The hippocampus is necessary for the consolidation of a task that does not require the hippocampus for initial learning

Anna C. Schapiro1,2,3 | Allison G. Reid4 | Alexandra Morgan1 | Dara S. Manoach2,5,6 | Mieke Verfaellie4,7 | Robert Stickgold1,2

1Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, Massachusetts
2Harvard Medical School, Boston, Massachusetts
3Department of Psychology, University of Pennsylvania, Philadelphia, Pennsylvania
4Memory Disorders Research Center, VA Boston Healthcare System, Boston, Massachusetts
5Department of Psychiatry, Massachusetts General Hospital, Charlestown, Massachusetts
6Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts
7Department of Psychiatry, Boston University School of Medicine, Boston, Massachusetts

Correspondence
Anna Schapiro, Department of Psychology, University of Pennsylvania, 425 S University Ave, Philadelphia, PA 19104, USA.
Email: aschapir@sas.upenn.edu

Funding information
Clinical Science Research and Development Service, Department of Veterans Affairs; National Institutes of Health, Grant/Award Numbers: F32-NS093901, K24-MH099421, R01-MH092638, R01-MH48832, R01-MH67720

Abstract
During sleep, the hippocampus plays an active role in consolidating memories that depend on it for initial encoding. There are hints in the literature that the hippocampus may have a broader influence, contributing to the consolidation of memories that may not initially require the area. We tested this possibility by evaluating learning and consolidation of the motor sequence task (MST) in hippocampal amnesics and demographically matched control participants. While the groups showed similar initial learning, only controls exhibited evidence of overnight consolidation. These results demonstrate that the hippocampus can be required for normal consolidation of a task without being required for its acquisition, suggesting that the area plays a broader role in coordinating memory consolidation than has previously been assumed.

KEYWORDS
amnesics, memory, motor sequence learning, offline consolidation, sleep

1 | INTRODUCTION

The hippocampus plays an important and active role in memory consolidation during sleep (Antony & Paller, 2017). It replays recent experiences during high frequency ripple oscillations that often co-occur with sleep spindles in neocortex, which are themselves associated with memory replay (Cainey, Guttesen, El Marj, & Staresina, 2018; Ji & Wilson, 2007; Nadasdy, Hirase, Czurko, Csicsvari, & Buzsaki, 1999; Peyrache, Khamassi, Benchenane, Wiener, & Battaglia, 2009; Siapas & Wilson, 1998; Sirota, Csicsvari, Buhl, & Buzsaki, 2003; Staresina et al., 2015). This hippocampal–cortical dialogue is thought to facilitate the transfer of new memories encoded in the hippocampus to long term neocortical stores (Siapas & Wilson, 1998). Accordingly, studies to date have focused on uncovering evidence for hippocampal involvement in sleep-dependent consolidation for types of memory that depend on the hippocampus for initial encoding (Antony & Paller, 2017).

The hippocampus could conceivably play a broader role, however, by helping to reinstate extra-hippocampal memory traces for processing during sleep, an idea supported by recent findings in rodents (Sawangjit et al., 2018). There are hints that this may be the case in humans for a motor learning paradigm known as the motor sequence task (MST; Karni et al., 1995). In this task, participants type a five-digit sequence (e.g., 4–1–3–2–4) as quickly and accurately as they can for a number of timed trials. The hippocampus seems unlikely to be necessary for performing this task, as the similar serial reaction time task (SRTT) does not require a healthy hippocampus (Nissen, Willingham, &
Hartman, 1989; Reber & Squire, 1994) for learning simple sequential dependencies (Curran, 1997). At the same time, performance on this task has been consistently found to benefit from sleep (King, Hoedlmoser, Hirschauer, Dolfen, & Albouy, 2017) and there is strong evidence that the hippocampus is involved in this offline consolidation: Hippocampal activity and connectivity with other regions during initial learning is associated with performance improvement across sleep (Albouy et al., 2015; Albouy, King, Maquet, & Doyon, 2013; Albouy, Sterpenich, et al., 2013; Genzel et al., 2015), post-learning hippocampal activity during sleep is associated with improvement (Moroni et al., 2013; Sterpenich, et al., 2013; Genzel et al., 2015), and post-learning hippocampal consolidation, they have often been associated with improvement in tasks (Moroni et al., 2008) and, after sleep, there is increased activity in the hippocampus while performing the task (Albouy, Sterpenich, et al., 2013; King, Saucier, et al., 2017; Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005).

