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The Impact of Sex Hormones and Aging on Sleep-Dependent Memory Formation

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Cognitive Neuroscience

by

Negin Sattari Barabadi

Dissertation Committee:
Dr. Sara Mednick, Cognitive Sciences Department, Chair
Dr. Susanne Jaeggi
Dr. Aaron Bornstein

2021

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DEDICATION

To my family, friends and mentors who have supported and inspired me throughout my life. This, full of obstacle, chapter of my life was a dream became true and it would have not happened without your love and encouragement. I am who I am today for all you all have taught me, and I am forever thankful.

To my committee:

Sara, you have been, and will always be, my mentor in life not just academia! I am beyond blessed for being your mentee. You have always reminded me that with passion and persistency even mountains can be pushed away. *Thank you* is not a fair phrase here as you have been unbelievably supportive and a cheerleader in every single step.

Susanne and Aaron, you have been incredibly kind and supportive in every step of the way. My gratitude to you for willing to be on this committee and for making me to think deeper. I appreciate your support during this past year of global pandemic.

To my friends:

Lauren, Ben and Kyla, your friendship over these last few years made me to not give up and keep climbing. I am overwhelmed with the love and support I received from you. I look forward to being your friend and colleague for many years to come.

Maryam & Ramin, thank you for showing me that all the sacrifices are worth it, and a bright future is awaiting at the end of the path. I look forward to being your friend for lifetime and for our children, Lena, Ariana and Ryan, to grow up together and feel the love and connections we have for each other.

To my family:

Maman, you are my courage. I am here today enjoying being a mom and a scientist only because of all your support and encouragement. Thank you for literally always being there for me. You are a proof of unconditional love. You are my first and forever role model and I only hope to become someone like you one day. You have sacrificed your life for me and dedicating this dissertation to you does not do it justice. I love you.

Baba, thank you for all you did and still are doing for me. Thank you for bearing all these years that I was not able to be with you and for always reminding me of the purpose of my immigration and the sacrifices we all made for a brighter and better future for our family. I love you.

Amin and Amirreza, the lessons I learned growing up with the two of you made me who I am today. You two are my strength. We practiced questioning and discovering the world together. Thank you for always lifting me up and being my cheerleaders. I love you.

Ariana and Ryan, my heart is beating outside my body since you two are born. Thank you for bearing with mama's crazy schedule. Thank you for making me stronger in this journey. Because of you two now I know dreams do come true even if you create two lives along the way. Even if you are a woman from a different culture and speaks a different language. I look forward to being there for you when you are discovering your own world. I love you.

Yousef, my love, my rock, my forever inspiration, what can I say? Words can not explain the support and confidence you gave me. Thank you for always trusting in the person I am and for always supporting me. You have pushed me to my limits and fears and made me a stronger woman. Your unconditional love has always brightened the path and I am always the luckiest person in world for having you by my side. My life is dedicated to you let aside this dissertation.

To my uncles, *Ali* and *Morry*, my aunties, *Stephani*, *Mahin* and *Marilyn*, to all my cousins, you are my world and it feels amazing to be surrounded by your love and support.

I would also like to dedicate my work to the land of opportunities, to the USA. Thank you for hosting me all these years and thank you for all the opportunities you provide for human beings regardless of their color, gender, culture, and beliefs.

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ACKNOWLEDGEMENTS

I would like to express the deepest appreciation to my committee chair, Professor Sara Mednick, who has supported me throughout this journey and has always conveyed a spirit of adventure regarding research and scholarship. Without her guidance and persistent help this dissertation would not have been possible.

In addition, a thank you to the department pf Psychology at University of California Riverside who has hosted me the first two years of my academic life, when I stepped into the science of cognition.

I thank the Division of Teaching Excellence and Innovation at University of California Irvine for all their guidance and learning opportunities. Only with their support my dream of becoming a valuable teacher became true.

VITA

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FIELD OF STUDY

My research entails the effects of biological factors, such as aging and sex differences, on sleep dependent memory consolidation and learning. I have investigated the effects of napping on memory formation among young women across different phases of menstrual cycle in comparison to young men. In addition, I have studied older adults' nap and working memory improvement. Also, the association between long-term and working memory considering the role of sleep and aging.

