Sleep Spindle Production in Different Phases of the Menstrual Cycle

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Abstract

Sleep spindles are high-frequency oscillatory activity generated by interplay of the thalamic reticular nucleus and other thalamic nuclei during stage 2 NREM sleep in a frequency of ~10 -12 Hz. Research strongly supports sleep spindles' role in actively mediating declarative memory consolidation; most studies, however, neglect to control for sex and menstrual cycles in women. Both sex and menstruation have been implicated to affect sleep and online learning periods. Recent studies have shown that the influence of sleep spindles during the declarative memory process may be affected by fluctuating estrogen levels during the menstrual cycle. The potentially significant relationship between offline declarative memory consolidation and the influence of menstrual cycle phase has not been well established and was further investigated in this study. This study categorized women into perimenses (-5 days to + 6 days from the start of menses) and nonperimenses phases (outside of the perimenses phase). The results of a face-name paired association task with a polysomnographic nap between morning and evening testing were used to determine the relationship between sleep spindle production and memory improvement. The sleep spindles recorded in the parietal lobe had a significant correlation with improved performance in the name recognition task in women in the nonperimenses phase. This implies that parietal spindle density plays a distinct role in declarative memory consolidation.

Introduction

Sleep spindles are high-frequency oscillatory activity generated by interplay of the thalamic reticular nucleus and other thalamic nuclei during stage 2 NREM sleep. The functional role of sleep spindles remains unclear, although research strongly supports that sleep spindles actively mediate declarative memory consolidation. Recent studies have shown that the influence of sleep spindles during the declarative memory process may be affected by modulatory menstrual cycle effects in females. Although sex and menstruation have been implicated to affect sleep and online learning periods, most sleep spindle studies neglect to control for sex and menstrual cycles in women.

Sleep spindle production differs in both women and men. As a whole, women tend to have twice as many sleep spindles as men and a female advantage has been found for episodic, emotional, and spatial memories as well as recognition of odors, faces, and pictures (Dzaja, 2005). These differences are believed to be due to hormonal influences, especially that of estrogen. The female sex hormone estrogen primarily plays a role in sexual maturation and reproduction (Reinisch, 1991) but has also been found to facilitate other brain functions, including cognition and memory (Protopopescu et al., 2008; Maki et al., 2002). On verbal tasks where women scored higher than men, women scored higher during the mid-luteal phase, when women have higher estrogen levels, when compared to the menstrual phase (Manber et al., 1999). A recent study found that local brain estrogen production within cognitive circuits may be important for the acquisition and consolidation of memories (Vahaba, 2016). Sleep spindles are heavily influenced by the secretion of hormones, and they are in charge of prioritizing sensory input received during the day. Studies have established that estrogen has an effect on sleep spindles and cognitive function; however, estrogen levels fluctuate with the phases of the menstrual cycle. The full effects of different phases have yet to be explored. Local sleep spindle production and spike location may potentially be affected by this production of estrogen.

Sleep spindles travel across multiple neocortical regions with varying frequencies and peak at different times throughout the cortex; this heterogeneity is likely indicative of different psychological processes during sleep. Research strongly suggests sleep spindles play an active role in offline declarative

consolidation, the processes by which a memory trace is stabilized after initial acquisition (Genzel et al., 2014). Spindle parameters, especially density, are associated with memory improvement after sleep: the density of spindles has been shown to increase after extensive learning of declarative memory tasks (Hennies et al., 2016) and the degree of increase in stage 2 spindle activity correlates with memory performance (Tamminen et al., 2010).

