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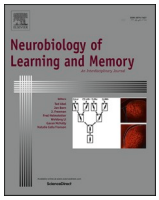

The effect of interference, offline sleep, and wake on spatial statistical learning

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ABSTRACT

Statistical learning, the ability of the human brain to uncover patterns organized according to probabilistic relationships between elements and events of the environment, is a powerful learning mechanism underlying many cognitive processes. Here we examined how memory for statistical learning of probabilistic spatial configurations is impacted by interference at the time of initial exposure and varying degrees of wakefulness and sleep during subsequent offline processing. We manipulated levels of interference at learning by varying the time between exposures of different spatial configurations. During the subsequent offline period, participants either remained awake (active wake or quiet wake) or took a nap comprised of either non-rapid eye movement (NREM) sleep only or NREM and rapid eye movement (REM) sleep. Recognition of the trained spatial configurations, as well as a novel configuration exposed after the offline period, was tested approximately 6–7 h after initial exposure. We found that the sleep conditions did not provide any additional memory benefit compared to wakefulness for spatial statistical learning with low interference. For high interference, we found some evidence that memory may be impaired following quiet wake and NREM sleep only, but not active wake or combined NREM and REM sleep. These results indicate that learning conditions may interact with offline brain states to influence the long-term retention of spatial statistical learning.

1. Introduction

The ability of the human brain to uncover patterns organized according to probabilistic relationships between elements and events in the environment is called statistical learning (Fiser & Lengyel, 2019). Statistical learning is hypothesized to be a domain-general learning mechanism (Perruchet, 2019; Perruchet & Pacton, 2006) that may underlie several higher-order cognitive processes, including language learning (Saffran et al., 1996) and object and scene recognition (Fiser & Aslin, 2001). Statistical learning is rapid and implicit – it is evident after only a few minutes of exposure (Aslin et al., 1998; Kim et al., 2009; Saffran et al., 1996; Szegedi-Hallgató et al., 2017) and occurs without explicit awareness of the underlying statistical structure (Fiser & Aslin, 2002a; Kim et al., 2009), though attention to the stimuli may be beneficial (Richter & de Lange, 2019; Turk-Browne et al., 2005). In typical laboratory studies of statistical learning, participants are passively exposed to stimuli that have been organized into patterns based on a probabilistic rule. These patterns may be arranged according to temporal regularities (e.g., item B follows item A in a visual stream) (Fiser & Aslin, 2002a; Saffran et al., 1999), spatial configurations (e.g., item B is located to the left of item A) (Fiser & Aslin, 2001, 2002a; Karuza et al., 2017), or a combination of temporal and spatial components (Janacsek et al., 2012). After a brief exposure period, people can correctly recognize familiar patterns (Fiser & Aslin, 2001) with a decreased reaction time on a detection task (Bays et al., 2016; Kim et al., 2009; Turk-Browne et al., 2005). However, observers are not typically aware of

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this implicit knowledge and cannot recreate patterns on an explicit matching test (Kim et al., 2009; Turk-Browne et al., 2005).

Many studies have examined the initial, fast-learning phase of statistical learning that occurs during initial exposure and allows for the rapid extraction of associative relationships that are tested shortly after exposure (Aslin & Newport, 2012; Schapiro et al., 2012). However, given that statistical learning is posited to be a general learning mechanism (Aslin, 2017; Fiser & Aslin, 2001; Kirkham et al., 2002; Thiessen et al., 2013), it should also persist over extended delays and perhaps generalize to novel stimulus sets. In other words, following the initial fast-learning phase, there may also be a slow-learning phase that occurs offline and allows for further processing of the previously learned material (i.e., consolidation), which could lead to myriad behavioral outcomes, including maintenance of the learning (Kim et al., 2009; Kobor et al., 2017), improved recognition of the statistical structure (Durrant et al., 2011), abstraction of the underlying structure (Gómez et al., 2006), and insight (Wagner et al., 2004). Sleep has been shown to benefit consolidation in many learning domains (Diekelmann & Born, 2010), including declarative memory (Gais et al., 2006; Mednick et al., 2013), motor skill learning[5], implicit priming (Cai et al., 2009), and perceptual learning (McDevitt et al., 2013, 2015; Mednick et al., 2003). In studies examining the role of sleep for consolidation of statistical learning, some have reported a sleep-related benefit for learning temporally-structured sequences (Durrant et al., 2011, 2013, 2016; Lutz et al., 2018), whereas others have not found sleep effects on the consolidation of implicit statistical learning in temporal probabilistic learning tasks (Simor et al., 2019).

In contrast to prior studies that have studied consolidation of temporal regularities, the current study examined the role of sleep for consolidation of visual statistical learning of probabilistic relationships between elements in space (Fiser & Aslin, 2001). Spatial statistical learning is distinct from the large subdomain of temporal statistical learning, and it refers to the fact that all relevant statistical structure during training is conveyed in the spatial domain (Fiser & Aslin, 2001, 2002b, 2005; Lee et al., 2021; Orban et al., 2006; Plaut & Vande Velde, 2017). That is, the order of the sequentially appearing scenes provides no information that could be learned; all information is provided through the relative spatial position of two (or more) given shapes within a scene. Some of this spatial information is useless as various pairs of shapes can be positioned next to each other in random arrangements in a given scene, while other spatial information is highly relevant as it indicates the fixed spatial relation of two shapes across the entire training session. Since the pairs are typically placed on a grid, there is no apparent segmentation of shape-pairs within a scene; all that the observer sees is six shapes next to each other in an apparently random arrangement. From this initial perception, the observer evolves an implicit realization by the end of the familiarization that some shape pairs are more related to each other, and they are able to reliably distinguish between such fixed pairs and not so fixed pairs during the test.