Further indirect evidence that the hippocampus is important for sleep-dependent MST consolidation comes from associations between MST improvement and sleep spindles. Sleep spindles and stage 2 sleep (a stage defined by spindle events) are associated with improvement on the MST (Albouy, Fogel, et al., 2013; Barakat et al., 2013; Barakat et al., 2011; Boutin et al., 2018; Fogel, Albouy, et al., 2017; Fogel, Vien, et al., 2017; Fogel et al., 2014; Laventure et al., 2016; Laventure et al., 2018; Manoach et al., 2010; Nishida & Walker, 2007; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002), and spindles are in turn often associated with hippocampal replay (Ji & Wilson, 2007; Peyrache et al., 2009; Siapas & Wilson, 1998; Sirotta et al., 2003; Staresina et al., 2015). Consistent with the idea that spindles can provide an index of hippocampal involvement in consolidation, they have often been associated with improvement in tasks that are known to depend on the hippocampus (Saletin & Walker, 2012; though not all hippocampally dependent tasks show spindle correlations; Ackermann, Hartmann, Papassotiriopoulos, de Quervain, & Rasch, 2015). In addition, patients with hippocampal sclerosis due to temporal lobe epilepsy and patients with amnestic mild cognitive impairment, which is associated with hippocampal dysfunction (Petersen et al., 2006), have fewer spindles than normal and deficits in consolidation of hippocampally dependent memory (Fuentemilla et al., 2013; Westerberg et al., 2012).

It is unclear from this collection of findings whether the hippocampus plays a causal role in MST learning and consolidation. First, is the hippocampus required for initial learning? There is extensive neuroimaging evidence that the hippocampus is engaged by performing the MST and other motor learning tasks like the SRTT (Albouy, King, et al., 2013; Fernandez-Seara, Aznarez-Sanado, Mengual, Loayza, & Pastor, 2009; Gheyse, Van Opstal, Roggeman, Van Waesvelde, & Fias, 2010; Harrison, Duggins, & Frisén, 2006; Schendan, Searl, Melrose, & Stern, 2003), but we cannot determine from neuroimaging studies whether the hippocampus is necessary for normal MST performance or whether it is merely engaged by it. Amnesics' normal performance on the SRTT (Nissen et al., 1989; Reber & Squire, 1994) favors the latter possibility, though the MST may engage the hippocampus differently. Second, is the hippocampus necessary for normal consolidation of the task? The hippocampus is associated with offline gains in performance in neuroimaging studies, but, again, this may be epiphenomenal.

To answer these questions, we tested learning and consolidation of the MST in patients with severe amnesia due to hippocampal damage and demographically matched control participants. We found that amnesic patients performed similarly to control participants in their initial learning of the MST, indicating that, as in the SRTT, the hippocampus is not required for normal learning. In contrast, unlike controls, the patients exhibited no evidence of overnight consolidation. These findings are consistent with the prior literature but indicate that the previously observed hippocampal engagement in the initial learning of the MST may be primarily setting the stage for later offline involvement. Our results demonstrate that the hippocampus is necessary for the consolidation of a form of memory that does not require the hippocampus for acquisition, suggesting that the hippocampus plays a broader role in memory consolidation than was previously understood.

## 2 METHODS

### 2.1 Participants

Eight patients with medial temporal lobe lesions (6 males, 7 right-handed) and 12 control participants (10 males, 8 right-handed) participated in the study. Etiology for the patients was hypoxic–ischemic injury secondary to cardiac or respiratory arrest (n = 5), encephalitis (n = 1), stroke (n = 1), and status epilepticus followed by left temporal lobectomy (n = 1). All patients were in the chronic phase of illness, with time post-injury ranging from 3.5 to 36.4 years (mean = 21.1).