Offline declarative memory is primarily seen through reconsolidation, which is the repetition of memory for retention in long-term memory (Stickgold & Walker, 2007). The reconsolidation of hippocampal neurons is especially intense during spindles (Siapas et al., 2005). This intense reconsolidation is influenced by a number of factors, especially by sex hormones in females. Most studies neglect to control for sex and menstrual cycles in women, although both sex and menstruation have been implicated to affect sleep (Manber et al., 1999) and online learning periods (Maki et al., 2002). Studies have shown that the influence of sleep spindles during the declarative memory process may be affected by modulatory menstrual cycle effects in females (Genzel, 2012; Driver, 1996; Ishizuka, 1994). These findings have contributed to a proposed waxing and waning effect of estrogen on the memory performance of women due to fluctuating estrogen levels, which could potentially predict a decrease in memory performance during menses. Because of the novelty of these studies, the waxing and waning effect has been overlooked in every prior study.

Because sleep spindle production is synonymous with declarative memory consolidation, our understanding of declarative memory has potentially been corrupted by focusing solely on men or combining women and men into one category, which assumes that the results apply to both. The potentially significant relationship between overnight declarative memory consolidation and the influence of estrogen has not been well established and should be further investigated.

The purpose of this study is to examine the relationship between menstrual phases and offline declarative memory consolidation, with special attention to the specific role of different brain regions in accordance with Muller, et al. 2016. This study investigated how spindles produced in different regions play different roles in sleep consolidation and whether menstrual phase had an impact. This study focused

on two groups of women: group 1 was in their perimenses phase (within +5 to -6 days of starting their menses) and group 2 was in their nonperimenses phase (any phase outside of perimenses). Women in their nonperimenses phases were expected to perform better, and the parietal lobe was expected to play a significant role in the production of sleep spindles.

Methods

1.1 Subjects: Seventeen healthy women between ages 18 and 29 were studied at two time points of their menstrual cycles, defined from self-report and separated by 2 weeks. This study did not distinguish between established phases of the menstrual cycle (i.e. luteal, menses, follicular, ovulation); participants were categorized in the perimenses and nonperimenses groups. The perimenses group was defined as women with -5 days to + 6 days from the start of menses, and non-perimenses women were outside of the perimenses phase. Subjects self-reported seven hours of sleep a night. Woman who drank excessive amounts of caffeine (>240mg) and/or used oral contraceptives were excluded from the study.

Sleep spindle parameters are typically observed using EEG. EEGs recorded brainwaves from four regions: the frontal, central, occipital, and parietal lobes. This study used eight electrodes (two electrodes per region) to record spindle parameters.

1.2 Task: Women kept sleep diaries recording the period of time that they slept and whether or not they were on their periods. The responses to these questions were used to determine what phase the women were in during the study. The order of studies was randomized so that nine women had their first visit during their perimenses phase and eight had their visit in the nonperimenses phase. If a subject was in the perimenses phase during their first visit, it was assumed that she was in the nonperimenses phase when she visited for a second time two weeks later.

1.3 Test: The data was obtained through an assessment of face-name associations (FNA) following a daytime nap. Nap sleep spindles are representative of night spindle activity because they are similarly associated with neuroplasticity processes (Ujma et al., 2015). 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). Thalamic activity could not be directly assessed in the current study. Cortical areas were investigated showing spindle-related activity (i.e. number of times spindles appeared). The characteristics of cortical spindles appear to reflect important properties for spindle generation at the level of thalamic cells.

Recognition memory was tested using a face-name paired associates (FNA) task with a polysomnographic nap between morning and evening testing. Two sets of 44 face and name stimuli were created and piloted to ensure equivalent performance difficulty across each set. 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.

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 4000ms, with an inter-stimulus-interval of 500ms. 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-hr 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).

1.4 Data Analysis: Data from all of the women participants were included in the analyses. All statistical analyses were carried out using SPSS version 24 was used to run ANOVAs and Pearson Correlations with repeated measures. Tests examined how consolidation in women was influenced by sleep spindles and the influence of different brain regions in those specific regions. The amount of sleep spindles produced and spindle density (number of sleep spindles/min of sleep) were recorded. Face and name recognition tasks both test declarative memory, but this study only focused on the name recognition

task for data analysis for simplicity and consistency. The performance variables recorded include hits (number of correct responses), false alarms (hits when subjects believed they were correct, but were wrong), dprime (difference between hits and false alarms) and accuracy (percentage of number of trials given/number of correct hits). Sleep architecture was analyzed using the variables TIB (time in bed), TST (total sleep time), N1 min (minutes spent in stage 1), WASO (wake after sleep onset), sleep latency, and sleep efficiency (TST/TIB). Pearson Correlations were used to examine the relationship between change in performance and characteristics of spindles at each electrode. The number of spindles and their densities at each electrode site (frontal, parietal, central and occipital) were observed.