PUBLICATIONS

- **N.Sattari**, Whitehurst, L. N., & Mednick, S. C. (*under review*). The role of working memory in age-related emotional memory bias. *Journal of Affective Science.*
- Chen, P. C., Simon, K. N., **N.Sattari**, Whitehurst, L. N., & Mednick, S. C. (2021). Autonomic/Central Coupling during Daytime Sleep Differs between Older and Younger People. bioRxiv, 2020-09.
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ABSTRACT OF THE DISSERTATION

The Impact of Sex Hormones and Aging on Sleep-Dependent Memory Formation

by

Negin Sattari Barabadi

Doctor of Philosophy in Cognitive Neuroscience

University of California, Irvine, 2021

Professor Sara Mednick, Chair

Age and sex are two of the three major risk factors for Alzheimer's disease. Sex differences have been shown across a wide range of cognitive skills in young and older adults. In addition, the aging brain results in decreases in both Long-Term Memory (LTM) and Working Memory (WM). A growing body of evidence shows that sleep is critical for the formation of memories, with several electrophysiological events, including slow oscillations (SO 0.5-1Hz) and sleep spindles (12-15Hz), linked with memory consolidation. Sleep has been shown to be influenced by sex, sex hormones' fluctuation and aging. Therefore, it is possible that sleeping brain processes memory differently among men and women and among older and younger adults. This dissertation investigates the role of both menstrual phase and aging on sleep related memory formation. In Chapter 1, I explore the role of sex differences and menstrual phase on sleep dependent LTM consolidation among

younger adults. I find superior pre-nap memory performance on a verbal memory task in women compared with men. Among women, post-nap memory retention was modulated by menstrual phase, with women showing more forgetting following a nap in their perimenses phase (−5 days to +6 days from the start of menses) compared to their non-perimenses (outside of the perimenses phase). In addition, three profiles emerged between brain activity and performance. In men, performance was associated with the temporal coupling of spindles and slow oscillations (i.e., spindle/SO coincidence) as well as the number of spindles. During non-perimenses, women's performance was related with SOs only, whereas performance during perimenses was associated with sleep spindles only. In Chapter 2, I explore the role of sleep, wake and quiet rest on WM training among older adults. I show that WM improved within a day of practice only after offline periods containing nap and quiet rest, but not wake, with similar sleep-dependent mechanisms as LTM consolidation (e.g., SOs and the coupling of sigma and SOs). Finally in Chapter 3, I investigate the role of WM on emotional LTM performance among younger and older adults. I find a superior memory performance for younger adults, a positivity memory bias among older adults, and a positive relation between WM and LTM only among younger adults. Together, the studies from this dissertation show evidence for a role of sex, sex hormones' fluctuation, and aging, on sleep and memory. With the reported declines in sleep and memory emerging in older adulthood and menopausal women experiencing a sudden drop in sex hormones, this dissertation highlights the importance of possible interactions among biological factors, such as sex and aging, while studying sleep and memory with the goal of illuminating new paths towards the prevention of Alzheimer's disease.

INTRODUCTION

Sex and age are two of the three major risk factors for Alzheimer's disease (ApoE-e4 allele is the third), with women having a two-fold greater risk for Alzheimer's disease after the age of 75 years (Hamson, et al., 2016). Sex differences have been shown across a wide range of cognitive skills in young (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) and older adults (parsons et al., 2005; McCarrey et al., 2016) and evidence supports a role for sex steroids, especially estradiol, in protecting against the development of cognitive decline in women (Luine 2014). Studies in young women have shown changes in cognition across the different phases of the menstrual cycle (Genzel et al., 2012; Sattari et al., 2017). Importantly, the influence of sex steroids on memory may be mediated by their effect on other modifiable, protective biological factors that influence memory, such as sleep. A growing body of evidence shows that sleep is critical for the formation of memories, with several electrophysiological events, including slow oscillations (SO, 0.05-1Hz) and sleep spindles (12-15Hz), linked with memory consolidation (Abel, Havekes, Saletin, & Walker, 2013; Diekelmann and Born, 2010; Rasch and Born, 2013; Walker and Stickgold, 2004). Furthermore, studies in young women have shown fluctuations in sleep events and sleep-dependent memory consolidation during different phases of the menstrual cycle that are associated with the levels of sex steroids (Genzel et al., 2012; Sattari et al., 2017). An under-appreciated possibility is that there may be an important interaction between these two protective factors (sex steroids and sleep) that may play a

role in daily fluctuations in cognitive processing, in particular memory, across a woman's lifespan.

