Online, Offline), and their interaction as fixed effects. Young adults did not differ from older adults in total learning ($F_{(1,30)} = 0.001$, $p = 0.97$), but their pattern of offline and online gains differed significantly, with only young adults showing significant improvement offline (Group × Gains, $F_{(1,60)} = 12.71$, $p < 0.001$; young, $t_{(21)} = 3.94$, $p < 0.001$; older, $t_{(9)} = 0.01$, $p = 0.99$; Fig. 5).

Discussion

Contrary to expectations, the improvement in motor performance across wakeful rest reported in young participants was absent in older participants. For both groups, improvement occurred only during typing. Across training, both groups improved almost the same amount: they started out and ended up typing at approximately the same speed. Despite similar total gains in speed, as expected, amnesic patients showed a different pattern of learning than their healthy peers. Controls maintained their performance across the offline rest breaks, whereas amnesic patients slowed down. Amnesic patients achieved a similar total amount of learning as controls by making up for their offline losses by showing greater gains during online typing. These findings lead us to conclude that the hippocampus is necessary for the maintenance of motor procedural memory across brief periods of wakeful rest.

The present findings differ from those of previous studies of young healthy individuals (mean age, ~24) who show most of their performance improvement across offline periods (Bonstrup et al., 2019; Jacobacci et al., 2020). In contrast, both groups in the present study (mean age, 58) only improved online. Across rest periods, controls showed no gains and amnesic participants showed a trend to get slower. The absence of micro-offline gains in older adults is unlikely to reflect the longer typing/rest trials of the present study. When we compare our older control participants to a sample of young adults performing the same task, only the young adults show improvement offline. In the present study, the sequence remained on the screen so that amnesic patients would not forget the task. This may have encouraged explicit rehearsal and disrupted spontaneous hippocampal processing in controls, thereby contributing to their lack of micro-offline gains. Alternatively, the lack of offline learning in older adults may reflect that hippocampal function and memory decline with normal aging (Small et al., 2002). Clearly more research is needed to understand the effects of healthy aging on offline memory.

Recent neuroimaging findings in healthy people show that hippocampal activity increases during brief rest breaks during motor learning (Jacobacci et al., 2020) and that replay of motor sequences during these breaks predicts subsequent performance (Buch et al., 2021). In parallel, rodent studies show hippocampal ripple-related memory replay during wakeful rest (Foster and Wilson, 2006; Diba and Buzsaki, 2007) and that disrupting these ripples impairs memory (Girardeau et al., 2009; Roux et al., 2017). Accordingly, the decrement in performance across rest periods in amnesic patients could result from a loss of hippocampal ripple-related memory reactivation. This loss of reactivation could lead either to forgetting or a failure to stabilize some aspect of the motor memory for ready access when the next typing period begins. The strong correlations between offline losses and online gains in amnesic patients argue strongly against forgetting. Instead they support the hypothesis that the offline deterioration results from the loss of access to memory, a loss that is reversed during the subsequent trial and that is reflected in the large online gains. The increased speed from the end of one trial to the end of the next trial (total gains) would then simply result from practice-dependent learning during that online period that presumably depends on striatal circuitry. Given evidence of competition between hippocampal and striatal circuitry during

learning (Packard et al., 1989; Lee et al., 2008), hippocampal impairment may have facilitated practice-dependent online learning in the amnesic patients.

This temporary loss of access interpretation is also consistent with the finding that amnesic patients exhibited increased latency to begin typing the first sequence of each trial. An access problem may have also been reflected in the slowness of typing the first sequences, although these measures were not correlated. In this view, the failure to maintain performance over rest breaks reflects a struggle to regain access to motor memory. What aspect of the motor memory is temporarily lost is unclear, but recent work suggests a role for the hippocampus in the retrieval of action selection strategies (McDougle et al., 2022) and in linking contexts to existing motor memories (Heald et al., 2023), both of which may depend on cooperative interplay between hippocampal and striatal memory systems (Shohamy, 2011).

A limitation of the present study is that the sample size is small, though comparable with other studies of amnesic patients (Hayes et al., 2012; Hilverman and Duff, 2021). Notably, we observed the same pattern of differential performance improvement during MST testing the following day, suggesting that the results are reliable.

In conclusion, whereas a functional hippocampus is not necessary for the acquisition of procedural motor memory, it influences its course. In addition to being necessary for the offline consolidation of motor memories during sleep (Schapiro et al., 2019), the hippocampus maintains access to motor memory across brief offline periods during wake.

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