For between subject analysis (perimenses v. nonperimenses), Pearson Correlations were used. p-values were considered significant if less 0.05. To determine baseline memory ability, accuracy difference for both face and name recognition were analyzed through paired samples correlations. Total differences in hits for the name recognition task were used to determine total memory improvement for both groups. The results from both phases were combined to represent a general population of women, and perimenses and nonperimenses were analyzed separately. Women were not separated per visit because there was no visit effect (all ps > 0.01). Bivariate Pearson Correlations were used to explore the associations between sleep spindle variables and memory performance.

Results

Table 1: Accuracy of Name Recognition Accuracy during the AM & PM v. Face Recognition Accuracy during the AM & PM Paired Samples Correlation (Perimenses and Nonperimenses)

Name Recognition Accuracy AM & Name Recognition Accuracy PM	Perimenses	N Correlation Sig.	17 0.558 0.020
Face Recognition Accuracy AM & Face Recognition Accuracy PM	Perimenses	N Correlation Sig.	17 0.714 0.001
Name Recognition Accuracy AM & Name Recognition Accuracy PM	Nonperimenses	N Correlation Sig.	17 0.562 0.019
Face Recognition Accuracy AM & Face Recognition Accuracy PM	Nonperimenses	N Correlation Sig.	17 0.592 0.012

Table 1: This table shows the paired samples correlation between the accuracy of name and face Recognition results AM v. PM results for the perimenses phase and the nonperimenses phase.

The paired samples correlation between the accuracy of name and face recognition results between AM and PM for women in perimenses show a strong correlation between AM and PM results for both face recognition ($p = 0.001$) and name recognition ($p = 0.020$), indicating that sleep performance increased after sleep (Table 1). For women in the nonperimenses phase, paired samples correlations between the accuracy of name and face recognition results between AM and PM showed a strong correlation between AM and PM results for both face recognition ($p = 0.012$) and name recognition ($p = 0.019$), indicating that sleep performance increased after sleep (Table 1).

Table 2: S2 Spindle Number v. Memory Improvement in Name Recognition Task (Both)

		Hits Name Recognition Difference (Perimenses)	Hits Name Recognition Difference (Nonperimenses)	Hits Name Recognition Difference (Both)
F3 S2 Spindle Number	Pearson Correlation	-0.152	0.296	0.072
	Sig. (2-tailed)	0.575	0.265	0.696
	N	16	16	32
F4 S2 Spindle Number	Pearson Correlation	-0.097	0.424	0.182
	Sig. (2-tailed)	0.731	0.131	0.344
	N	15	14	29
C3 S2 Spindle Number	Pearson Correlation	-0.074	0.378	0.109
	Sig. (2-tailed)	0.784	0.149	0.554
	N	16	16	32
C4 S2 Spindle Number	Pearson Correlation	-0.438	0.443	0.120
	Sig. (2-tailed)	0.102	0.086	0.521
	N	15	16	31
O1 S2 Spindle Number	Pearson Correlation	-0.074	0.385	0.166
	Sig. (2-tailed)	0.801	0.156	0.390
	N	14	15	29
O2 S2 Spindle Number	Pearson Correlation	0.138	0.506	0.365
	Sig. (2-tailed)	0.686	0.077	0.080
	N	11	13	24
P3 S2 Spindle Number	Pearson Correlation	0.208	0.568*	0.303
	Sig. (2-tailed)	0.440	0.043	0.110
	N	16	13	29
P4 S2 Spindle Number	Pearson Correlation	0.208	0.854*	0.318
	Sig. (2-tailed)	0.440	0.030	0.150
	N	16	6	22

Table 2: This table shows the Pearson Correlations the number of S2 spindles v. the total hits difference in name recognition. Significant values ($p \leq 0.05$) are indicated by an asterisk.