The aging brain results in decreases in memory (Glisky et al., 2001; Charles et al., 2003) in both long-term memory (LTM) (Miller and O'Callaghan, 2005; Park and Reuter-Lorenz, 2009) and working memory (WM) (Wingfield et al., 1988, Park et al., 2002). WM, the ability to hold information in mind for a short period of time, is a key determinant of several higher-order cognitive functions (Engle, 2002; Borella et al., 2010; Nettelbeck and Burns, 2010). Like many other cognitive domains, WM capacity declines with age (Wingfield et al., 1988). Thus, brain training protocols have been focusing on WM improvement in older populations with the hope that improved WM will generalize to a wide range of cognitive functions (see meta analysis Au et al., 2015; Karbach and Verhaeghen, 2014, but see also Melby-Lervåg and Hulme, 2016). WM training protocols require multiple days of practicing, therefore, sleep, that is critical for restoring information (Marr et al., 1991; Mednick et al., 2013), may play a role. In fact, sleep deprived brain has been shown to negatively impact WM performance among younger adults (Chee et al., 2006; Chee and Choo, 2004; Mu et al., 2005). On the other hand, compared to younger, older adults experience reduction in sleep, both in quantity (e.g., time spent in each sleep stage) and quality (e.g., reduction in number of SOs) however, it is possible that aging brain opportunistically uses low interference situations, such as "daydreaming" [i.e., "mind wandering", which occurs when thoughts are not controlled, but instead drift off to inner thoughts, fantasies and feelings (Foulkes and Fleisher, 1975, Smallwood and Schooler, 2006)], to process information, an idea proposed by Opportunistic Consolidation Hypothesis (Mednick et al., 2013). In summary, with age-related marked deterioration in

WM it is possible that aging may give rise to plasticity mechanisms that opportunistically activate consolidation processes during non-sleep offline states. Therefore, understanding offline mechanisms (both during sleep and quiet rest) of working memory function in older adults may help slow this age-related WM decline by providing potential paths to brain training intervention protocols.

Similar to WM, LTM declines with age (Luo & Craik, 2008; Miller & O'Callaghan, 2005; Barnes, 1979; Gage et al., 1984; Markowska et al., 1989). Interestingly, a shift in valenced LTM functioning has also been reported (Spaniol et al., 2008; Fernandes et al., 2008) where young adults display retention for negative memories over positive (terms negative memory bias), whereas older adults show better retention of positive over negative memories (terms positive memory bias). Although the reason for this age-related change in emotional memory bias is not clear, theories such as socioemotional selectivity theory (SST; Carstensen, 2006; Carstensen et al., 1999), have hypothesized a role for prioritizing positive memories, consistent with the goal of emotional well-being among older adults compared to younger adults who prioritize knowledge acquirement instead. Other studies have considered a role for WM (Mather et al., 2005). In fact, a higher proportion of memory for positive pictures was found for older adults with superior WM, while older participants with inferior WM recalled fewer positive pictures, thus WM may play a role (Mather et al., 2005). In addition, controversial results have been reported in terms of the role of sleep on emotional memory formation across the life span. In fact, sleep has been shown to benefit negative memory among younger adults (Nishida et al., 2009; Wagner et al., 2006), while no differences in sleep and wake for negative memory formation was found among middle-age subjects (Jones et al., 2018), and there are

evidence for a selective role for sleep while processing positive memories among older adults (Jones et al., 2016). Together, knowing that the age-related diminishment in sleep features contribute to age-related decline in memory (Helfrich, Mander, Jagust, Knight, & Walker, 2018; Mander et al., 2013), and the trainability of WM and its relation to other cognitive domains such as LTM, investigations on the possible associations between WM and sleep-related valenced LTM in the context of aging, may help illuminate the mechanisms underlying the age-related emotional memory bias.