We aimed to test how visual statistical learning of spatial patterns was consolidated across four offline brain states – active wake (AW), quiet wake (QW), naps with non-rapid eye movement (NREM) sleep only, and naps with both NREM and REM sleep. Since our prior work reported that REM sleep was critical for consolidating perceptual learning that was disrupted by interference (McDevitt et al., 2015), we also asked whether spatial statistical learning is vulnerable to task-specific interference, and if interference effects interact with offline consolidation states. Finally, we examined the abstraction of statistical learning rules to a novel stimulus set following the sleep or wake period. This is an important question because prior studies have implicated sleep, in particular REM sleep, in the development of rule abstraction (Walker & Stickgold, 2010), while other work has shown that REM sleep contributes to the high specificity of perceptual learning (Mednick et al., 2003). The current design will test the specificity of spatial statistical learning and the role of sleep therein.

We created two within-subject interference conditions by varying the time between learning exposures of different task sets (McDevitt et al., 2015; Seitz et al., 2005). Each set was composed of unique objects paired together in probabilistic spatial relationships. For the *high interference* condition, subjects were exposed to two, unique sets close together in time (~1 min). For the *low interference* condition, a third, unique set was exposed in isolation an hour after exposure to the first two sets. Following these exposure periods, we used a between-subjects nap paradigm, which provides experimental control of sleep stages and circadian influences (Mednick et al., 2003), to create four distinct brain states for offline processing of the high and low interference statistical learning. Following an offline period containing either AW, QW, NREM only, or NREM + REM sleep, participants were exposed to a novel configuration and were tested for recognition of the trained and novel configurations.

In summary, the present study tested the following three predictions: (i) memory for visual statistical learning of spatial patterns would be impaired for the task sets encoded under conditions of high interference compared to low interference; (ii) NREM sleep alone would be sufficient for producing a sleep-related performance benefit in the low interference condition, whereas REM sleep would be necessary in the high interference condition; and (iii) if REM sleep facilitates abstraction of statistical learning rules, then learning a novel stimulus set would be boosted by REM sleep during the preceding offline period.

2. Materials and methods

2.1. Subjects

183 healthy, non-smoking adults between the ages of 18 and 35 with no personal history of neurological, psychological, or other chronic illness gave informed consent to participate in the study. All experimental procedures were approved by the Institutional Review Boards of the University of California, San Diego and University of California, Riverside. Subjects were asked to maintain their usual sleep-wake schedule during the week prior to the experiment and to refrain from consuming caffeine, alcohol, and all stimulants for 24 h prior to and including the study day. Heavy caffeine users (>3 servings per day) were not enrolled to exclude the possibility of significant withdrawal symptoms during the experiment. Subjects completed sleep diaries during the entire week prior to the experiment and wore actigraph wrist monitors (Actiwatch-64, Respironics) the night before the experiment to provide subjective and objective measures of sleep-wake activity, respectively. We also surveyed the napping habits of a subset of participants (n = 150, those who participated in the full-day study). 81% of our participants (n = 122) were considered "habitual" nappers (they reported napping at least once per week), and the remaining 19% (n = 28) reported napping less than once per week or never (McDevitt et al., 2018).

2.2. Stimuli and task (Fig. 1)

Subjects completed a task similar to that developed by Fiser and Aslin (Fiser & Aslin, 2001). Twenty-four complex shapes were created from simple two-dimensional figures. The shapes were black on a white background and were displayed within a 5 × 10 grid. The maximum height and width of the shapes were scaled to be equal and half of the size of a grid cell. Stimuli were presented using the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997) for Matlab (See Fig. 1).

The stimulus set was divided into four sets (Sets A, B, C and Y) of six

[5] However, it remains debated if the benefit of sleep for motor learning is due to release from reactive inhibition (Pan & Rickard, 2015; Rickard et al., 2008), recovery from waking decay (Cellini & McDevitt, 2015; Nettersheim et al., 2015), stabilization (Brawn et al., 2010), or absolute enhancement (Korman et al., 2007; Walker et al., 2003) of the practiced motor sequence.