Four patients and two controls did not meet the inclusion criterion on their first session, which required a minimum of 10 correct sequences on average over the last three trials of training. The average scores for the excluded controls were 8.3 and 9.1 sequences and for patients were 8.6, 3.7, 3.2, and 3.1 sequences. The patient with the highest score was tested on a second sequence, but again failed to meet threshold, with a score of 9.3. The other three patients were not tested on a second sequence. We do not believe that these low scores reflect a sequence learning deficit, but rather a motor deficit. These four patients were also the slowest of all participants on the warmup task (described below), which does not require sequence learning. They average time between key presses during the warmup was 679, 900, 965, and 586 ms, relative to a mean of 348 ms (SD = 180) for other patients and mean of 408 ms (SD = 153) for controls. The group of included patients was no different than the control subjects in warmup task speed (t[14] = .38, p = .71) whereas the excluded patients were much slower (t[14] = 4.97, p = .0002). We include analysis of the data for the excluded participants in the Supporting Information.

Demographic and neuropsychological characteristics for the four included patients are provided in Table 1. The neuropsychological profiles of each patient indicated severe episodic memory impairment (mean General Memory Index = 64.5), with otherwise preserved cognition (mean VIQ = 110.3; mean Working Memory index = 108.5). Lesions for three of the patients are shown in Figure 1. The remaining patient (P03) had suffered cardiac arrest, and could not be scanned due to medical contraindications. Medial temporal lobe pathology for this patient was inferred based on etiology and neuropsychological profile. Two patients (P02 and P04) had lesions restricted to the hippocampus, and one patient had volume loss extending outside of the hippocampus (P01). P04 has a general anxiety disorder, both...
The task was presented to participants on a laptop using MATLAB with Psychophysics Toolbox (Brainard, 1997). Participants were instructed to rest four fingers of their left hand on a button box with buttons labeled 1, 2, 3, and 4. At the beginning of each session, participants completed a warmup task, where they were instructed to repeatedly type the sequence 1-2-3-4 when the screen turned from red to green and to “try to be as fast and accurate as you can.” The sequence was always displayed on the screen, during both rest and typing periods. The number of seconds until the screen turned green was then displayed as spelled out numbers (“ten”, “nine”, “eight”…). The screen remained green for 30 s. With every key press, a new dot appeared in a horizontal line on the screen to provide feedback to the participant that their key press was registered. After the line reached the right side of the screen, the dots then disappeared one at a time with each additional key press. The experimenter wore one earbud through which she would hear a beep whenever the participant pressed a button out of sequence. This allowed her to provide rapid feedback if the participant was not pressing the buttons correctly.

After 30 s, the screen turned red, and participants were instructed to stop typing and take a 30-s break. A 30-s countdown immediately began with the number of seconds left again spelled out on the screen. At the end of the countdown, the screen turned green again for 30 s, and the participants again typed the warmup sequence. If the participant did not yet seem comfortable with the task, the experimenter had the option to initiate additional warmup trials.

Once the participant was accustomed to the task, the experimenter initiated the training phase. The training had the same structure as the warmup, with 30 s of typing interspersed with 30 s of rest. One of four sequences was used: 4-1-3-2-4, 1-4-2-3-1, 3-1-4-2-3, or 2-4-1-3-2. The sequence assignment was counterbalanced across subjects. In addition to the sequence being displayed continuously on the screen, an index card displaying the sequence was also placed next to the key-pad so that participants did not have to look at the screen while typing. Participants completed 12 trials of training. Throughout the session, the experimenter reminded participants to start and stop typing as needed.

This first session took place at a time that was convenient for the participant. Twenty-four hours later, participants completed another warmup and then the test, which consisted of 12 additional trials of the same sequence that they had typed the previous day. Because...
there were a limited number of patients, we aimed to obtain high fidelity estimates of each patient's performance. Patients who met the performance criterion (10 sequences correct across the last three trials of training) for their first sequence were therefore tested again several months later on a second sequence. The sequence assignment was again counterbalanced across participants. Patients completed the same 2-day procedure with the second sequence.

On each day of training or testing, participants filled out a survey asking how well they slept the previous night, the duration of their sleep, and how alert they felt. On the morning of test days, participants also answered these questions using a paper survey filled out at home around the time of awakening.

