Neurobiology of Learning and Memory 145 (2017) 119–128

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

The effect of sex and menstrual phase on memory formation during a nap

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ARTICLE INFO

Keywords:
Menstrual cycle
Memory consolidation
Slow oscillation
Spindles
Sex differences

ABSTRACT

Memory formation can be influenced by sleep and sex hormones in both men and women, and by the menstrual cycle in women. Though many studies have shown that sleep benefits the consolidation of memories, it is not clear whether this effect differs between men and women in general or according to menstrual phase in women. The present study investigated the effect of sex and menstrual cycle on memory consolidation of face-name associations (FNA) following a daytime nap. Recognition memory was tested using a face-name paired associates task with a polysomnographic nap between morning and evening testing. Seventeen healthy women (age: 20.75 (1.98) years) were studied at two time points of their menstrual cycles, defined from self-report and separated by 2 weeks (perimenses: −5 days to +6 days from the start of menses, and non-perimenses: outside of the perimenses phase), and compared with eighteen healthy men (age: 22.01 (2.91) years). Regardless of menstrual phase, women had better pre-nap performance than men. Further, menstrual phase affected post-nap memory consolidation, with women showing greater forgetting in their perimenses phase compared with their non-perimenses phase and men. Interestingly, post-nap performance correlated with electrophysiological events during sleep (slow oscillations, spindles, and temporal coupling between the two), however, these correlations differed according to menstrual phase and sex. Men's performance improvement was associated with the temporal coupling of spindles and slow oscillations (i.e., spindle/SO coincidence) as well as spindles. Women, however, showed an association with slow oscillations during non-perimenses, whereas when they were in their perimenses phase of their cycle, women appeared to show an association only with sleep spindle events for consolidation. These findings add to the growing literature demonstrating sex and menstrual phase effects on memory formation during sleep.

1. Introduction

Men and women differ across a range of laboratory tested cognitive domains including memory, visual and acoustic perception, navigation, and audition (Astur, Ortiz, & Sutherland, 1998; Canli, Desmond, Zhao, & Gabrieli, 2002; Giret, Menardy, & Del Negro, 2015; Lewin, Wolgers, & Herlitz, 2001; McDevitt, Rokem, Silver, & Mednick, 2014; Murai, Saito, Masuda, & Itoh, 1998; reviewed in Cahill, 2006). For example, memory performance that relies on the hippocampus, such as word and picture recall and recognition, story recall and name recognition, is better in women than men (reviewed in Herlitz, Airaksinen, & Nordström, 1999). In contrast, men outperform women on visual-spatial tasks and certain mathematical abilities (Halpern, 1992; Lewin et al., 2001). Furthermore, women and men use different strategies in tasks that involve mental rotation, (e.g. spatial navigation), where men rely more on Euclidean directions, while women focus on memory for landmarks (Dabbs, Chang, Strong, & Milun, 1998; Lawton, 1996). Although complete mechanistic explanations of these sex-based differences have not been identified, prior work suggests that sex hormones play an important role (Brinton, 2009; Mizuno & Giese, 2010).

In women, sex hormones fluctuate across a monthly cycle (Rousseau, 1998). Along with several other hormones (Baker & Driver, 2007), estrogen and progesterone cycle through two main phases across a typical 28-day menstrual cycle in women (Fig. 1A). The first half of the cycle (i.e., follicular phase; days 1–14) begins with menses (day 1–6) with low levels of estrogen and progesterone, followed by a rise in estrogen that peaks on days 12–14, just before ovulation. The second part of the cycle (i.e., luteal phase; days 15–28) is characterized by an increase in progesterone and estrogen, as they are released from the corpus luteum. If there is no implantation, hormone levels decline

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http://dx.doi.org/10.1016/j.nlm.2017.09.007
Received 6 June 2017; Received in revised form 8 September 2017; Accepted 12 September 2017
Available online 18 September 2017
1074-7427/

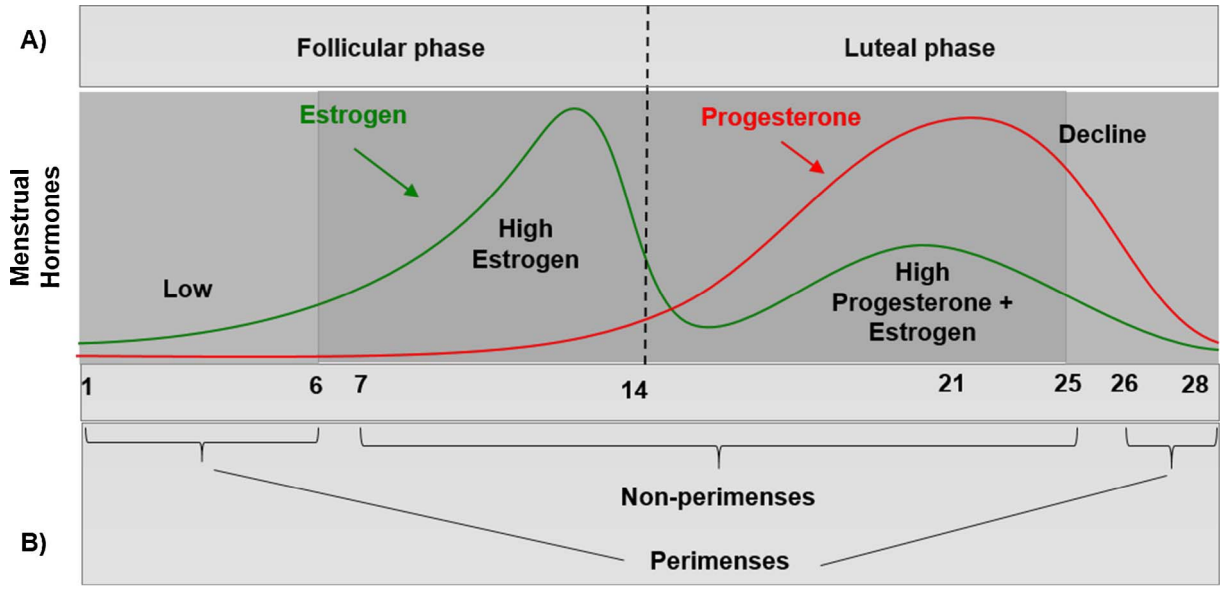

Fig. 1. The panel demonstrates fluctuations in hormones across the menstrual cycle. (A) Shows the follicular and luteal phases and (B) shows categorization in the current study defined from self-report.

during the last week of the luteal phase and menstruation occurs.