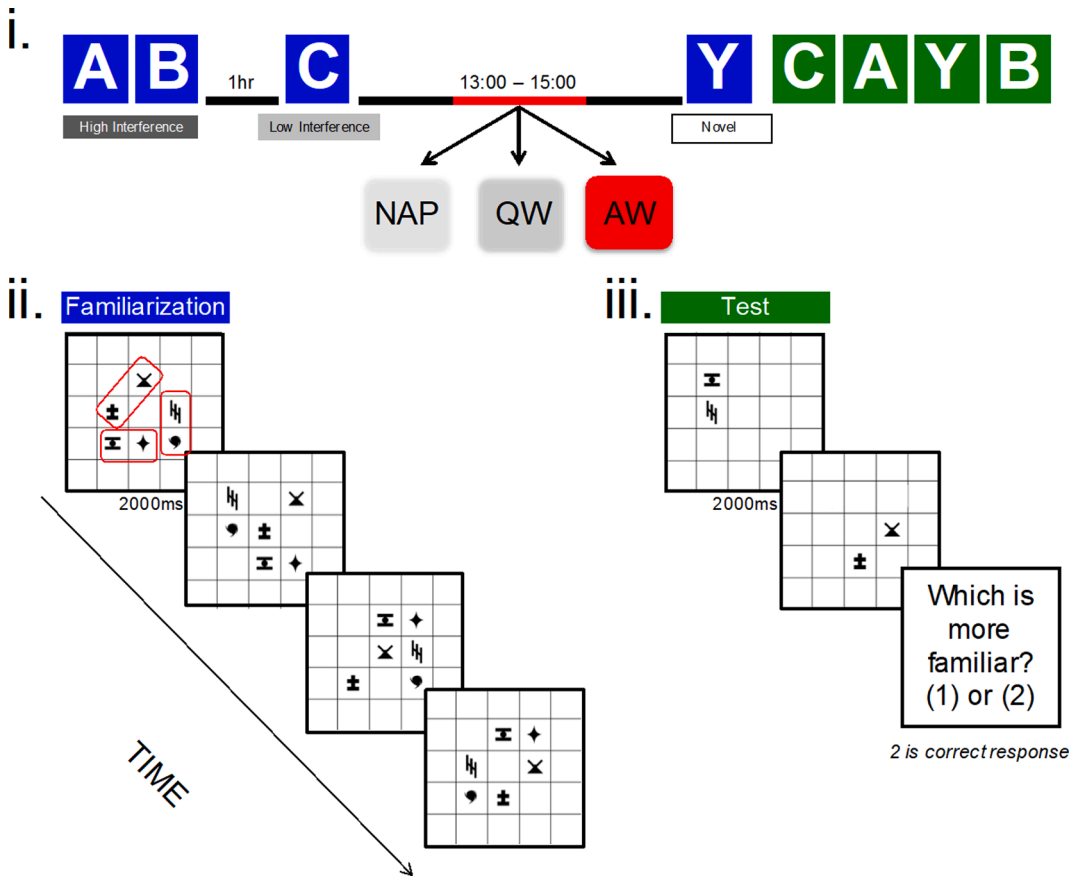

Fig. 1. Experimental methods. **i.)** Participants were familiarized (blue boxes) and tested (green boxes) on four tasks sets (A, B, C and Y) following a specific time-course that created the following three within-subject task conditions: high interference, low interference, and novel. Between sessions, participants took a nap, rested quietly (quiet wake, QW) or carried out their usual daily activities outside of the lab (active wake, AW). **ii.)** In the familiarization phase, participants passively viewed scenes composed of six shapes that, unbeknownst to the participant, were consistently organized into three base pairs. Base pairs followed a specific spatial relationship – either horizontal, vertical, or oblique (red outlines are for demonstration purposes only; participants were not explicitly informed about base pair relationships). **iii.)** In the test phase, participants completed a two-alternative forced-choice (2AFC) recognition test. On each trial, a base pair and non-base pair were shown sequentially in different positions in the grid; base pairs always maintained the same spatial relationship (horizontal, vertical, or oblique) as the familiarization phase. Participants were asked to judge if the first or second pair of shapes was more familiar. Note that the actual displays used in the experiment were 5 × 10 (not 5 × 5) grids, but that the six shapes were always grouped together on the right or left half of the grid, so the relative distances between shapes displayed here are accurate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

shapes each, thereby creating four versions of the task each with unique shapes. The six shapes within each version were organized into three base pairs. Each base pair consisted of two given shapes in a particular, invariant spatial relationship (horizontal, vertical or oblique), hence base pairs can be conceptualized as rigid unknown objects in a scene (**see** Fig. 1.**ii**). The assignment of shapes to one of the four task versions was set. Within a version, the specific assignment of the six shapes to the three base pairs was randomized across subjects to ensure that specific shape pairs were not more (or less) easily learned.

Scenes were created by positioning the three base pairs in the grid so that each base pair would neighbor at least one of the other pairs. Positioning was determined pseudo-randomly with the constraint that within a version all base pairs were grouped either on the right side or left side only of the display. Since the two shape elements of a base pair always appeared together, the joint probability of the two shapes in each base pair was 1.00. The configuration of the base pairs resulted in accidental co-occurrences when one shape of one base pair was located next to another shape of a different base pair. However, the joint probability of such coincidental non-base pairs was much smaller than that of the base pairs.

The task consisted of two phases: familiarization and test. During familiarization (Fig. 1.**ii**), subjects saw 90 scenes per version one time each (a total of 4.5 min per version). Each scene was shown for 2 s, with a 1 s inter-trial-interval between scenes. Subjects were told to pay attention to the continuous sequences of scenes so that they would be able to answer some simple questions after the familiarization phase. No further instructions were given, thereby ensuring that subjects were unaware of the spatial patterns in the scenes. During the test phase (Fig. 1.**iii**), subjects completed a two-alternative forced-choice (2AFC) recognition test. Each test consisted of 18 trials in which a base pair and non-base pair were shown sequentially in different positions in the 5x10 grid. Base pair shapes were always shown in the same orientation relative to one another, but their position on the grid varied across trials. Each pair was presented for 2 s, with a 1 s pause between pairs. Subjects were asked to judge if the first or second pair of shapes was more familiar, and responded with a keypress ("1" or "2").

2.3. *Task paradigm and interference conditions*

Over the course of the study day (Fig. 1.**i**), participants were exposed to and tested on four task Sets. These Sets all contained unique shapes but followed the same underlying pattern of three base pairs constructed from two given shapes in a particular spatial relation (horizontal, vertical or oblique). Critically, the familiarization phase for each Set followed a specific time course, which created three within-subject task conditions: high interference, low interference, and novel. First, Set A

and Set B were shown one after the other with only a short break between Sets (~1 min) when the experimenter entered the room and launched the Set B task. Set C was exposed 1 hr after Set B. Finally, Set Y was exposed following a 7 hr offline period that contained either wake or sleep (see section *2.4 Protocol*).

Together, Set A and Set B formed the high interference condition, since learning two similar pieces of information back-to-back is known to impair memory retention (Wixted, 2004). Set C was the low interference condition, since it was neither immediately preceded nor followed by another task Set (Seitz et al., 2005), but could still be impacted by interference due to general mental exertion (Wixted, 2004). The novel Set Y allowed us to examine if sleep or wake during the 7 hr offline period aided abstraction of the underlying rules, thereby facilitating learning of new base pairs that followed the same spatial configuration rules as Sets A-C. The four versions of the task were counterbalanced across Sets and subjects.