There were no significant relationships between the number of S2 sleep spindles per electrode and improved memory performance when both groups are considered together (Table 2). The difference between hits in the name recognition was calculated using the formula ($Hits_{Difference} = Hits_{PM} - Hits_{AM}$). Improvement in scores is indicated by the difference between name recognition hits.

There were no significant relationships between the number of S2 sleep spindles per electrode did not correlate with an increase in performance for women in perimenses. This lack of a correlation indicates that the number of sleep spindles produced has no effect on performance. All EEG regions, except for the parietal lobe, lacked a correlation between the number of sleep spindles produced at each electrode and the total hits difference in women in nonperimenses (Table 2). Out of the four regions, the parietal lobe was the only one to show a significant correlation with memory improvement (Table 2: P3, $p = 0.043$; P4, $p = 0.030$).

Table 3: S2 Spindle Density v. Hits Name Recognition Difference (Both)

		Hits Name Recognition Difference (Perimenses)	Hits Name Recognition Difference (Nonperimenses)	Hits Name Recognition Difference (Both)
F3 S2 Spindle Density	Pearson Correlation	-0.092	-0.048	-0.027
	Sig. (2-tailed)	0.736	0.859	0.882
	N	16	16	32
F4 S2 Spindle Density	Pearson Correlation	-0.021	0.153	0.087
	Sig. (2-tailed)	0.940	0.602	0.652
	N	15	14	29
C3 S2 Spindle Density	Pearson Correlation	0.327	0.076	0.157
	Sig. (2-tailed)	0.217	0.781	0.390
	N	16	16	32
C4 S2 Spindle Density	Pearson Correlation	0.159	0.088	0.125
	Sig. (2-tailed)	0.572	0.746	0.503
	N	15	16	31
O1 S2 Spindle Density	Pearson Correlation	0.200	0.134	0.188
	Sig. (2-tailed)	0.492	0.633	0.329
	N	14	15	29
O2 S2 Spindle Density	Pearson Correlation	0.350	0.421	0.398
	Sig. (2-tailed)	0.291	0.152	0.054
	N	11	13	24
P3 S2 Spindle Density	Pearson Correlation	0.408	0.454	0.390*
	Sig. (2-tailed)	0.117	0.103	0.033
	N	16	14	30
P4 S2 Spindle Density	Pearson Correlation		0.605	0.529*
	Sig. (2-tailed)		0.150	0.035
	N		7	16

Table 3: This table shows the Pearson Correlations between S2 spindle density and the total hits difference in name recognition. Significant values ($p \leq 0.05$) are indicated by an asterisk.

Pearson correlations between S2 spindle density and total hits difference in name recognition for the combined groups showed that there was only a significant correlation between sleep spindle density and memory improvement was associated with parietal lobe electrodes (Table 3: P3, $p = 0.033$; P4, $p = 0.035$). Spindle density was calculated using the following equation (density = number of sleep spindles produced/minutes of sleep). Pearson Correlations between S2 spindle density and the total difference in hits for the name recognition task for women in nonperimenses found no significant correlation between S2 spindle density and memory improvement (Table 3). The Pearson Correlations between S2 spindle density and the total difference in hits for the name recognition task for women in nonperimenses. There is no significant correlation between S2 spindle density and memory improvement (Table 3).