2.3 | Mixed effects model

To assess whether the patients and controls differed in their behavior across the training and test days, we fit a mixed effects model, with participant as random effect and group, day, trial, and sequence as fixed effects:

$$\text{performance} \sim (1 | \text{participant}) + \text{group} \times \text{day} + \text{trial} + \text{sequence}$$

where day indicates training versus test, and sequence indicates the first or second sequence used for patients. Significance of factors was assessed by removing the factor (or interaction between factors) from the model and assessing the difference between the original and modified models using the $\chi^2$ statistic.

2.4 | Trial outlier removal

As a preprocessing step for percent change analyses, where a small subset of trials was used (making the analyses potentially sensitive to trial outliers), we removed trials for each participant that fell far from an estimated learning curve, as follows. For each participant and each day, a power function ($y = bx^m$) was fit to performance across the 12 trials. The squared residuals for each trial were calculated, and trials falling more than 2 SD outside the distribution of squared residuals across all trials and subjects were excluded. This resulted in exclusion of 19 trials out of 432 (4.4%). Twelve of these trials came from patients and seven from controls. We then averaged the data across the two sequences that each participant completed. When a trial was missing from one sequence and not the other, the non-missing data point was used. This resulted in just one missing trial across all the patient data. Figure 2b,c shows the data for individual controls and patients after this trial exclusion process (dashed blue line indicates the one missing trial for patient data). These preprocessing steps served to provide smoother estimates of patient performance given the small number of patients, minimizing the influence of outlier trials.

2.5 | Percent change calculation

Our estimate of the “initial” percent change from the end of training to the beginning of test was $100 \times (\text{mean of first 3 test trials} - \text{mean of last 3 training trials}) / \text{mean of last 3 training trials}$. The “plateau” change was calculated as $100 \times (\text{mean of last 6 test trials} - \text{mean of last 3 training trials}) / \text{mean of last 3 training trials}$. Percent improvement over the course of training was $100 \times (\text{mean of last 3 training trials} - \text{first training trial} / \text{first training trial})$. Two control subjects were not included in this analysis: For one, the first trial of training was excluded as an outlier, and for the second, a technical issue resulted in loss of data for the first three trials of training (this was the only data loss that occurred during the study). Differences between groups and differences of each group from zero were calculated using two-tailed t tests.

2.6 | Data availability

Behavioral data are available as a Supporting Information File.

3 | RESULTS

3.1 | Sleep and alertness surveys

Controls and patients reported similar amounts of sleep both the night before training (controls = 7.2 ± 1.1 (SD) hr; patients = 8.0 ± 1.5; $t_{[12]} = 1.05, p = .32$) and the night between training and test (controls = 7.3 ± 1.1 hr, patients = 7.8 ± 1.8; $t_{[12]} = .65, p = .53$). They also reported similar sleep quality on both nights (1 = slept very poorly to 7 = very well; pre-training: controls = 6.1 ± .9; patients = 5.3 ± .3; $t_{[12]} = .63, p = .54$; post-training: controls = 5.3 ± 1.1; patients = 5.8 ± .6; $t_{[12]} = .78, p = .45$) and similar alertness (1 = may fall asleep to 7 = wide awake) both at the time of training (controls = 6.2 ± .8, patients = 6.1 ± .9; $t_{[12]} = .16, p = .88$) and at test (controls = 5.9 ± 1.2; patients = 6.3 ± 1.5; $t_{[12]} = .46, p = .65$).

3.2 | Learning time course

Control and patient learning curves were remarkably similar throughout the course of training, whereas the two groups separated in the test phase, with patients performing worse than controls (Figure 2a). Both groups displayed a drop in performance from the end of training to the beginning of test and then a quick rise to a stable performance level that was maintained for the rest of test. This pattern has been observed before in older adult participants performing the MST and may reflect a need for older participants to re-establish a task set before true performance levels can be expressed (Tucker, McKinley, & Stickgold, 2011). A similar lag in test performance has also been seen in younger subjects performing a nine-digit bimanual version of the task (Kuriyama, Stickgold, & Walker, 2004).