2.4. Protocol (*Fig. 1.i*)

Subjects completed familiarization of Sets A and B from 09:00–09:10 and familiarization of Set C at approximately 10:10. During the 1 hr interval between Set B and Set C familiarization, subjects were engaged in other (unrelated) laboratory tasks. At 11:00, subjects were randomly assigned to one of four groups. Subjects in the AW group ($n = 48$) left the lab and carried out their normal daily activities, but were instructed to abstain from exercise, caffeine, and napping. Wakefulness in the AW group was monitored using actigraph wrist monitors. Subjects in the QW group ($n = 34$) rested in the lab for 75-min (from ~ 13:00–14:15) while sitting in a recliner with their eyes closed and listening to classical music, with online polysomnographic (PSG) monitoring to make sure they did not fall asleep. During QW sessions, experimenters woke subjects at the first sign of Stage 1 sleep. Subjects in the two nap groups were randomly assigned to take either a 60-min or 90-min nap with PSG-recording between 13:00 and 15:00. Given that shorter naps tend to have less REM sleep than longer naps, the use of these two durations increased the likelihood of having naps with and without REM sleep (Mednick et al., 2003). Post-hoc sleep stage scoring was used to categorize subjects into either the REM ($n = 38$, naps contained more than one minute of REM sleep) or NREM ($n = 30$) group. At 16:30, Set Y familiarization was completed, followed immediately by the test phase of all four sets in one of two counterbalanced orders (ACBY or CAYB).

Most statistical learning studies measure learning shortly following familiarization (~5–15 min). However, the design of our experiment required that we test learning following a longer retention interval (~7hrs), and as such, we could not include an immediate test without confounding the delayed test. Therefore, we obtained a measure of immediate test performance 10 min after familiarization of one Set of stimuli (i.e., no interference) in a separate group of subjects ($n = 14$). These subjects completed the familiarization phase of one Set only (i.e., Set A) between 9:00–12:00, followed by a 10 min distractor task (coloring a picture) and the Set A test phase.

2.5. Polysomnography

PSG data were collected using Astro-Med Grass Heritage Model 15 amplifiers and Grass Gamma software. Scalp electroencephalogram and electrooculogram electrodes were referenced to unlinked contralateral mastoids (C3/A2, C4/A1, O1/A2, LOC/A2 and ROC/A1), and electromyogram electrodes were attached under the chin to measure muscle tone. PSG data were digitized at 256 Hz and visually scored in 30-second epochs according to the sleep staging criteria of Rechtschaffen and Kales (Kales & Rechtschaffen, 1968), except that we adopted the AASM standard of combining stages 3 and 4 into one stage N3 (which we also refer to as slow wave sleep). A participant's data were excluded and replaced if sleep efficiency during the nap was <60% ($n = 18$), or if post-hoc sleep scoring indicated that a subject had >5 min of Stage 1 sleep in the QW group ($n = 1$).

We used the automated spindle and slow oscillation (SO) detectors described in Zhang et al. (Zhang et al., 2020) to quantify the number and density of spindle and slow oscillation events during stage 2 and slow wave sleep. Power spectra were calculated by Fast Fourier Transform for frequency bands of interest: delta (0.5–4 Hz) in stage 2 and slow wave sleep, and theta (4–8 Hz) in REM sleep.

2.6. Statistical analyses

Performance was quantified as the percentage of trials (out of 18 trials per Set) during the test phase in which the base pair was selected as being more familiar than the non-base pair. Chance performance was 50%. Performance in the immediate test comparison group served as a measure of learning shortly after familiarization without interference or offline sleep/wake manipulations, henceforth referred to as ImmTest.

Data were analyzed using SPSS 23.0 and JASP 0.9.2. We ran one-way and mixed-model ANOVAs (task condition as the within-factor and offline group as the between-factor), and we employed contrast analyses to test our *a priori* hypotheses. If the omnibus ANOVA was non-significant, we conducted additional exploratory analyses to examine simple effects (all *t*-tests were family-wise corrected for multiple comparisons such that total alpha for a family of comparisons never exceeded 0.05). One-sample *t*-tests compared performance to chance to determine if significant learning was detected. Independent sample *t*-tests compared performance in our experimental groups and conditions to ImmTest to determine if significant disruption or enhancement of learning was detected.

Pearson correlations examined the relation between sleep physiology and behavioral performance. Benjamini–Hochberg correction with a false discovery rate set at 5% was used to control for multiple correlations (Benjamini & Hochberg, 1995).

3. Results

3.1. Experimental nap polysomnography

Nap PSG data are summarized in Table 1. By design, the REM group had greater total sleep time ($t(66) = 4.84$, $p < .001$) and minutes of REM ($t(66) = 8.62$, $p < .001$) than the NREM group. The REM nap group also had greater sleep efficiency than the NREM group ($t(66) = 2.11$, $p = .04$). There was no difference in sleep latency ($p = .61$), minutes of stage 1 ($p = .91$), stage 2 ($p = .20$), slow wave sleep ($p = .83$) or wake after sleep onset ($p = .95$) between groups. The groups also did not differ in the count and density of sleep spindles, SO count or density, or delta power

Table 1
Nap polysomnography sleep descriptives.