Taken together, biological factors such as sex and age may affect the well-known relation of sleep and memory. Thus, more clarification on the impact of these factors on sleep-related memory formation, can contribute to better understand the mechanisms underlying sex and age-related differences in memory across the lifespan. In the following sections I present three studies in which I examine the interaction of sleep, sex and menstrual cycle among younger adults on LTM (Chapter 1) and a possible role for sleep on WM training among older adults (Chapter 2). Lastly, I explore the possible predictive role of WM on emotional LTM in the context of aging (Chapter 3). These studies illuminate the important role of sex and sex hormones in sleep dependent memory formation as well as how aging can impact WM in relation to sleep and LTM. Findings from these studies could lead to the development of unique non-invasive, sleep-focused interventions to counteract cognitive decline across the lifespan.

CHAPTER 1:

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

Brain behavior function are sexually dimorphic across a range of 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, on verbal memory tasks, such as word and picture recall and recognition, story recall and name recognition, women perform better 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 (**Figure 1-1**.A). 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 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).

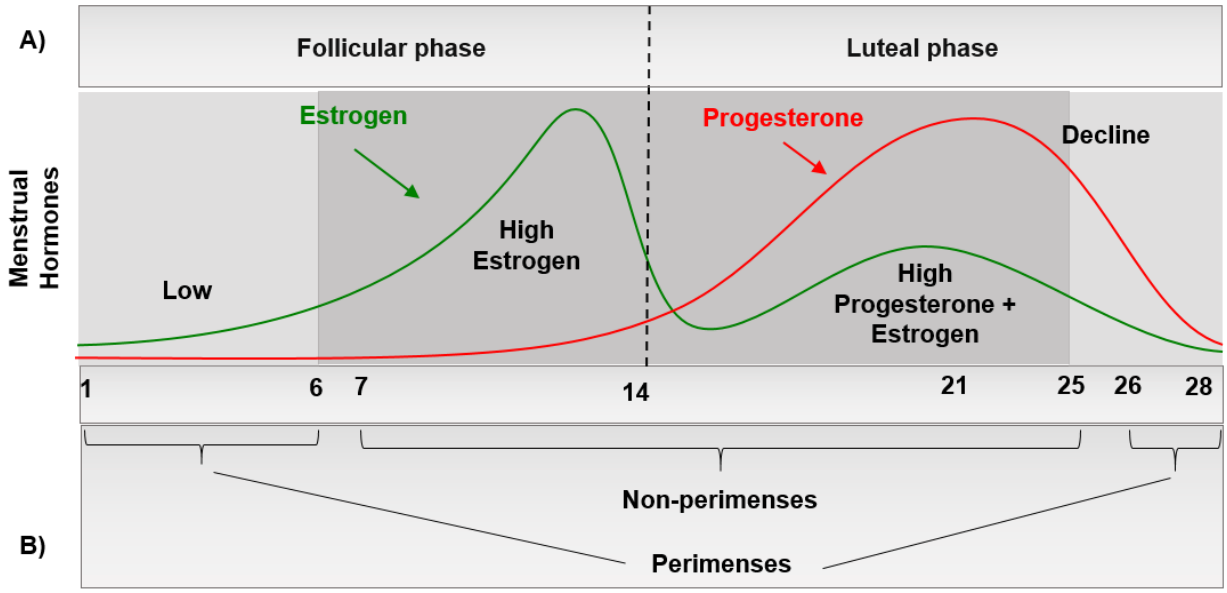

Figure 1-1: The panel demonstrates fluctuations in hormones across the menstrual cycle. (A) Shows the follicular and luteal phases and (B) shows categorization in the current study defined from self-report.

In addition to sex and sex hormone, 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. Here in study 1 we 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) (**Figure 1-1**.B). 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.

Materials and Methods:

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.

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 "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 (**Figure 1-1**.B). 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.