To test whether group differences were statistically reliable, we ran a mixed effects model. The model revealed reliable effects of day ($\chi^2[1] = 13.65, p = .0002$), trial ($\chi^2[1] = 78.46, p < .0001$), and, critically, a group by day interaction ($\chi^2[1] = 5.63, p = .018$), with the difference between controls and patients larger at test than during training. This indicates that the amnesic patients showed less offline improvement on the MST than controls. There was no effect of first
versus second sequence ($\chi^2[1] = .06, p = .80$), indicating that patients did not perform differently on their first versus second set of 2-day sessions. The number of correct sequences was very similar for these two sets of sessions: Mean performance across training trials was 13.5 in the first set of sessions and 14.4 in the second set, and mean performance across test trials was 15.9 in the first set of sessions and 15.2 in the second set.

3.3 | Change from end of training to test

Following the analysis strategy of a prior paper assessing MST consolidation in a patient group (Manoach et al., 2010), we calculated for each participant the percent change from the last three training trials to both the first three (initial change) and last six (plateau change) test trials. For the initial change, patients exhibited a near-significant decline in performance (Figure 3; mean = −13.6%, $t[3] = 2.68, p = .075$, Cohen’s $d = 1.34$) whereas at plateau performance they almost fully recovered to the level of performance achieved at the end of training (mean = −1.9%, $t[3] = .36, p = .74$, $d = .18$). Controls, in contrast, performed at the same level at the beginning of test as at the end of training (mean = −.05%, $t[9] = .02, p = .99$, $d = .01$) and showed reliable improvement at plateau (mean = 12.4%, $t[9] = 2.54, p = .032$, $d = .80$). The difference between groups was reliable for the initial change ($t[12] = 2.51, p = .027, d = 1.49$) but not for plateau change: $t[12] = 1.68, p = .118, d = 1.0$.

We verified that these results were qualitatively similar (albeit noisier) when considering only the first of the 2-day sessions completed by the patients. For the initial change, patients exhibited a numerical decline in performance of the same magnitude as seen for the combined visits (mean = 13.3%, $t[3] = 1.60, p = .21$) and a return to training performance at plateau (mean = .0%). Patients performed marginally worse than controls for initial change ($t[12] = 2.00, p = .07$) and numerically worse than controls at plateau ($t[12] = 1.54, p = .15$).

3.4 | Training performance

To verify that there was no difference in initial learning between the two groups, we assessed the percent change from the first training trial to the last three training trials. Percent improvement across training averaged 131% for patients and 176% for controls, levels which were not significantly different between the groups ($t[10] = .41, p = .69$, $d = .25$).

4 | DISCUSSION

These findings demonstrate a critical role for the hippocampus in the consolidation of a task that does not require the hippocampus for initial learning. Performance on the MST was assessed in two sessions separated by 24 hr in patients with amnesia due to hippocampal...
How might the hippocampus be involved in consolidation of the MST? There is evidence that the hippocampus is engaged during initial learning of the task, and that this activity predicts sleep-dependent consolidation (Albouy et al., 2013; Albouy et al., 2008). One version of this possibility is that the hippocampus binds incidentally encoded contextual information with sequential representations stored in other areas. This contextual information could then be revisited during sleep, in turn helping to reinstate the sequential representations stored in the other areas. In other words, the hippocampus could be reminding the sleeping brain that it did a sequence learning experiment earlier that day. Future work will be needed to investigate and adjudicate between these possibilities.

These possibilities assume that patients and controls employed the same learning mechanisms during acquisition, as suggested by their similar learning curves. However, it is worth noting the possibility that patients might have used compensatory mechanisms that are not representative of typical function, for example using their striatum while controls relied more on the hippocampus. This could be assessed in future work by testing whether patients were learning egocentric or allocentric representations of the task.

We based our protocol on a prior MST study in older adults (ages 60–79) who completed a training session and then a test 24 hr later, including a night of sleep, as in the current study, or a training session in the morning and a test 12 hr later, with no intervening sleep (Tucker et al., 2011). The participants in the sleep condition showed a similar pattern to our control subjects, with no initial improvement but reliable plateau improvement. A direct statistical comparison between the control group in the current study and the sleep group from the Tucker et al. (2011) study found no difference for immediate or plateau percent change (ps > .69). The results for participants in the Tucker et al. (2011) wake group were remarkably similar to those for our amnesic patients, with worse initial performance and plateau performance at the same level as performance at the end of training (testing for differences between these two groups: ps > .82). The similarity between the amnesic patients and the healthy older adults in
the wake group suggests that the impact of hippocampal damage on
sleep-dependent memory processing is similar to that of not having
any post-training sleep.