	NREM group	REM group
Total sleep time (min)	58.3 ± 15.9	77.4 ± 16.4
Stage 1 (min)	5.0 ± 4.3	5.1 ± 3.1
Stage 2 (min)	38.3 ± 15.3	42.9 ± 14.1
Slow wave sleep (min)	15.0 ± 11.6	15.6 ± 11.8
Rapid eye movement (min)	0.0 ± 0.0	13.9 ± 9.9
Sleep latency (min)	7.4 ± 4.4	6.8 ± 4.7
Wake after sleep onset (min)	7.6 ± 6.3	7.7 ± 8.1
Sleep efficiency (%)	80.0 ± 9.4	84.5 ± 8.1
Spindle count (stage 2)	183.47 ± 87.26	222.32 ± 81.28
Spindle count (SWS)	65.97 ± 60.82	81.92 ± 67.69
Spindle density (stage 2)	5.05 ± 1.14	5.30 ± 1.21
Spindle density (SWS)	4.61 ± 1.71	5.39 ± 1.55
SO count (stage 2)	104.40 ± 65.92	129.53 ± 49.20
SO count (SWS)	43.97 ± 37.02	50.21 ± 41.17
SO density (stage 2)	4.84 ± 2.02	5.14 ± 1.32
SO density (SWS)	5.70 ± 1.92	5.77 ± 1.62

Note: Data are mean ± SD. Spindle count and density, SO count and density are selected from the channel C3.

during stage 2 and slow wave sleep (all *ps* > 0.10; we did not compare theta power since the NREM group had zero minutes of REM sleep).

3.2. Immediate test performance

Performance in the immediate test comparison group was significantly better than chance [$t(13) = 4.44, p = .001$] (ImmTest performance is the blue line plotted in Figs. 2 and 3). Mean accuracy was 63.1% (SD = 11.0). Subsequent analyses will compare performance in the experimental groups to this performance benchmark to examine whether performance is disrupted or enhanced following low or high interference and consolidation.

3.3. Interference effects on statistical learning

First, we confirmed that the test order of the sets (ACBY or CAYB) did not impact performance on any set (i.e., cause interference at retrieval; Set A (p =.94), Set B (p =.50), Set C (p =.46), Set Y (p =.29)).

We examined if offline brain state interacted with interference condition (Fig. 2, see also Supplementary Fig. 1). A 3 × 4 mixed ANOVA with Set (A/B/C) as the within-subject factor and Group (AW/QW/NREM/REM) as a between-subject factor did not find significant main effects of Set [$F(2,292) = 2.00, p = .14$] or Group [$F(3,146) = 1.24, p = .30$], and no significant Set × Group interaction [$F(6,292) = 1.35, p = .24$]. This suggests that overall, the different task conditions did not create detectable amounts of impairment due to interference, and interference at encoding did not interact with offline brain states to modulate performance 7 h later. However, examining group differences within each task condition (high and low interference) separately showed a more nuanced picture.

3.4. Low interference condition

Both wake and sleep groups showed performance significantly greater than chance (all *ps* < 0.003) in the low interference (Set C) condition, although there was no difference in Set C performance between groups [$F(3,146) = 0.18, p = .91$]. Performance in each group also did not differ from the ImmTest benchmark (all *ps* > 0.30). We also ran a contrast analysis to specifically test our *a*-priori hypothesis that the NREM and REM nap groups would show a sleep-related benefit compared to AW and QW (using contrast weights AW: -0.5, QW: -0.5, NREM: +0.5, REM: +0.5). However, the contrast analysis revealed that the data did not follow the predicted pattern of results [$t(146) = 0.38, p = .71$]. In further support of the finding that final performance did not depend on sleep, there were no significant correlations between total sleep time or minutes in any sleep stage and Set C performance in the nap groups (all *ps* > 0.07). There was a significant correlation between delta power and Set C performance in the NREM group (during both stage 2 and slow wave sleep) that we report in Supplementary Table 1 for descriptive purposes, but given the lack of an overall sleep effect, we hesitate to interpret these correlations as extremely meaningful.

Together, these results demonstrate that when exposure to one task Set was isolated in time (i.e., low task-specific interference), the magnitude of learning measured in Session 2 did not depend on a period of sleep between familiarization and test. Additionally, performance was neither enhanced nor disrupted compared to ImmTest, suggesting that 1) low interference did not disrupt learning, and 2) all four offline conditions maintained (but did not enhance) the magnitude of learning apparent shortly after familiarization.

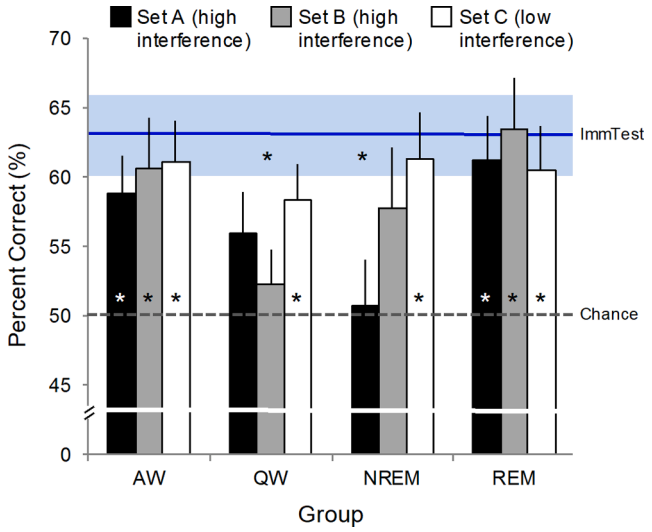

Fig. 2. Set A, B and C performance. Sets A and B are the high interference condition; Set C is the low interference condition. The darker blue line indicates ImmTest mean performance and light blue bands are ± 1 SEM. Asterisks above chance line indicate recognition performance significantly greater than chance (all *ps* < 0.001). Memory impairment (i.e., not greater than chance performance) was apparent for high interference Sets A and B in the QW and NREM groups. All groups showed performance greater than chance for low interference Set C. Asterisks below the blue ImmTest line indicate recognition performance significantly worse than the ImmTest comparison group for Set B in QW and Set A in NREM. All asterisks indicate p <.05. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