These fluctuations in sex hormones may influence cognitive performance across a woman's cycle. Studies have shown cognitive differences between women in the early follicular phase when hormones are low (i.e., menses) compared with other phases of the menstrual cycle (Hampson, 1990a,b; Maki, Rich, & Rosenbaum, 2002). For example, one study found that spatial abilities were increased in women during the early follicular phase, whereas fine motor skills and verbal fluency were enhanced during the mid-luteal phase (Hampson, 1990a,b). Similarly, another study reported enhanced articulatory and fine motor skills, but poorer spatial ability, during the late follicular phase (days 13–15, high estrogen) compared to the early follicular phase (days 3–5, low estrogen and progesterone) (Hampson, 1990a,b). These findings suggest that female cognition may be dynamically modulated by sex hormone levels. Although sex hormones could directly impact cognitive processing, it is also possible that hormones interact with other brain functions that mediate the relation between sex hormones and cognition, especially the interaction between sleep and memory consolidation (Genzel et al., 2012).

In addition to sex and sex hormones, sleep and sleep-related neural activity influence cognitive performance. Studies have shown that sleep supports transforming new experiences into long-term memories (i.e., consolidation) (Diekelmann & Born, 2010). For declarative memory, i.e., explicit memory for events and facts, consolidation is demonstrated by decreased forgetting of information after a period of sleep, compared to an equivalent amount of time awake (Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011). Furthermore, several pieces of evidence converge to suggest that improved memory retention is directly related to specific events during sleep including sleep spindles (bursts of fast, 12–15 Hz thalamic activity) and slow oscillations (SO, high voltage up and down states < 1 Hz that reflect periods of neuronal spiking and neuronal silence, respectively). Specifically, in rats hippocampal ripples were found to occur in temporal proximity to cortical sleep spindles, suggesting an information transfer between the hippocampus and neocortex, which is supposed to underlie the consolidation of declarative memories during sleep (Girardeau, Benchenane, Wiener, Buzsáki, & Zugaro, 2009; Ji & Wilson, 2007; Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016). In particular, spindles and SOs have independent features that correlate with improvements in declarative memory formation (Clemens, Fabo, & Halasz, 2005; Gais, Mölle, Helms, & Born, 2002; Mednick et al., 2013; Oyanedel et al., 2014; Schabus et al., 2004). Interestingly, experimentally increasing spindles (Mednick et al., 2013) and SOs (Binder et al., 2014; Marshall, Helgadóttir, Mölle, & Born, 2006) improves declarative memory performance, suggesting a causal role for these sleep features for memory consolidation. Further, the coincidence or coupling of SOs and spindle events may be a key mechanism of memory consolidation during sleep (Mölle, Bergmann, Marshall, & Born, 2011; Staresina et al., 2015), with several studies suggesting spindles that occur during the SO up-state are optimal (Gais & Born, 2004; Mölle, Eschenko, Gais, Sara, & Born, 2009). In line with these studies, Niknazar, Krishnan, Bazhenov, and Mednick (2015) showed pharmacologically boosting the temporal consistency of SO/spindle events during Stage 2 sleep benefitted verbal memory. Together, these findings suggest that declarative memory consolidation benefits from coupling of neural oscillations associated with thalamically-generated spindles and cortically-generated SOs. However, few studies have considered sex or menstrual phase effects on sleep-related memory consolidation.

McDevitt et al. (2014) examined the effect of sleep on a non-declarative, visual learning task in men and women. Although no baseline differences were found, post-sleep performance revealed differences between men and women, with men showing learning that was highly specific to the trained visual target, whereas learning in women transferred to an untrained target condition. Genzel et al. (2012, 2015) investigated the interaction between sex hormone levels and sleep-related memory consolidation in women and found that, women in their mid-luteal phase (i.e. third week of the cycle) and men performed better compared to women during menses, on a declarative and procedural motor memory task after a nap. Estrogen correlated with declarative and progesterone correlated with motor performance improvement (Genzel et al., 2012). In addition, sleep spindles were related to memory enhancement, but only for women during their luteal phase and men, suggesting that sex hormones and phase in menstrual cycle in women may moderate the relation between sleep features and sleep-dependent memory consolidation.

The present study aimed to investigate further the influence of sex and menstrual phase on sleep-related memory consolidation using a nap paradigm, and considered possible links between memory performance and SOs and spindle dynamics. Women were tested at two time points in their menstrual cycles, two weeks apart. One visit occurred in the perimenses phase, based on self-report (between 5 days before and 6 days after menses onset) and the other visit occurred outside of this

phase (non-perimenses) (Fig. 1B). Considering the verbal memory nature of the task, we hypothesized that women in both menstrual phases would perform better than men at baseline. In line with prior findings, we further predicted that retention during perimenses would be poorer compared with the non-perimenses phase. We also, predicted that these differences in memory consolidation would interact with brain activity; in particular, that greater improvement would correlate with stronger spindle/SO coupling.

2. Material and methods

2.1. Subjects

Thirty-five (17 females) healthy, non-smoking adults between the ages of 18 and 29 years ($M = 21.41$, $SD = 2.55$) gave informed consent to participate in the study. Inclusion criteria included having a regular self-reported sleep schedule, which was defined as getting at least 7 h of total sleep per night on average. Subjects had no personal history of sleep, neurological or psychological disorders, or other chronic illnesses. Heavy caffeine users (> 240 mg per day) were not enrolled to exclude the possibility of significant withdrawal symptoms during the experiment. In addition, women reporting use of oral contraceptives were not enrolled. All experimental procedures were approved by the Institutional Review Board of the University of California at Riverside.

2.2. Actigraphy, daily diaries and menstrual phase categorization

Subjects were asked to maintain a regular sleep-wake schedule for five weeks, starting one week prior to their first visit, which was monitored with sleep diaries and actigraphy (Actiwatch Spectrum, Respironics). Women's daily sleep diary included a question asking, "Did you start or were you on your period today?" with the following response options: "Yes, I started my period today," "Yes, I was on my period today," and "No, I was not on my period today." We used the responses to this question to approximate each woman's position in her menstrual cycle during her two visits, which were scheduled two weeks apart. Women were categorized in the perimenses phase, when a visit fell within 2 days prior to and 6 days after their self-reported first day of menses, and in the non-perimenses phase, for their other visit (Fig. 1B). Order of visits were randomized according to menstrual phase: nine women had their first visit in the perimenses phase and eight had their first visit in the non-perimenses phase. As prior research has shown the largest differences in cognitive performance between women during their menses and all other phases, the current taxonomy maximized our chances of capturing performance profiles associated with presumed-low versus higher sex hormone levels, given our lack of other physiological data points including day of ovulation and blood work.

2.3. Protocol

Subjects were asked to refrain from consuming caffeine, alcohol, and all stimulants for 24 h prior to and including the study day. During each visit, session 1 began at 9:00 AM (Fig. 2). Subjects completed the face name association (FNA) task, which consisted of an encoding phase followed by an immediate test, followed by a 2-h break during which they were instructed to abstain from caffeine, alcohol, exercise and napping. Electrodes for polysomnography (PSG) recording of sleep were attached at 12:00 PM, and all subjects took a PSG-recorded nap between 1:00 PM and 3:00 PM. The FNA delayed test took place during Session 2 between 5:00 PM and 6:00 PM. Subjects completed the Karolinska Sleepiness Scale (KSS) (Åkerstedt & Gillberg, 1990) at the beginning and end of each test session. Women returned for a second visit two weeks later (Fig. 2). In addition, subjects completed a mood questionnaire at the beginning of each testing session. The mood questionnaire was a list of five negative and four positive feelings. Subjects were asked to use a seven-point scale to rate their feelings with zero being "not at all" and seven being "Extremely".