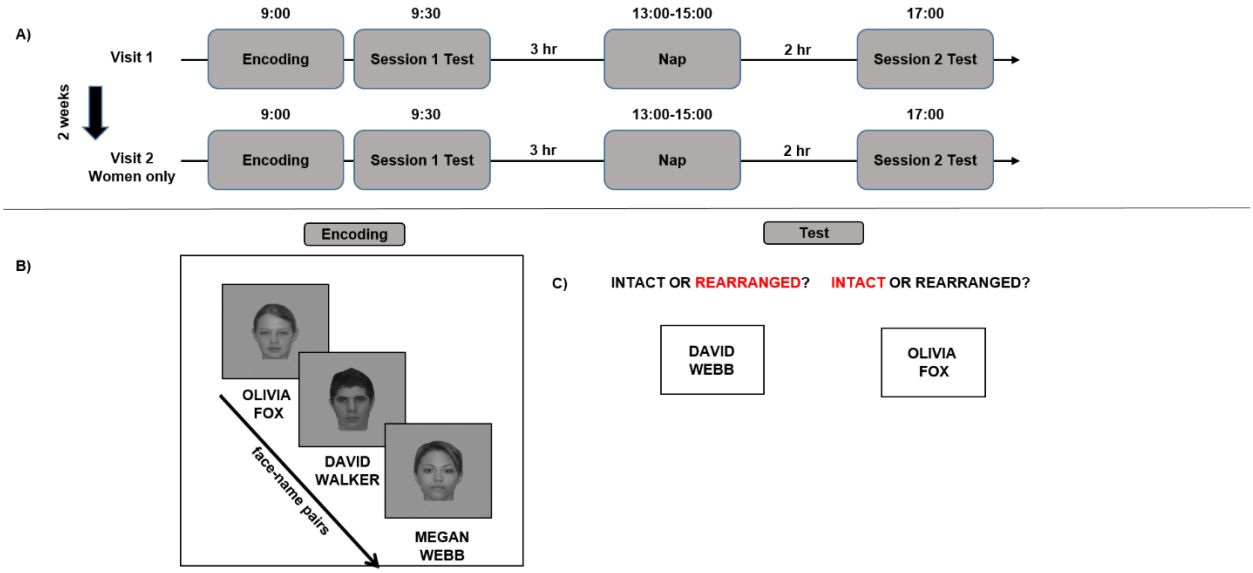

Figure 1-2: The panel demonstrates (A) the nap paradigm and visit 2 procedure for women only. During Visit 1 subjects encoded the face-name pairs at 9 am and immediate memory was tested at 9:30 am. Subjects took a 90 min PSG-recorded nap after. Session 2 testing occurred 2 h after the nap. Female subjects 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.

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 (**Figure 1-2**). 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 (**Figure 1-2**). 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".

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.

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).

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 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 halfwave). 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.

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.

Results:

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.

Immediate memory performance Session 1: Looking at men and women (once during their perimenses and once during their non-perimense) separately, as shown in **Figure 1-3**, 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); nonperimenses: 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].

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

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.