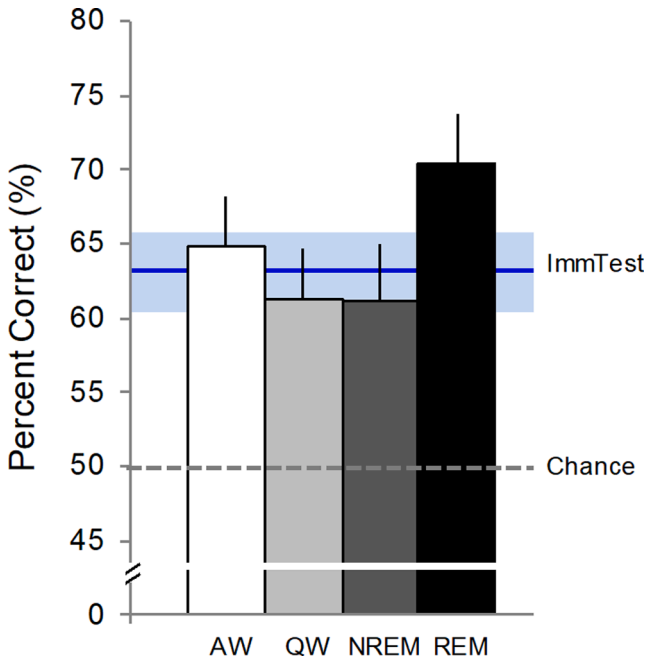

Fig. 3. Set Y performance across conditions. Set Y showed greater than chance performance in all groups, and no difference between groups. Learning may have been facilitated in the REM group, however, this did not reach statistical significance compared to ImmTest (dark blue line is ImmTest mean and light blue bands are ± 1 SEM). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.5. High interference condition

Next, we examined memory in the high interference task conditions (Sets A and B). Overall, there was no interaction between Set (A/B) and Group [$F(3,146) = 1.21, p = .31$]. Comparing performance on each Set to chance, we found that only the AW and REM groups showed memory above chance (all *ps* < 0.005); subjects in the QW and NREM groups did not recognize base pairs over non-base pairs better than chance level (all *ps* > 0.05). Compared to ImmTest, the NREM group showed retroactive

interference of Set A (p =.03, all other groups $ps > 0.17$), whereas the QW group showed proactive interference of Set B (p =.02, all other groups $ps > 0.32$). No Group/Set combination showed significant enhancement compared to ImmTest. Total sleep time and minutes in each sleep stage were not correlated with Set A or B performance in the nap groups (all $ps > 0.12$; see Supplementary Table 1 for correlations with sleep events and power spectra). Together, these data suggest that learning may have been impaired due to the combination of high interference during encoding and QW/NREM brain states during offline consolidation. AW and REM consolidation brain states appeared to be resilient to the detrimental effects of interference.

3.6. Novel set (Fig. 3)

All four groups performed greater than chance level on the novel Set Y (all $ps < 0.009$), and a one-way ANOVA found no differences between groups [$F(3,146) = 1.39$, p =.25]. Further, there were no significant correlations between total sleep time or minutes in any sleep stage and Set Y performance (all $ps > 0.16$) in the nap groups. We next asked if learning of novel Set Y would be facilitated due to prior experience with similar learning rules in Sets A-C. We compared Set Y performance to ImmTest since these two conditions had an equivalent retention interval (i.e., 10 min). Set Y performance was not statistically different from ImmTest in any group (all $ps > 0.12$), suggesting that prior experience with the task did not provide a learning boost.

Despite the lack of statistical significance, visual inspection of the data shows that performance on Set Y in the REM group ($M = 70.3\%$, $SE = 3.5$) was numerically better than any other group [AW ($M = 64.8\%$, $SE = 3.4$), QW ($M = 61.3\%$, $SE = 3.3$) and NREM ($M = 61.1\%$, $SE = 4.0$)] or task condition. We conducted exploratory within-subject comparisons between performance on Set Y and Set C to see if new Set Y learning was facilitated compared to low interference Set C learning. The difference in performance between Set C and Y was only significant in the REM group [$t(37) = 3.06$, p =.004; all other $ps > 0.26$), which may suggest that Set Y performance was boosted in the REM group. Within the REM group, Set Y performance was correlated with both the number of spindles and slow oscillation events during stage 2 sleep (Supplementary Table 1). Although we cannot claim that REM sleep facilitates abstraction in this task, we also cannot completely rule out an effect of REM.

3.7. Task awareness

At the conclusion of the study, we asked a subset of our participants (n = 60) if they noticed any patterns in the task, and 3 participants (5%) reported noticing the spatial positions of the base pairs relative to one another.

4. Discussion

The goals of the current study were three-fold. Using a spatial statistical learning task in which participants passively learned spatial relations between unique shapes, we asked if 1) sleep benefits consolidation of spatial statistical learning; 2) statistical learning is impaired by task-specific interference, and if so, does REM sleep "rescue" learning; and 3) sleep, specifically REM sleep, supports abstraction of learning rules, thereby facilitating statistical learning of a novel stimulus set. Contrary to our predictions, we found no evidence of sleep-dependent consolidation of statistical learning in the low interference condition. When we introduced additional task-specific interference, both AW and REM sleep groups showed robust amounts of learning, whereas learning was disrupted in both the QW and NREM groups. This suggests that, similar to perceptual learning, task-specific interference does render some impairment for spatial statistical learning, and that REM sleep can help overcome this interference, but this benefit is not exclusive to REM sleep. Finally, we found weak evidence of a REM sleep benefit for abstraction, but further studies are needed to confirm this finding.