2.4. FNA memory task

Two sets of 44 face and name stimuli were created and piloted to ensure equivalent performance difficulty across each set. Face stimuli were chosen from a UC Riverside IRB-approved database of photographs of diverse UC Riverside undergraduate students. All students whose photographs were included in the database provided informed consent for their picture to be used to create experimental stimuli. Each set had an equivalent number of male and female faces (22 each) and sets were matched for the number of faces from each race. All faces were forward-facing, shown from the shoulders up against a plain gray background, and edited to be gray scale. First and last names were selected from the 2010 United States Census data. The five most frequent male names, female names, and last names (e.g., Smith) were excluded. Unisex names that are commonly used for both men and women were also excluded, as were last names that are also commonly used as first names (e.g., Thomas) or contain a common first name base (e.g., Richardson). The remaining names were equally distributed across the three sets based on frequency in the population. Stimulus sets were randomized between participants, and counterbalanced across the two visits for female participants. Although stimuli within a set were fixed, individual face-name pairings were randomly generated for each participant so that no two participants saw the same face-name pairs. During each encoding session, 44 faces were presented in the center of the screen with a first and last name shown below the face. Each face/name pair was presented for 4000 ms, with an inter-stimulus-interval of 500 ms. Subjects were instructed to view each face-name pair and try to remember each person's name for a later test. Immediately following encoding (immediate test), as well as after an 8-h retention interval (delayed test), subjects were tested on two tasks (without feedback) in the following order: (1) recognition of intact versus rearranged first-last name pairings (Name Recognition) and (2) recognition of intact versus rearranged face-name pairings (Face-Name Recognition). Because Name Recognition and Face-Name Recognition was not counterbalanced, we analyzed Name Recognition only to avoid test order effects. In addition, we did not test the first two and last two face/name pairs presented at encoding to mitigate primacy and recency effects. Of the remaining 40 face-name pairs, 20 pairs were used at immediate test (10 for Name Recognition, 10 for Face-Name Recognition) and the other 20 pairs were used at delayed test. In other words, a unique subset of the encoded stimuli were used during each test session to avoid confounds due to re-encoding or interference at immediate test.

2.5. Polysomnography

PSG data were collected using Astro-Med Grass Heritage Model 15 amplifiers and Grass Gamma software. Eight scalp electroencephalogram (EEG) and two electrooculogram (EOG) electrodes were referenced to unlinked contralateral mastoids (F3/A2, F4/A1, C3/A2, C4/A1, P3/A2, P4/A1, O1/A2, O2/A1, LOC/A2 and ROC/A1), and two electromyogram electrodes were attached under the chin to measure muscle tone. PSG data were then digitized at 256 Hz and visually scored in 30-s epochs according to the sleep staging criteria of Rechtschaffen and Kales (1968). Sleep architecture variables included minutes and percentage of Stage 1, Stage 2, slow wave sleep (SWS) and rapid eye movement (REM), as well as total sleep time (TST), sleep latency (SL), wake after sleep onset (WASO) and sleep efficiency (SE).

2.6. Electrophysiological data

Due to our a priori hypothesis that memory consolidation is related to spindle events, and specifically the coupling of spindles and slow oscillations (SOs), we focused our analysis on these two classes of events. For the sake of simplicity and since F3 and F4 were not different

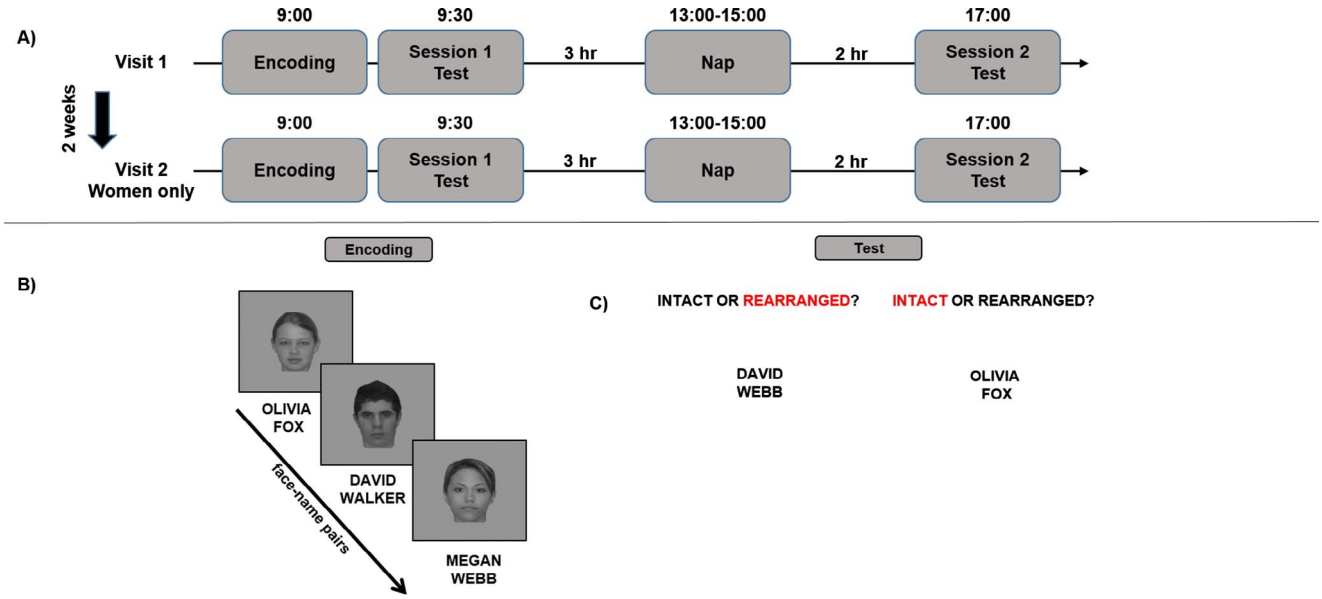

Fig. 2. The panel demonstrates (A) the nap paradigm and visit 2 procedure for women only. During Visit 1 subjects encoded the face-name pairs at 9 am and immediate memory was tested at 9:30 am. Subjects took a 90 min PSG-recorded nap after. Session 2 testing occurred 2 h after the nap. Female subjects returned after 2 weeks for Visit 2. (B) FNA task design. Subjects were shown 44 face-name pairs during encoding. At Session 1 test, half of the pairs were tested on recognition of intact versus rearranged first-last name pairings (Name Recognition) and face-name pairings (Face-Name Recognition). At Session 2, the other 22 pairs were tested. (C) Shows and example of Name Recognition test.

from each other on all physiological measures (all *ps* > 0.20), we averaged across F3 and F4 and correlated performance with the averaged frontal electrodes. We also, checked for the reliability of F3 and F4 correlations for all the sleep physiology measures prior to the averaging using intraclass correlation (all intraclass correlation coefficients > 0.41 and all *ps* < 0.01). We computed the following measures from the average frontal electrode during Stage 2 sleep: absolute number of detected spindles (from 12 to 15 Hz frequency band), absolute number of SOs (from 0.05 to 1 Hz frequency band), and the number of coincident spindle/SO events. We focused on Stage 2 sleep because sleep spindles are most prominent during this stage, also, prior studies have shown that sleep coordination between spindles and SOs during Stage 2 (as compared to slow wave sleep) may have a specific memory benefit (Niknazar et al., 2015).