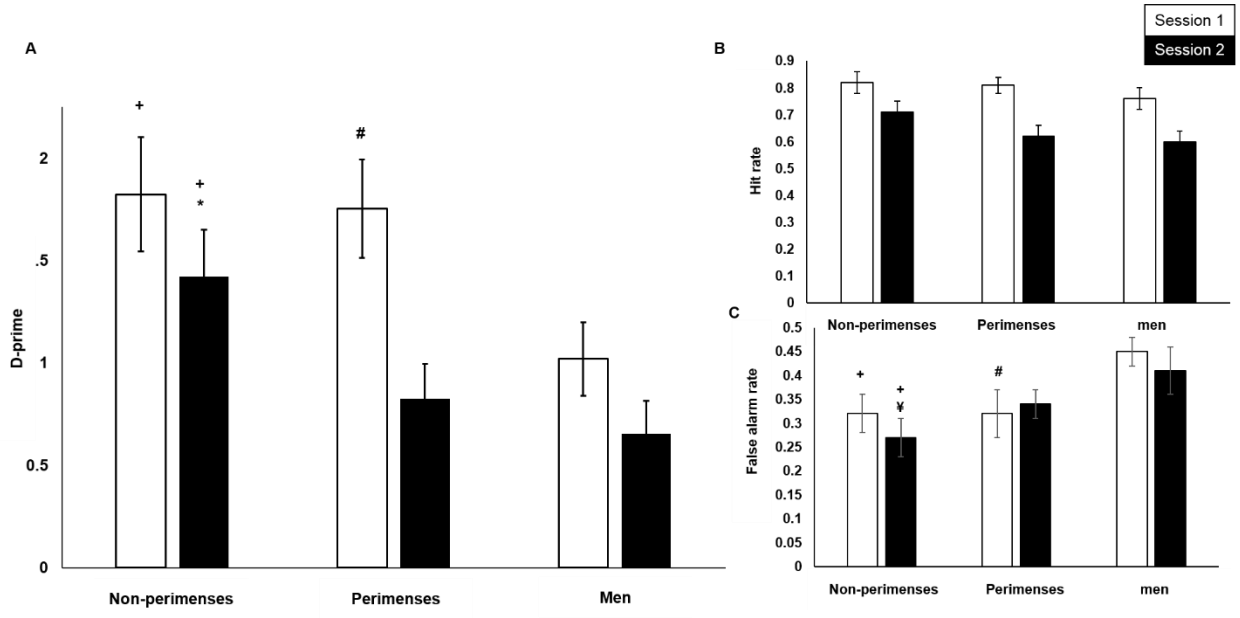

Figure 1-3: Memory performance on Name Recognition. (A) D-prime score; women performed better than men at Session 1 (white bar). Non-perimenses women performed better compared to perimenses and men after the nap at Session 2 (black bar). Difference score (Session 2-Session 1): perimenses showed significant 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 ($0.02 < p \leq 0.06$).

Group differences in sleep architecture: Nap descriptive can be found in Table 1.1. 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 nonperimenses phase compared to men [minutes: t(32) =2.48, p = 0.02; percentage: t(32) =2.28, p = 0.03 (trend)]. Table 1.2 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).

Table 1-1: 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)	.27	.79	.47

S2 (min)	36.65(3.21)	39.55(3.30)	41.00(2.93)	.40	.32	.74
SWS (min)	21.12(3.40)	21.71(3.56)	25.42(3.71)	.92	.40	.36
REM (min)	19.40(2.45)	13.46(2.99)	10.94(2.35)	.07	**.02**	.42
S1 (%)	10.44(2.01)	11.86(2.43)	9.15(1.59)	.51	.61	.42
S2 (%)	44.94(3.47)	45.76(4.03)	48.90(3.10)	.87	.40	.54
SWS (%)	23.21(3.73)	24.62(4.40)	29.15(4.31)	.78	.31	.45
REM (%)	21.40(2.58)	15.39(3.36)	12.80(2.71)	.09	**.03**	.47
WASO (min)	7.34(2.12)	14.93(4.92)	11.11(3.32)	.07	.39	.60
SL (min)	7.03(2.22)	6.78(1.92)	6.55(1.65)	.92	.86	.96
SE (%)	84.11(4.98)	80.41(4.97)	82.95(3.68)	.44	.85	.83
TST	84.81(3.81)	82.12(3.88)	84.55(3.51)	.55	.96	.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 percentage) compared to men. P-values are significant if less than/equal .02 and trending if greater than .02 and less than/equal .06 using Bonferroni correction.

Sleep and behavioral 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. **Figure 1-4** and **Figure 1-5** show separate color-coded, electrophysiology/behavior profiles for all our participant's first visit (**Figure 1-4**) 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.

Table 1-2: 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>.19). Mean (SEM).

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

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.

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 nonperimenses phase.