Only a handful of prior studies have examined statistical learning over the "long-term" (i.e., >30 min) (Kim et al., 2009; Kobor et al., 2017). Kim et al. (Kim et al., 2009), exposed subjects to a stream of abstract objects for 5 min and tested implicit learning of the temporal relationships either immediately after exposure or 24hr later. They found that implicit learning was *maintained* across the 24hr delay, with neither deterioration nor enhancement of performance. However, this study design did not consider the possible evolution of memory across a day of wake, or the possibility that sleep was a critical factor contributing to the maintenance of the learning. For example, it has been demonstrated in the motor domain that waking provides an early boost to performance 30 min after learning, followed by performance decay over the next 4 hr, and subsequent sleep restores performance to the early-boost level (Nettersheim et al., 2015). As such, sleep eliminated the detrimental effects of waking, but did not actually provide any performance enhancement. Another study sought to further define the time-course of statistical learning by testing people 30 min, 1 hr, 2 hr, 4 hr, or 24 hr post-familiarization (Arciuli & Simpson, 2012). They found that memory was evident at each test delay, with no differences in the magnitude of performance based on test delay. These data suggest that statistical learning remains stable up to 4 hr after familiarization and is not enhanced by sleep. Our findings contribute to this growing body of work by demonstrating that statistical learning under conditions of low interference (Set C) did not deteriorate across 7 hr of wake, and, therefore, sleep was not required to maintain performance.

Further, similar to findings from a recent study (Simor et al., 2019), we did not find a sleep benefit for consolidating this memory. Our results are also in concordance with previous work that reported an equivalent benefit of sleep, quiet wake and active wake on a contextual cueing visual search task (Mednick et al., 2009). Similar to the spatial statistical learning in this study, contextual cueing involves implicit memory for repeated patterns in visual displays.

However, our results differ from previous studies that found improved recognition of statistical relationships after sleep (Durrant et al., 2011, 2013). In these experiments, participants were exposed to a sequence of auditory tones arranged according to a probabilistic structure. Then, they were tested on recognition of novel sequences that either followed the same structure or a random structure. Performance on the recognition task was *enhanced* after both daytime naps and nighttime sleep compared to equivalent amounts of time awake (Durrant et al., 2011). Sleep also facilitated cross-modal transfer of statistical learning from the auditory to visual domain (Durrant et al., 2016). In both studies, the magnitude of behavioral enhancement/transfer was associated with minutes of slow wave sleep (SWS) obtained. Furthermore, in both the unimodal and cross-modal paradigms, SWS was also shown to predict changes in brain activation (weaker parahippocampal and stronger striatal responses) following sleep (Durrant et al., 2013, 2016). These data suggest that sleep consolidation of statistical learning may involve a gradual shift of the representation to the striatal network and less dependence on the hippocampus (Durrant et al., 2013), in line with models of systems-level consolidation that predict a decrease in hippocampal involvement as connections in the long-term store are strengthened (Frankland & Bontempi, 2005). Another study found that sleep improved predictive sequence coding of implicitly learned visual-temporal sequences, suggesting that sleep worked to consolidate an internal model of the trained sequence which led to better prediction ability (and stronger prediction errors) at test (Lutz et al., 2018).

Given the conflicting findings on the role of sleep for statistical learning, one possibility is that spatial statistical learning without a temporal component may not rely on sleep-dependent consolidation to the same extent as sequence-based learning. The temporal scaffolding hypothesis (Lerner & Gluck, 2019) proposes a bias toward sleep-dependent explicit detection of temporal, compared to stationary, regularities. This is because exposure to temporal regularities during real-

time waking experience often occurs over much longer timescales than typical Hebbian mechanisms (several seconds vs. 50–200 ms). If these sequential, episodic experiences, which likely depend on the hippocampus (Schapiro et al., 2012), are subsequently replayed at a compressed timescale during sleep as suggested by research in rodents (Ji & Wilson, 2007), they now fall within the Hebbian timescale. Thus, revisiting the regularities during sleep will help build up the cortical representation, thereby yielding a sleep-dependent benefit.

Another interesting comparison to consider is the difference between novel object learning and spatial learning in rodents. The novel object learning task tests an animal's ability to discriminate between a familiar and novel object; although the objects extend in space, the learning does not depend on space (or temporal, sequential information) itself. This is in contrast to spatial navigation learning, which involves an animal making sequential movements through space, and inherently involves a critical temporal component. Spatial navigation learning is known to strongly engage the hippocampus and depends on sleep consolidation (Ego-Stengel & Wilson, 2010; Nguyen et al., 2013; Orban et al., 2006). On the other hand, novel object learning may be more supported by the cortical structures of the medial temporal lobe and shows less dependence on sleep consolidation (Buffalo et al., 2006; Cohen & Stackman, 2015; Ishikawa et al., 2014; Oliveira et al., 2010). Our spatial SL task can be viewed as a simple instantiation of novel object learning, where the base pairs are objects in a cluttered, unknown environment (Fiser, 2009), and is in line with research suggesting object recognition does not depend on sleep consolidation to the same extent as more complex types of learning involving temporal sequences or other associative information (Ishikawa et al., 2014; McDevitt et al., 2014)

However, there are many studies that do show sleep effects on visuospatial learning in humans, including many that used targeted memory reactivation during SWS to presumably bias replay of object-location learning (Rasch et al., 2007; Rudoy et al., 2009). In many of these studies, the tasks involve explicit memory (i.e., declarative memory) for object-location associations. In contrast, although the test phase is explicit recognition, the initial learning in our study was implicit – participants were only instructed to watch the scenes and never given an explicit learning goal or strategy. Furthermore, in the previous declarative memory studies, the behavioral benefit of sleep was seen as a reduction in forgetting, not performance enhancement. In contrast, the spatial statistical learning in our study was not subject to forgetting (in the low interference condition), which hints at learning mechanisms fundamentally different from the declarative memory system. This study adds to the growing body of work suggesting that both statistical learning, and the effect of sleep on consolidation more generally, strongly depends on the characteristics of the task used to induce learning and probe memory (e.g., spatial vs. temporal, implicit vs. explicit, stronger hippocampal vs. weaker hippocampal engagement) (Arnon, 2020; Bays et al., 2016; Lerner & Gluck, 2019).