First, data were pre-processed using BrainVision Analyzer 2.0 (BrainProducts, Munich Germany). Raw EEG signals were digitally band-pass filtered between 0.3 and 35 Hz, and all epochs with artifacts and arousals were identified by visual inspection and rejected. Stage 2 sleep epochs were exported for further analysis in Matlab 2011b (MathWorks, Natick MA). Sleep spindles were automatically detected using a wavelet-based algorithm developed by Wamsley et al. (2012). Slow oscillations were detected using an algorithm based on methods previously reported (see Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004; Mölle, Yeshenko, Marshall, Sara, & Born, 2006; Mölle et al., 2011). The algorithm checks for negative half-waves between consecutive zero-crossings of the signal, which were labeled as SOs if the following criteria were met: a minimum width of 0.125 s, a maximum negative peak width of 1.5 s, and a minimum amplitude of −60 μV.

Detection of a spindle/SO coincidence occurred whenever a spindle center fell within ± 1.5 s of the detected SO center (denoted as the negative-to-positive zero crossing, under the assumption that the slow oscillation consists of a negative half-wave followed by a positive half-wave). Given that SOs show the strongest relative amplitude at frontal cites (Murphy et al., 2009), which was confirmed in our own results comparing frontal and central electrodes (all *ps* < 0.001), we made the a priori decision to use F3 and F4 for our detection and analysis of slow oscillations and the spindle/SO complexes. However, for reference, we also provide the results for the identical analyses in C3 and C4 in the Supplemental Materials Section.

Data for an individual channel were excluded if (1) the impedance was high at the beginning of the record, (2) the impedance increased significantly over the course of the recording (e.g., electrode became detached) as determined by visual inspection, or (3) the reference electrode became detached during the recording. One female subject was excluded from the sleep architecture analysis (e.g. sleep stages minutes, WASO, etc.) due to technical issues during her sleep recording. In addition, for sleep physiology analysis (i.e. spindles, SOs and spindle/SO coincidence) six subjects (1 male, 3 females from perimenses phase and 2 from non-perimenses) were excluded due to technical issues at one of the frontal electrode sites. In summary, for sleep architecture analysis, there were eighteen males and sixteen female subjects (both for perimenses and non-perimenses), and for sleep physiology analysis there were seventeen males, thirteen females in perimense phase and fourteen females in non-perimenses phase.

2.7. Statistical analysis

Memory performance was assessed by calculating the following variables for each Session for the Name Recognition test: hit rate (proportion of “intact” subject responses to intact trials), false alarm rate (proportion of “intact” subject responses to rearranged trials), and d-prime (Zhit rate – Zfalse alarm rate where Z is the inverse of the cumulative distribution function; a measure of memory discriminability). To assess sleep-related memory consolidation we measured change in memory performance across both immediate and delayed tests with difference scores (Session 2–Session 1), with negative values indicating forgetting.

In each section of the result, in order to compare our results with the typical comparisons in the literature, we first report the overall performance collapsing across sex and menstrual phase by analyzing visit 1 for all subjects. We chose to combine men and women only during their visit one (instead of using visit 2 in women) for two reasons; first, we did not find a visit effect in women (all *ps* > 0.1), second, men only had one visit therefore, combining men’s first visit with women’s first visit was most parsimonious.

Next, we examined differences according to sex and menstrual phase for performance and sleep physiology variables. Due to the study design, which holds a mixture of one independent group (men) and two

dependent groups (perimenses and non-perimenses women) no general ANOVA tests was possible. Since the same group of women were studied twice and we wanted to compare within the women (perimenses versus non-perimenses) as well as compare with the men we used a series of *t*-tests along with Bonferroni method to correct for multiple comparisons. For between-subject analyses (men vs. perimenses and men vs. non-perimenses), we used independent-sample *t*-tests; for within-subject analyses (perimenses vs. non-perimenses), we used paired-sample *t*-tests. Here for group comparisons using Bonferroni method, p-values are considered significant if less than/equal 0.025 and trending if greater than 0.025 and less than/equal 0.06. To examine the amount of forgetting across the groups we looked at the d-prime difference score using one sample *t*-test. Finally, bivariate correlations were used to explore the associations between sleep variables and memory performance. We report significant findings at p-values less than/equal 0.05 and trending significant for p-values greater equal to 0.06 for the correlations and one sample *t*-test analysis.

3. Results

3.1. Memory performance

Performance in all subjects during visit 1 ($N = 35$) showed significant forgetting in d-prime from Session 1 ($M = 1.41$, $SD = 0.16$) to Session 2 ($M = 0.76$, $SD = 0.10$) in the paired sample *t*-test ($t(34) = 3.39$, $p = 0.002$). Similarly, we found significant forgetting in hit rate score from Session 1 ($M = 0.80$, $SD = 0.03$) to Session 2 ($M = 0.63$, $SD = 0.02$) ($p < 0.001$). However, there was no change in false alarm rate from Session 1 ($M = 0.38$, $SD = 0.02$) to Session 2 ($M = 0.37$, $SD = 0.02$) ($p = 0.76$). In summary, overall performance in visit 1 revealed significant decrease in d-prime and hit rate performance but not false alarm rate.

3.2. Immediate memory performance Session 1

Looking at men and women (once during their perimenses and once during their non-perimense) separately, as shown in Fig. 3, we found no significant differences between women's perimenses and non-perimenses performance in Session 1 in any performance metric [d-prime: $t(16) = -0.54$, $p = 0.61$; hit rate: $t(16) = -0.34$, $p = 0.74$; false alarm rate $t(16) = 0.49$, $p = 0.65$].

At Session 1, women in both menstrual phases performed better than men [d-prime: perimenses: $t(33) = 2.26$, $p = 0.03$ (trend); non-perimenses: $t(33) = 2.67$, $p = 0.01$]. The superior d-prime performance in women was not due to increased hit rate [perimenses: $t(33) = 0.94$, $p = 0.35$; non-perimenses: $t(33) = 1.23$, $p = 0.23$], but rather was driven by a lower false alarm performance compared to men [perimenses: $t(3) = -2.11$, $p = 0.04$ (trend); non-perimenses: $t(34) = -2.74$, $p = 0.01$].