This correspondence between the two studies helps to rule out an
alternative explanation for our results, which is that the hippocampus
is not needed for consolidation but instead for reinstating context of
the task from the previous day (Palombo, Di Lascio, Howard, &
Verfaellie, 2018). If improved performance at test in healthy subjects
is due to the hippocampus reinstating context, then the Tucker et al.
(2011) study should have found improved performance at test in both
the wake and sleep group, as both groups had functioning hippo-
campi. Thus, hippocampal context reinstatement does not appear to
explain MST improvement, and therefore, in turn, is not likely to
explain the difference between patients and controls in the current
study. Taking the results from the two studies together, it seems likely
that hippocampal damage impairs sleep-dependent consolidation of
the MST.

Due to constraints on patient availability, we were limited to a
24-hr design for this study, where the time between training and test
included long periods of both sleep and wake. This design does not
permit direct claims about the sleep-dependence of the observed
effects, separate from effects of elapsed time. However, prior studies
have shown that change in MST performance is similar across 12 hr of
mostly sleep and across 24 hr including both wake and sleep
(Manoach et al., 2004, 2010; Walker et al., 2002). We therefore
expect that the behavior we observed would be similar in a 12-hr
sleep design and that the effects we observed are very likely to be
sleep-dependent.

Older adults do not show the same overall typing speed nor the
same sleep-dependent benefit in initial improvement as younger
adults on the MST (Fogel et al., 2014; Gudberg, Wulff, & Johansen-
Berg, 2015; King et al., 2013; Tucker et al., 2011). Younger adults tend
to show more robust consolidation and a boost in performance in the
first three trials of the test phase after sleep (Walker et al., 2002, 2003).
We followed the same protocol as the study described above
that found no improvement in initial test performance in older adults
but an improvement in plateau performance (Tucker et al., 2011), and
we replicated those findings here in our control participants. Other
studies have looked only at initial performance and found results con-
sistent with ours (Gudberg et al., 2015; King, Saucier, et al., 2017).
One additional study found no benefit of a nap for the MST in older
adults (Fogel et al., 2014), which may have been related to poor per-
formance in the training phase (King, Saucier, et al., 2017). An intrigu-
ing possibility is that the difference between younger and older adults
on this task may be functionally similar to the difference we observed
between patients and controls. There is a known reduction in hippo-
campal function with healthy aging (Golomb et al., 1993) as well as a
reduction in sleep spindles with age (Nicolas, Petit, Rompre, &
Montplaisir, 2001), and the reduction in sleep spindles in older adults
has been related to MST consolidation (Fogel et al., 2014). Thus,
young adults, older adults, and patients with amnesia may fall on a
spectrum of decreasing contribution of the hippocampus and spindles
to consolidation.

There is debate in the literature as to whether the benefit of sleep
to the MST for young adults is to boost performance or simply to sta-
bilize it (Nettersheim, Hallschmid, Born, & Diekelmann, 2015; Pan &
Rickard, 2015), alternatives which tend to support either an active
role for sleep or a passive period of rest and reduced interference.
Though the present findings do not directly speak to this debate or
hinge on it, we believe they are easier to explain from the perspective
of an active role for sleep: If a brain region is not critical for initial
performance of a task but becomes critical offline, it seems likely that
the region is playing an active role during that offline period.