Discussion

The objective of this study was to investigate whether sleep spindle number and sleep spindle density could account for differences in performance for women in different phases of the menstrual cycle, and whether or not these differences were affected by spindle production in different regions. This was the first study to investigate the influence of sex differences and the menstrual phase on declarative memory across a nap. 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 perimenses (Table 1)**.** Although women in the perimenses phase had more forgetting, there was still a significant memory consolidation after a nap. Regarding N2 sleep spindles, there were no significant differences in total spindle numbers based on sex and hormone phase, which may be due to the use of perimenses and nonperimenses categories rather than the traditional phases. However, the sleep spindle numbers in the parietal lobe had a significant correlation with improved performance in the name recognition task in women in the nonperimenses phase (Table 2). These findings imply that parietal spindle density plays a distinct role in declarative memory consolidation, and that women in different phases of their menstrual cycle may rely on different consolidation mechanisms across their cycle. These

consolidation mechanisms may be region-dependent, so that certain regions of the brain compensate for inferior performance in others during the perimenses phase. 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.

This is the first study to consider the importance of each lobe in the production of sleep spindles. Electrodes recorded activity in frontal, central, occipital, and parietal lobes, but the parietal lobe was implied to play a separate role in declarative memory in women. The parietal lobe is responsible for perceiving and processing somatosensory events (e.g. touch, temperature, body position). A recent study showed that spindles peak in one area and then another, spiraling forward out of the temporal lobe to the frontal lobe and then back to the parietal (Muller et al., 2016). Two different types of sleep spindles have been established: fast parietal spindles and slow frontal spindles. Fang et al, 2016 found that only fast parietal spindles are directly related to reasoning abilities but not verbal abilities. Fang found that the relationship between fast spindles and reasoning abilities is independent of the indicators of sleep maintenance and circadian chronotype, thus suggesting that spindles are biological markers of cognitive abilities. Spindle numbers in the current study were found also to be trait-like (i.e. no significant differences across the menstrual cycle) but the findings were also limited because EEG electrodes were used to observe scalp spindles. The study conducted by Fang et al. in 2016 involved women between the ages of 19 - 40 (i.e. menstruating women); however, they failed to account for differences in the menstrual cycle. Other studies have found that sleep spindles are only trait-like in females (Ujma, 2016), and no study has yet to examine whether the menstrual cycle has an effect on these outcomes. In order to study the difference between the two, an ECoG is required to see thalamic activity (Muller et al., 2016).

Differences between the perimenses and nonperimenses phases should be re-evaluated to see whether the finding that they are trait-like still holds. In this study, when women from both groups were combined in a Pearson Correlation, a significant correlation between the sleep spindle number in the

parietal lobe and improved name recognition performance was found (Table 2). However, when observed separately, women in the perimenses phase did not show a significant correlation between sleep spindle number and improved name recognition while women in the nonperimenses phase did (Table 2). When they are studied as separate groups, only women in phases associated with higher levels of estrogen show a greater association with parietal spindles. A study conducted by Ishizuka et al. found differences in frequency across the menstrual cycle (women with lower estrogen levels experienced a decreased spindle frequency). These findings challenge the blanket statement that all sleep spindles are trait-like in women (Fang et al., 2016).

Future studies should determine if there is a correlation between sleep spindle density in a particular region and memory consolidation in men to see if this difference is associated with sexual dimorphism. Perhaps accounting for this newfound effect in women in future studies could further our understanding of the role of the parietal lobe. 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. A recent study found that local brain estrogen production within cognitive circuits may be important for the acquisition and consolidation of memories (Vahaba, 2016). Sleep spindles are heavily influenced by the secretion of hormones, and they have a role in prioritizing sensory input received during the day. Where local spindle production occurs and where they spike may potentially be affected by the production of estrogen. Women in perimenses phase have lower estrogen levels than women in the nonperimenses phase. This study is limited because hormone levels were not recorded. Future studies should incorporate sex hormone differences to more accurately see the relationship between hormones, especially estrogen, and whether this affects where spindles peak. A phase influence may account for differences in spindle density. A compensatory role of parietal lobe may explain why this region had a significant correlation with memory consolidation while other did not.

Citations

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