3.3. Delayed memory performance Session 2

At Session 2, women performed better in their non-perimenses phase than in their perimenses phase [d-prime: $t(16) = 2.46$, $p = 0.02$]. Hit rate in women was not different comparing non-perimenses with perimenses phase [hit rate: $t(16) = 1.60$, $p = 0.13$] however, women in non-perimenses phase tended to have a lower false alarm rate [false alarm rate $t(16) = -2.19$, $p = 0.04$] compared to their perimenses phase. Next, we compared women in each menstrual phase to men. We found that when in their non-perimenses phase, women performed better at Session 2 compared to men [d-prime: $t(3) = 2.73$, $p = 0.01$] however, when in their perimenses phase, women's performance was comparable to that of men [d-prime: $t(33) = -0.57$, $p = 0.70$]. Again, there were no significant differences in hit rate between men and perimenses women ($t(33) = 0.39$, $p = 0.71$) or non-perimenses women ($t(33) = 1.96$, $p = 0.61$) in Session 2. However, men had significantly higher false alarm rate after the nap compared to women in the non-perimenses phase ($t(33) = 2.37$, $p = 0.02$), but not

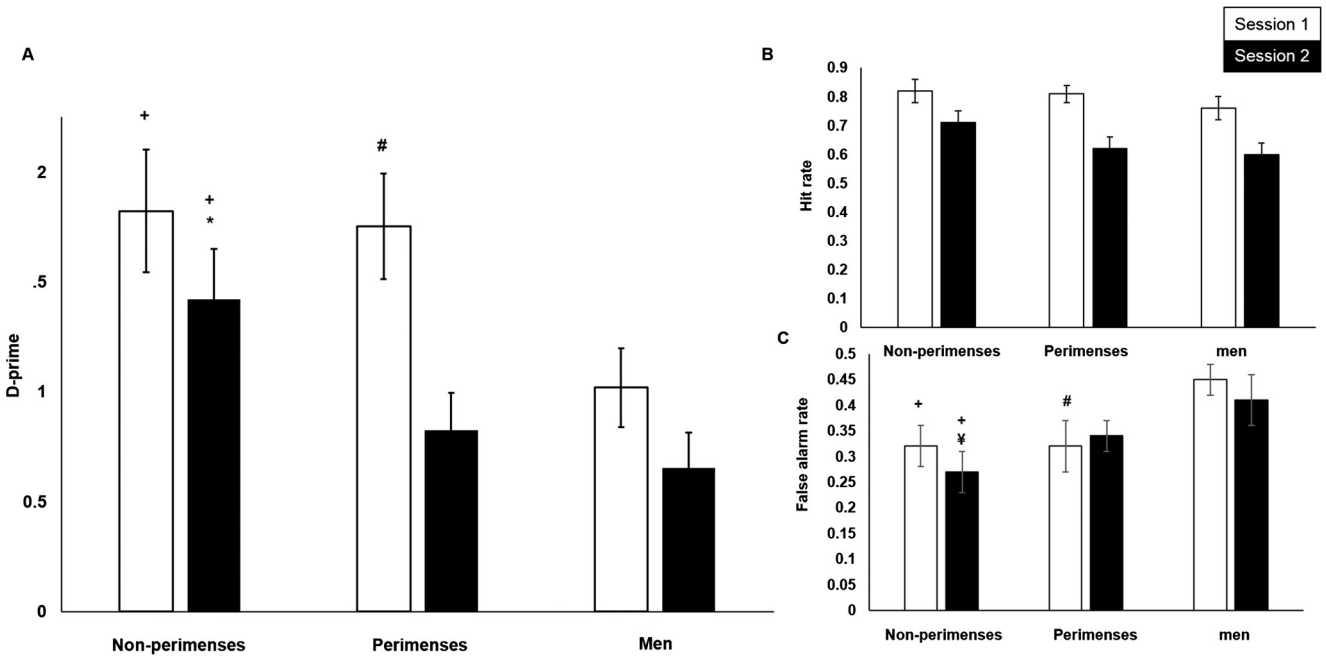

Fig. 3. Memory performance on Name Recognition. (A) D-prime score; women performed better than men at Session 1 (white bar). Non-perimenses women performed better compared to perimenses and men after the nap at Session 2 (black bar). Difference score (Session 2-Session 1): perimenses showed significant forgetting. (B) Hit rate: no changes across groups. (C) False alarm rate: men had higher false alarm compared with women, and perimenses showed nominal increased false alarms after the nap. Error bars are ± 1 SEM. P-values are significant if less than/equal 0.02 and trending if greater than 0.02 and less than/equal 0.06 using Bonferroni correction. In each Session (1 and 2): * represents statistical significance in women ($p \leq 0.02$). + represents statistical significance between women and men ($p \leq 0.02$). The ¥ represents the trending significance of women's comparisons ($0.02 < p \leq 0.06$). The # represents the trending significant of women and men's comparisons ($0.02 < p \leq 0.06$).

Table 1
Sleep summaries during nap and comparison across groups.

Sleep stages	1. Non-perimenses (n = 16)	2. Perimenses (n = 16)	3. Men (n = 18)	p-value 1 vs. 2	p-value 1 vs. 3	p-value 2 vs. 3
S1 (min)	7.62(1.21)	8.68(1.26)	7.19(1.15)	0.27	0.79	0.47
S2 (min)	36.65(3.21)	39.55(3.30)	41.00(2.93)	0.40	0.32	0.74
SWS (min)	21.12(3.40)	21.71(3.56)	25.42(3.71)	0.92	0.40	0.36
REM (min)	19.40(2.45)	13.46(2.99)	10.94(2.35)	0.07	0.02	0.42
S1 (%)	10.44(2.01)	11.86(2.43)	9.15(1.59)	0.51	0.61	0.42
S2 (%)	44.94(3.47)	45.76(4.03)	48.90(3.10)	0.87	0.40	0.54
SWS (%)	23.21(3.73)	24.62(4.40)	29.15(4.31)	0.78	0.31	0.45
REM (%)	21.40(2.58)	15.39(3.36)	12.80(2.71)	0.09	0.03	0.47
WASO (min)	7.34(2.12)	14.93(4.92)	11.11(3.32)	0.07	0.39	0.60
SL (min)	7.03(2.22)	6.78(1.92)	6.55(1.65)	0.92	0.86	0.96
SE (%)	84.11(4.98)	80.41(4.97)	82.95(3.68)	0.44	0.85	0.83
TST	84.81(3.81)	82.12(3.88)	84.55(3.51)	0.55	0.96	0.64

Notes: Data are reported as mean (SEM). REM, rapid eye movement, SL; sleep latency, SE; sleep efficiency, SWS: slow wave sleep, WASO; wake after sleep onset, TST; Total Sleep Time. Non-perimenses women had significantly higher REM (minutes and (trending) percentage) compared to men. P-values are significant if less than/equal 0.02 and trending if greater than 0.02 and less than/equal 0.06 using Bonferroni correction.

the perimenses phase ($t(33) = 0.98$, $p = 0.33$).