A recent study assessed MST performance in patients experienc-
ing transient global amnesia, a form of hippocampal amnesia lasting
less than 24 hr (Dohring et al., 2017). During training, these patients
typed fewer sequences overall than controls but exhibited similar per-
cent improvement across training. Patients were tested on the same
sequence again 2 days later, when they were no longer experiencing
amnestic symptoms, and they performed in the same range as control
subjects who were learning a new sequence. Improvement across
days was larger in patients than controls, which the authors inter-
preted as evidence that consolidation boosted performance more in
patients than controls. However, the findings can also be interpreted
simply as better overall performance outside of an acute amnestic
state. We therefore do not view these findings as inconsistent with
ours. Another recent study assessed learning of the MST in patients
with hippocampal dysfunction associated with medial temporal lobe
epilepsy (Long, Feng, Liao, Zhou, & Urban, 2018). During training,
patients initially performed at the same level as controls, but their per-
cent improvement across training was reliably lower than controls.
This is a counterintuitive finding, as the disruption to hippocampal
function in these patients is likely much less than that in our patients,
who have substantial hippocampal lesions. One possibility is that hip-
nocampal dysfunction in epilepsy patients may disrupt hippocampal-
striatal interactions during learning (Albouy, King, et al., 2013),
whereas larger hippocampal lesions may leave the striatum to act
more functionally and independently. This is an interesting possibility
to explore in future work. For now, our sample of patients demon-
strates that it is possible to exhibit normal MST learning despite
extensive hippocampal damage.

While we have demonstrated that the hippocampus can be
involved in the consolidation of a task that does not require the hip-
pocampus for initial learning, we are not claiming that the hippocam-
pus is necessarily involved in the offline processing of all such tasks. It
is possible that the hippocampus is involved in consolidation of the
MST specifically because it is attuned to sequential information, for
example (Fortin, Agster, & Eichenbaum, 2002). The classic literature
looking at retention of nondeclarative memory across days in amne-
sics may seem to support this idea, as the general claim has been that
amnestic shows impressive retention of hippocampally independent
memory across days (Cohen & Squire, 1980; Corkin, 1968; Gabrieli,
Corkin, Mickel, & Growdon, 1993; Nissen et al., 1989; Warrington &
Weiskrantz, 1968). However, (a) the evidence is mixed or absent as to
whether the forms of memory tested in these studies have consolid-
ation components that are sleep-dependent, (b) initial task learning is
typically not comparable between amnesics and controls in these studies (or there are no controls), making it difficult to assess whether there are deficits in offline changes, and (c) there often do appear to be deficits in performance change from the end of one day of training to the beginning of the next for amnesics in these studies. We thus view this literature as consistent with the possibility that the hippocampus plays a general enough role in encoding experience and its context that it will be important for a broad range of tasks that undergo sleep-dependent consolidation. A recent study in rats lends direct support to this claim, showing that the hippocampus is critical for the sleep-dependent consolidation of a hippocampus-independent novel object recognition task (Sawangjit et al., 2018). More work is still needed to determine the precise scope and nature of hippocampal involvement, but these findings open the door to new possibilities for the offline functions of the hippocampus by providing a proof of concept that the hippocampus can be critical for offline consolidation a task even when it is not necessary during initial learning.

ACKNOWLEDGMENTS

We thank James Antony for helpful discussions. This work was supported by NIH F32-NS093901 (ACS); NIH R01-MH48832 (RS); NIH R01-MH67720 (DSM); NIH R01-MH092638 (DSM); NIH K24-MH099421 (DSM); Senior Research Career Scientist Award from the Clinical Science Research and Development Service, Department of Veterans Affairs (MV). The contents of this manuscript do not represent the view of the US Department of Veterans Affairs or the US Government.

ENDNOTE

1 Two of these patients had basal ganglia damage: one had extensive volume reduction in caudate, putamen, and pallidum bilaterally (z’s < −2.29), and the other had reduction in left pallidum only (z = −2.58). The former patient additionally has bipolar disorder. It is possible that these factors contributed to the slower motor performance in these patients.

ORCID

Anna C. Schapiro https://orcid.org/0000-0001-8086-0331
Alexandra Morgan https://orcid.org/0000-0001-7787-0547
Dara S. Manoach https://orcid.org/0000-0001-9208-1167
Mieke Verfaellie https://orcid.org/0000-0001-5535-4584
Robert Stickgold https://orcid.org/0000-0003-3971-744X

REFERENCES


**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Schapiro AC, Reid AG, Morgan A, Manoach DS, Verfaellie M, Stickgold R. The hippocampus is necessary for the consolidation of a task that does not require the hippocampus for initial learning. *Hippocampus*. 2019;1–10. https://doi.org/10.1002/hipo.23101