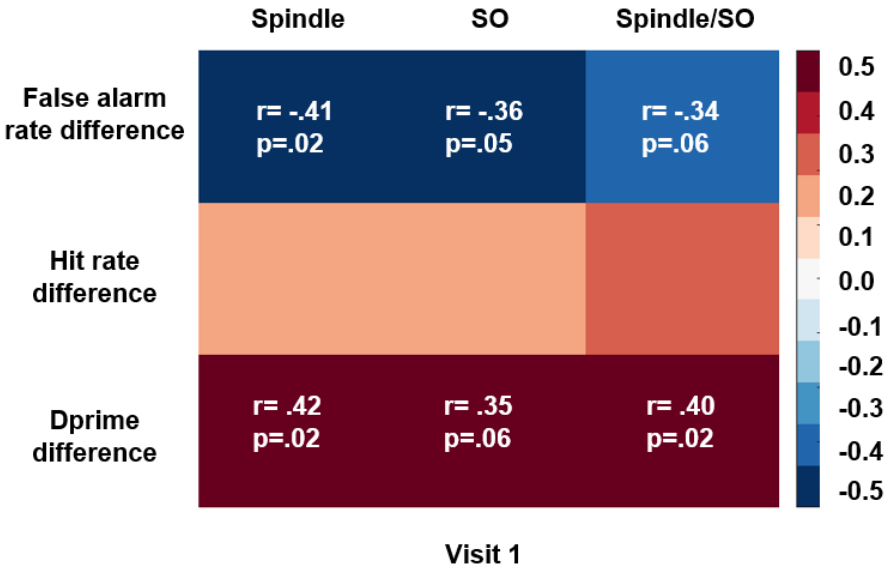

Figure 1-4: Shows separate color-coded, electrophysiology/behavior (Name Recognition) profiles for all subjects during their visit 1 with effect size (r) indicated by color. At the averaged frontal electrode, spindles, SOs and Spindle/SO correlated with memory retention. (For interpretation of the references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

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.

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).

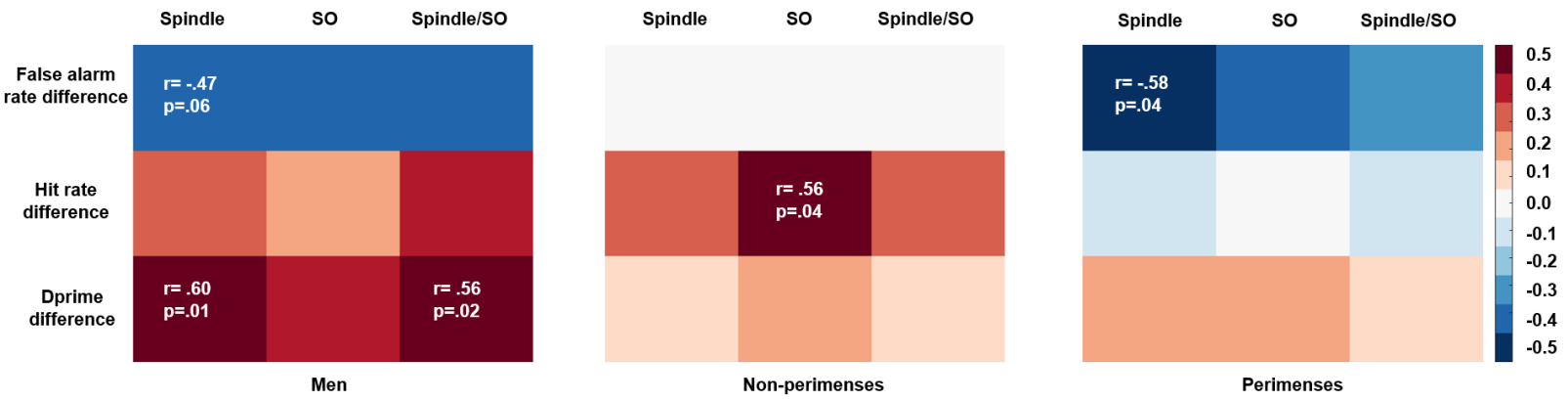

Figure 1-5: Color-coded, electrophysiology/memory profiles for men, non-perimenses, and perimenses women with averaged frontal electrode and performance measure effect sizes (r) indicated by color. Compared with men, women in different phases of their menstrual cycle appear to show different associations 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 color in this figure legend, the reader is referred to the web version of this article.)

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.

Limitation: 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.

Conclusion: 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.

CHAPTER 2

Does working memory improvement benefit from sleep in older adults?

Working Memory (WM), known to play a critical role in human cognition (Baddeley et al., 1986; Carpenter and Just, 1989), refers to the ability to hold information in mind for a short amount of time. It is hypothesized that WM includes storage mechanisms that maintain its content in an active state, and executive processes that can perform operations on the stored information (Baddeley et al., 1986; Jonides, 1995). WM is a key determinant of several higher-order cognitive functions, such as reasoning, problem solving, intelligence, and language comprehension (Engle, 2002; Borella et al., 2010; Nettelbeck and Burns, 2010). Like many other cognitive domains, WM capacity declines with age (Wingfield et al., 1988). This decline is thought to contribute to a range of cognitive impairments in older adults (Park et al., 2002), such as language learning, decision making, problem solving, and reading comprehension (Engle and Kane, 2004), as well as decreases in daily life functioning, such as medication adherence (Raz, 2000). Thus, WM improvement has been the focus of cognitive training in older adult populations with the expectation that enhanced WM will generalize to a wide range of cognitive functions (see meta analysis Au et al., 2015; Karbach and Verhaeghen, 2014, but see also Melby-Lervåg and Hulme, 2016). Typical WM training protocols require multiple weeks of daily practice, suggesting that training-induced changes are slow to form, and that the benefits can last up to 18 months (Dahlin et al., 2008). Little is known about the biological factors that may contribute to these long-term changes, but sleep may play a role. To be sure, a sleep deprived brain shows less effective executive functioning, including decreases in WM, attention, and goal-