3.4. Memory improvement

Next, we examined the amount of forgetting by comparing memory change from Session 1 to Session 2. Using this metric, women showed significant forgetting in the perimenses phase [d-prime difference: $t(16) = -4.27$, $p = 0.001$)]. They also trended towards forgetting in the non-perimenses phase [d-prime difference: $t(16) = -1.94$, $p = 0.07$]. Men did not show forgetting [d-prime difference: $t(17) = -1.25$, $p = 0.23$]. Thus, perimenses women showed forgetting but men and to some extent non-perimenses women showed preservation of memory.

3.5. Group differences in sleep architecture

Nap descriptive can be found in Table 1. Sleep architecture did not significantly differ between perimenses and non-perimenses phases in women after Bonferroni correction (all $ps > 0.07$). Further, neither female condition differed from men (all $ps > 0.31$) with the exception of REM sleep, which was significantly increased in women in the non-perimenses phase compared to men [minutes: $t(32) = 2.48$, $p = 0.02$; percentage: $t(32) = 2.28$, $p = 0.03$ (trend)].

Table 2 contains a summary of Stage 2 sleep spindle, SO and spindle/SO coincidences at the averaged frontal electrodes. Women did not differ in spindle number (all $ps > 0.61$) based on their menstrual phase condition. Additionally, women had similar number of spindles compared to men (all $ps > 0.33$). We found no differences in the number of SO events between female conditions (all $ps > 0.19$), or between men and women in either menstrual phase (all $ps > 0.43$). Lastly, we found no difference in the number of spindle/SO events between perimenses and non-perimenses phases in women (all $ps > 0.35$), and no difference between men and women, regardless of menstrual phase (all $ps > 0.68$). In addition, analysis for spindle frequency (the averaged peak of spindles in the range of 12–15 Hz) and spindle activity (spindle duration multiplied by spindle amplitude) is provided in the Supplemental Materials Section.

Table 2
Sleep electrophysiology features during nap at the averaged frontal electrodes (i.e., F3 and F4) and comparison across groups.

Sleep electrophysiology	Non-perimenses (n = 14)	Perimenses (n = 13)	Men (n = 17)
Spindle	73.57(8.62)	79.73(9.67)	78.52(7.90)
SOs	121.07(19.23)	145.73 (23.36)	137.47(17.60)
Spindle/SO	19.00(3.04)	20.61(2.80)	19.67(2.93)

Notes: Data are reported as mean (SEM). No significant difference were found across groups (all $ps > 0.19$). Mean (SEM).

3.6. Sleep and behavior associations

To assess relations between sleep architecture and memory consolidation, correlations were conducted between sleep physiology characteristics (spindles, SOs, spindle/coincidence) and behavioral difference scores that index the degree of memory change (differences in false alarms, hits, and d-prime). We first examined correlations across both men and women during their first visit to address the general pattern of relationship between memory improvements and sleep physiology characteristics at the frontal electrodes. We then examined these relationships separately in men, and in women in their perimenses and non-perimenses phases. Figs. 4 and 5 show separate color-coded, electrophysiology/behavior profiles for all our participant's first visit (Fig. 4) and for our three groups respectively, with effect size (r) indicated by color. Below, we report statistically and trending (at $p = 0.06$) significant correlations between sleep features and difference scores performance.

3.7. Spindle/SO coincidences

During visit 1 (collapsing across sex and menstrual phase), we found a significant positive correlation between spindle/SO coincidence

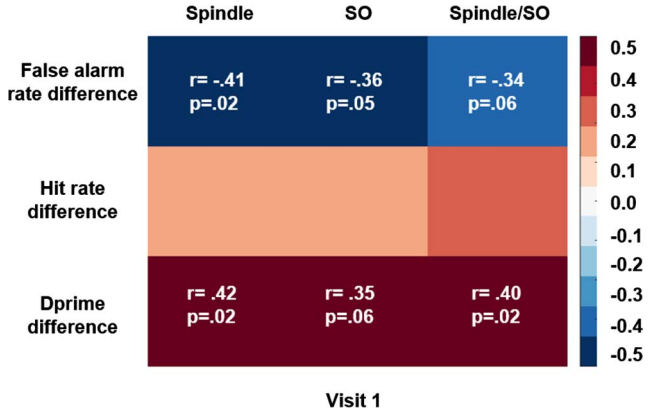

Fig. 4. Shows separate color-coded, electrophysiology/behavior (Name Recognition) profiles for all subjects during their visit 1 with effect size (r) indicated by color. At the averaged frontal electrode, spindles, SOs and Spindle/SO correlated with memory retention. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

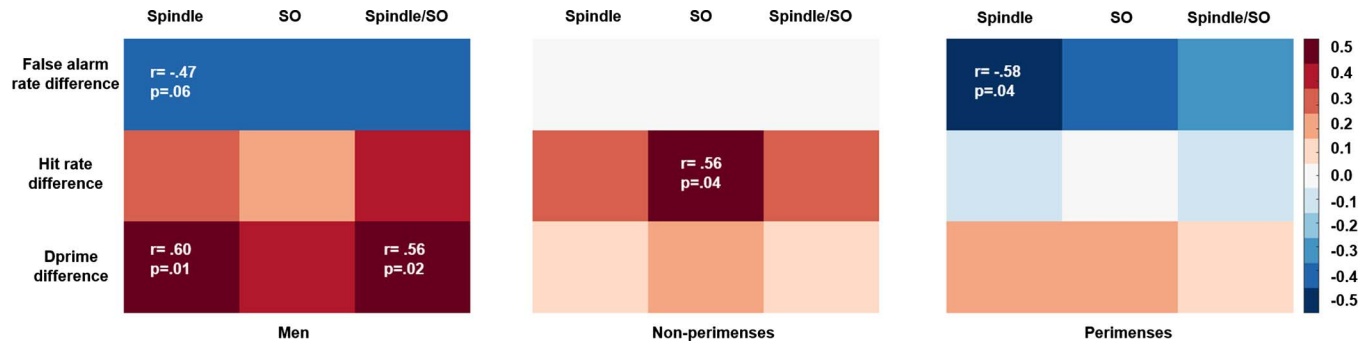

Fig. 5. Color-coded, electrophysiology/memory profiles for men, non-perimenses, and perimenses women with averaged frontal electrode and performance measure effect sizes (*r*) indicated by color. Compared with men, women in different phases of their menstrual cycle appear to show different associations with thalamocortical events. Men's performance was associated with the temporal coupling of spindles and SOs as well as spindles. Memory enhancement in women, however, show benefits from SOs during non-perimenses, whereas when perimenses women only show an association with spindles. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

events and d-prime difference score ($r = 0.40$, $p = 0.02$). In addition, coincidence events had a trending negative correlation with false alarm difference score ($r = -0.34$, $p = 0.06$). In women during both perimenses and non-perimenses phases, no significant correlation was found between spindle/SO coincidence events and performance at the frontal electrodes (all *ps* > 0.34). However, in men, SO/spindle events were significantly correlated with d-prime difference score ($r = 0.56$, $p = 0.02$). Thus, only men showed robust relation between memory improvement and spindle/SO coincidences.