We found that high interference at encoding could only be overcome by active wake (AW) and REM sleep during the offline period, whereas performance was disrupted in the QW and NREM groups. A similar pattern of results (i.e., parallel performance profiles between AW and REM nap groups, and between QW and NREM nap groups) was reported in a prior study examining novel object learning (McDevitt et al., 2014). The AW and REM naps facilitated segmentation of novel objects embedded in backgrounds of camouflage, whereas QW and NREM naps did not. We hypothesized that similar learning profiles in AW and REM may be explained in part by the shared functional and neuromodulatory features that promote synaptic plasticity in these two brain states (Buzsáki, 1989; Hasselmo, 1999; Hasselmo & Bower, 1993; Matsukawa et al., 1997), and are distinct from QW and NREM brain states, which do not favor synaptic plasticity (Jones Leonard et al., 1987; Mednick et al., 2011).

In the current study, performance deficits were specific to the combination of high task interference and QW/NREM offline states. If we assume that Set A and B representations were weaker than Set C at the time of QW/sleep onset (due to interference during learning), then one possibility is that consolidation during QW and NREM states prioritized stronger Set C information and punished weaker Set A/B information (Wei et al., 2016), although there is also evidence showing weaker information is prioritized during QW (Schapiro et al., 2018). Alternatively, there may have been relatively more downscaling of Set A/B synaptic connections compared to Set C (Tononi & Cirelli, 2014). In addition, although both groups showed interference, the interference profiles were different from each other, with the NREM group specifically demonstrated impairment of Set A (i.e., retroactive interference), whereas the QW group showed impairment of Set B (i.e., proactive interference). On a related note, computational models that simulate encoding multiple memories predict that NREM slow oscillations promote competition between distinct memory traces thereby biasing consolidation to the stronger trace (Wei et al., 2018). Crucially, the QW and NREM experimental conditions were not followed by a period of REM sleep, which may be an important brain state for recovering weak memories and resolving interference (Baran et al., 2010; McDevitt et al., 2015; Norman et al., 2005). Indeed, behavioral performance was intact in the REM sleep condition in which participants cycled through both NREM and REM sleep. In this framework, although AW and REM sleep conditions yielded similar behavioral outcomes, the underlying representations likely underwent different neural modifications. This highlights the importance of future research to understand the content and dynamics of memory reprocessing during wake and sleep, and to measure the transformation of the underlying neural representations.

Finally, we found weak evidence of a possible REM sleep benefit for abstraction. If REM sleep does benefit abstraction on this task, one possibility is that REM sleep (or the combination of NREM + REM sleep) helped to consolidate the general rules of the task so that they could be applied more flexibly in a new learning environment (Batterink et al., 2014; Nieuwenhuis et al., 2013). Another possibility is that synaptic downscaling during sleep helped reduce or eliminate weak or noisy connections, freeing networks for encoding of new, similar materials. According to the synaptic homeostasis hypothesis (Tononi & Cirelli, 2014), downscaling during sleep is indexed by slow wave activity, although there is emerging evidence that REM sleep is also important for synaptic rescaling (Grosmark, Mizuseki, Pastalkova, Diba, & Buzsáki, 2012; Klinzing et al., 2019; Niethard et al., 2021). Interestingly, we found that stage 2 spindles and slow oscillation events were correlated with Set Y performance, but only in the REM group. This suggests that memory processing during NREM sleep was modulated by a subsequent period of REM (Batterink et al., 2017) and that downscaling mechanisms may have played a role in Set Y performance in the REM group. However, our data does not necessarily support one hypothesis over the other, and further studies that examine the effect of sleep on rule abstraction should attempt to dissociate these factors.

A limitation of this study is that session 2 always started with the learning of the novel set, which could proactively interfere with subsequent retrieval testing. This proactive influence is difficult to predict as it may depend on multiple aspects of the design. For example, adding the novel set could impair learning, but this depends on a number of aspects of the context, including not only the sleep/wake condition but also similarities between the two shape sets and the overall complexity of the stimuli. Similarly, it could benefit the spatial configuration learning, but only to the extent to which there is a similarity in the configurations across the two sets, and even that link is modulated by sleep/wake conditions and the extent of the familiarization. Future studies are needed to tease apart the interaction between different statistical learning events. In the current study, we focused on investigating the sleep/wake effect by minimizing other variables: the spatial configuration structure was the same across the sessions; the familiarization and test conditions were kept identical, and the allocation of the shapes to different sessions was randomized to keep similarity effects counterbalanced. Another limitation is that the retention interval for set C set was about one hour shorter than for sets A and B, and it was familiarized

closest to the sleep intervention, both of which could contribute to the overall better performance for set C, regardless of low interference conditions.

In summary, we have found no evidence for sleep benefitting spatial statistical learning under low task-specific interference conditions. Exploratory analyses discovered some preliminary evidence that interference can impair statistical learning, although the damage was only evident following an offline period of QW or NREM sleep, whereas AW and REM sleep consolidation brain states were resilient to these effects.

CRediT authorship contribution statement

Elizabeth A. McDevitt: Investigation, Methodology, Data curation, Formal analysis, Writing – original draft, Project administration, Visualization. **Jing Zhang:** Software, Data curation, Formal analysis, Writing – review & editing, Visualization. **Kimberly J. MacKenzie:** Conceptualization, Methodology, Software, Data curation. **József Fiser:** Conceptualization, Methodology, Resources, Validation, Writing – review & editing, Funding acquisition. **Sara C. Mednick:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nlm.2022.107650.

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