3.8. Spindle events

During visit 1, all subjects together showed a significant positive correlation between spindle number and d-prime difference score ($r = 0.42$, $p = 0.02$) and a negative correlation between spindle number and false alarm difference score ($r = -0.41$, $p = 0.02$). Interestingly, when women were in the non-perimenses phase, spindles were not significantly correlated with memory measures d-prime, hit rate or false alarm rate (all p > 0.34). On the other hand, when women were in the perimenses phase, they showed a significant negative correlation between spindles and false alarm difference ($r = -0.58$, $p = 0.04$), indicating that more spindles were associated with decreased false alarm rate after the nap. In men, spindle number was associated with memory retention [d-prime difference score ($r = 0.60$, $p = 0.01$) and false alarm difference score ($r = -0.47$, $p = 0.06$ (trend))]. In summary, increased spindle events were correlated with memory improvement, and this relation was only apparent in men and perimenses woman, but not in non-perimenses women.

3.9. SO events

For all subjects, the number of SO events was significantly negatively correlated with false alarm difference score at visit 1 ($r = -0.36$, $p = 0.05$). In addition, SO events had a trending positive correlation with d-prime difference score ($r = 0.35$, $p = 0.06$). When women were in the non-perimenses phase, there was a significant positive correlation between SO events and hit rate difference score ($r = 0.56$, $p = 0.04$). However, no significant relationship was found between SO events and memory performance in perimenses women ($p > 0.10$). In men, SO events were not correlated with memory improvement ($p > 0.10$). These results indicate that more SO events were only associated with memory improvement but only in women during non-perimenses phase.

3.10. Self-reported sleepiness

The amount of self-reported sleepiness (Karolinska Sleepiness Scale; KSS1: 9 AM, KSS2: 10 AM, KSS3: 5 PM, KSS4: 6 PM) at the beginning and end of each session was similar in both female conditions (all ps > 1.00). Compared to men, women in both non-perimenses and perimenses phases reported significantly more sleepiness before (KSS3) and after (KSS4) Session 2 [KSS3: non-perimenses $t(33) = 3.71$, $p = 0.001$; perimenses $t(33) = 3.65$, $p = 0.001$; KSS4: non-perimenses $t(31) = 2.22$, $p = 0.04$; perimenses $t(31) = 2.91$, $p = 0.006$]. Further, only perimenses women showed a significant positive correlation in Session 2 hit rate with KSS3 ($r = 0.65$, $p = 0.01$) indicating that the sleepier women were, the higher their hit rate. However, this correlation was not in the expected direction. Together these results indicate that the post-nap performance differences were likely not due to sleepiness, as the groups with the best and worst memory performance were also highest on sleepiness.

3.11. Self-reported mood

From the mood questionnaire with a list of five negative and four positive feelings and based on subjects' ratings using a seven-point scale (with zero being "not at all" and seven being "Extremely"), we calculated a composite score for the negative and positive mood for both Session 1 and Session 2. We found no significant differences in mood in women (all *ps* > 0.19) and across our three groups (all *ps* > 0.12). In addition, there was no significant correlations between change in mood and change in memory across our three groups (all *ps* > 0.28).

4. Discussion

We investigated sex differences and the influence of menstrual phase on declarative memory consolidation across a nap. In line with known sex effects on general memory performance, we found superior pre-nap memory performance on a verbal, name recognition task in women compared with men. Although men did not perform as well as women initially, they had similar memory retention following the nap, with minimal forgetting. In women, memory retention following the nap was modulated by menstrual phase, with women showing more forgetting following a nap in their perimenses phase compared to other phases of their cycle (i.e. non-perimenses). Regarding Stage 2 sleep features (i.e., spindles, slow oscillations and spindle/SO events), unlike prior reports (Genzel et al., 2012; Ishizuka et al., 1994), we did not find differences in spindle events based on sex and hormone phase, which may be due in part to the use of different menstrual cycle categories in this study. Additionally, we did not observe differences in SO events or spindle/SO coincidences between men and women, and no differences due to menstrual phase. Despite the minimal differences in absolute levels of brain activity during sleep, three profiles emerged between brain activity and performance. In men, performance was associated with spindle/SO coincidences as well as spindle events. In non-perimenses women, performance correlated with SOs only, whereas

performance during perimenses was associated with sleep spindles only. Together, these findings suggest that the menstrual cycle impacts sleep-dependent memory consolidation. These performance variations in women may be related to underlying fluctuations in sex hormones across the menstrual cycle, which could drive changes in the coordination of brain networks thought to be involved in the transformation of recent to remote memories.

Sexually dimorphic patterns of performance have been shown for a range of cognitive domains (Jazin & Cahill, 2010), including memory (Canli et al., 2002; Lewin et al., 2001; McDevitt et al., 2014). Although the exact mechanisms for these differences are unknown, several potential differences have been found in brain structure (reviewed in Andreano & Cahill, 2009). It has been demonstrated that women have greater volume in memory-related areas including the hippocampus (Filipek, Richelme, Kennedy, & Caviness, 1994), caudate nucleus (Filipek et al., 1994; Murphy et al., 1996), anterior cingulate gyrus (Paus et al., 1996), and dorsolateral prefrontal cortex (Schlaepfer et al., 1995). In contrast, men have greater volume in the amygdala (Giedd et al., 1996) and paracingulate gyrus (Paus et al., 1996). Given that the hippocampus is particularly engaged by the processing of associative episodic memories (Davachi & Wagner, 2002; Yoon, Seo, Kim, & Lee, 2012), differences in hippocampal volume may at least partially explain why women outperformed men at baseline on the name recognition task used in the current study. Our findings of the general forgetting pattern throughout the day across all our subjects and different patterns of forgetting across sex and menstrual phase reveal the importance of the consideration of sex and menstrual cycle while studying memory formation during sleep. Further research is required to understand the potential association between sex differences in the function of hippocampal and medial temporal lobe structures with performance outcomes.

In the current study, although we did not find an effect of menstrual phase on general memory performance (e.g., no baseline differences), we did find that menstrual cycle had a measurable impact on memory consolidation during a nap. In fact, nap was not as beneficial for memory during the perimenses phase of the menstrual cycle when hormones are typically falling and/or at their lowest, whereas memory was numerically better preserved during the nap when women were in other phases of their cycle (e.g. late-follicular or early-luteal phase). Recent work suggests that menstrual phase and estrogen levels influence memory-related brain structures including the hippocampus. For example, Barth et al. (2016) recorded thirty MRI scans during two natural menstrual cycles of a single healthy female subject. Using diffusion weighted imaging to measure structural reorganization of the human brain, they reported significant positive association between fractional anisotropy (measure of restricted diffusion thought to reflect tissue integrity) in bilateral hippocampal structure and estrogen (Barth et al., 2016). In addition, enzymes for estrogen synthesis and estrogen receptor messenger RNA (mRNA) have been localized to the hippocampus (Fester, Prange-Kiel, Jarry, & Rune, 2011; Herman, Patel, Akil, & Watson, 1989), whereas androgen receptors are more prevalent in the amygdala (McGinnis, Williams, & Lumia, 1996). Taken together, the coincident changes in memory performance and menstrual phase reported here and elsewhere are likely related to structural underpinnings that require further investigation. Interestingly, our data suggest a significant impact of menstrual phase on sleep-dependent, memory processes, as well.

Few studies have considered both sex- and menstrual cycle effects on sleep-related memory consolidation. One prior study examined sleep-dependent learning in a non-declarative visual learning task in men and women (McDevitt et al., 2014), without considering menstrual cycle effects in the female subjects. In addition, the only two published studies that investigated the interaction between sex steroid levels and sleep-related memory consolidation in women, only focused on spindle activity (Genzel et al., 2012, 2015). Unlike the present study, prior results report increased spindles in females compared with males (Carrier, Land, Buysse, Kupfer, & Monk, 2001; Huupponen et al., 2002). It is unclear whether these sex differences in spindle activity relate to meaningful functional differences or whether they are simply an artifact from differences in skull thickness that amplifies the detection of spindles in women (Dijk et al., 1988). In addition, it has been shown that spindle activity increases during the luteal phase compare to follicular phase (Baker & Driver, 2007; Baker et al., 2012; Driver, Dijk, Werth, Biedermann, & Borbely, 1996; Ishizuka et al., 1994). Similarly, Genzel et al. (2012) reported higher spindle activity through learning only during the luteal phase. We did not find differences in spindle events, spindle activity and spindle frequency (see Supplemental Materials) across the menstrual phases. The discrepancies between the current results and previous studies related to menstrual phase and spindles may have been due to our categorization of phases based on self-reported onset of menstruation rather than follicular versus luteal phase.

Research has shown that electrophysiological features of NREM sleep, e.g., sleep spindles and slow oscillations, are linked with memory consolidation (Gais et al., 2002; Marshall et al., 2006; Mednick et al., 2013; Mölle et al., 2011; Schabus et al., 2004). Using pharmacological intervention, Mednick et al. (2013), increased sleep spindles with zolpidem and decreased sleep spindles with sodium oxybate during a nap in young adults. Pharmacologically increasing sleep spindles enhanced verbal memory performance compared with placebo, whereas decreasing spindles led to decreased memory performance compared with placebo. Similarly, in this study we found that greater numbers of spindles, SO events and SO/spindle coincidence were related to memory improvement across the combined group of men and women. However, despite the fact that there were no absolute differences in spindles between men and women in either menstrual phase or within women in the present study, the functional profile emerging between sleep spindles and memory consolidation was different. That is, only men and women during perimenses showed a relation with spindle events. A greater number of spindles was associated with a lower false alarm rate in both men and women in their perimenses phase, while in men spindle numbers were also related to higher d-prime. Together, the association between spindles and memory improvement is in line with the previously reported beneficial role of spindle events for sleep-related memory formation. Niknazar et al. (2015) further demonstrated that in addition to boosting spindle events, zolpidem also increased the temporal consistency of spindle occurrences during the down-to-up phase of SOs, and performance improvement was correlated with this spindle/SO coupling, suggesting that declarative memory consolidation is facilitated when thalamic spindles coincide with the down-to-up phase of cortical SOs. Indeed, this temporal coupling is proposed to be a key mechanism underlying the hippocampal-neocortical dialogue characteristic of systems consolidation, whereby SOs provide a top-down temporal frame for these oscillatory events (Inostroza & Born, 2013). Specifically, individual hippocampal sharp wave ripple events appear to be nested in the trough of succeeding spindles, and these “spindle-ripple” events may represent a bottom-up mechanism where reactivated hippocampal memory information (coded in ripples) is passed to spindles, which then reach neocortical networks via the SO (McDevitt, Krishnan, Bazhenov, & Mednick, 2017). Similarly, in our findings, men and women together showed better memory retention associated with greater amount of SO events and spindle/SO coincidences. However, looking at men and women in different menstrual phases separately, only men showed the predicted pattern of results with memory improvement associated with greater amount spindle/SO coincidences. Women, however, appear to differ according to different phases of their menstrual cycle. When women were in their non-perimenses phase, their performance was associated with the amount of SOs, but not related to spindles and spindles/SO events. In contrast, when women were in their perimenses phase, their performance was associated with spindles only, and not with SOs or the coupling of these thalamocortical events. Taken together, the present findings suggest

that menstrual phase may moderate thalamocortical communication during sleep, which can facilitate or inhibit consolidation of declarative memories. In addition, our results propose the importance of considering sex and menstrual phase effects when exploring the role of sleep features in sleep-related memory consolidation.

5. Limitations

A limitation of the present study is that sex hormones were not measured. Due to these deficiencies, we categorized women into two coarse groups based on self-reported onset of menses. This approach glosses over many important hormonal fluctuations that occur during the menstrual cycle and the non-perimenses phase likely included a heterogeneous mix of hormonal profiles, encompassing the mid-late follicular and early-mid luteal phases. Future studies that more accurately measure estrogen and progesterone levels are needed to replicate these results and clarify the role of different phases in the menstrual cycle, and different sex hormone levels, on sleep and memory consolidation. In addition, information about the regularity and length of the females' menstrual cycle was not collected in this sample and needs to be considered in future works. Further, while it was a strength to study the same women twice in different menstrual phases, to account for individual variability, it also limited our ability to statistically model the data. Future studies of larger samples of subjects could use more sophisticated statistical models like hierarchical mixed-effects linear models, and consider interaction effects of nap and menstrual phase, as well as other predictors like age.

6. Conclusions

Our results show a sex effect on baseline performance and a menstrual phase effect on sleep-dependent memory consolidation of a declarative associative memory task. Women performed better than men at baseline in a paired association memory task. However, compared with men, we find that women in different phases of their menstrual cycle may rely on different consolidation mechanisms across their cycle. Men's performance improvement was associated with the temporal coupling of spindles and slow oscillations (i.e., spindle/SO coincidence) as well as spindles. Women, however, showed benefits from slow oscillations during non-perimenses, whereas when they were in their perimenses phase of their cycle, women appeared to benefit only from sleep spindle events for consolidation. This work suggests that along with the known effects of sex hormones on cognitive processes including memory, they may specifically modulate sleep-dependent consolidation via changes in thalamocortical communication associated with systems consolidation.

Acknowledgement

This research was supported by R01AG046646, Office of Naval Research Young Investigator Prize to Mednick and NSF Cognitive Neuroscience BCS1439210.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nlm.2017.09.007.

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