directed behavior (Nilsson et al., 2005). In young adults, studies have shown significant reductions in WM performance after a night of sleep deprivation compared to controls (Chee et al., 2006; Chee and Choo, 2004; Mu et al., 2005). Interestingly, older adults may be somewhat resilient to prolonged wakefulness, with greater maintenance of WM performance after sleep deprivation compared with young adults (Philip et al., 2004; Stenuit and Kerkhofs, 2005; Adam et al., 2006; Duffy et al., 2009). In light of the significant reductions to sleep in older adults (Bliwise, 1993; Ohayon et al., 2004; Yetton et al., 2018), this resilience to sleep deprivation has been viewed as a potentially adaptive response to living with more fragmented and lighter sleep. However, no studies, that we are aware of, have compared whether sleep or wake improves WM among older population. If sleep does confer greater benefit, considering it as a controllable biological factor in cognitive training would likely enhance outcomes and quality of life of older adults (Raz, 2000). A growing body of studies showed that long-term memory is facilitated by sleep Diekelmann and Born, 2010). Marr's theory of memory consolidation (Marr et al., 1991) posits that information is transferred between the hippocampus and neocortex during periods of quiescence, including sleep and quiet rest. Neural activities in nonrapid eye movement (NREM) frequency bands including SO (<1 Hz), and spindles (12–15 Hz) have been shown to play critical roles in both formation and consolidation of long-term memory (Mednick et al., 2013). As mentioned earlier, SOs appear to be the fundamental cellular phenomenon that organize faster electrophysiological frequencies important for memory formation, like sleep spindles (Steriade et al., 1993; Mölle et al., 2011). As it was discussed in study 1, SO's originate more frequently in frontal brain areas and are hypothesized to play major role in time-dependent synaptic plasticity during sleep (Massimini et al., 2004). Intriguingly,

recent studies suggest that not only are the spindle frequency (sigma power) and SOs independently associated with performance improvement (Clemens et al., 2005; Gais et al., 2002; Mednick et al., 2013; Oyanedel et al., 2014; Schabus et al., 2004), but the coincidence or coupling of SOs and sigma (SO/sigma) may also be a key mechanism of long-term memory formation during sleep (Mölle et al., 2011; Staresina et al., 2015), with several studies suggesting that sigma activity during the SO up-state are optimal (Niknazar et al., 2015; Gais and Born, 2004; Mölle et al., 2009).

Older adults typically show decreased amplitude of SOs (0.5–1 Hz) (Carrier et al., 1997; Martin et al. 2000). Additionally, a recent study examining coupling of sigma and SO in relation to fMRI brain activity and memory performance in older adults (Helfrich et al., 2018), reported changes in spindle/SO coupling and decreased coupling over the frontal pole with age. Note that in both age groups spindle/SO coupling predicted post-sleep declarative memory improvement. Together, these findings suggest that long-term memory formation benefits from increased sigma and SO activity independently, as well as from the coordination of these brain rhythms. However, no studies have probed the relationship between these electrophysiological features that usually occur during sleep and working memory in older adults. It is important to note that memory consolidation may also occur during wake. In particular, post-encoding wake periods free of interference from new learning, such as quiet wake, may engage similar consolidation mechanisms, an idea proposed by the Opportunistic Consolidation Hypothesis (Mednick et al., 2011). This hypothesis posited that replay processes underlying consolidation may initiate under any condition of reduced interference. Consistent with this hypothesis, Rieth and colleagues, demonstrated equivalent levels of learning from sleep and quiet wake on a motor learning

task, in which non-sleep factors (i.e., massed practice and circadian confounds) were controlled (Rieth et al., 2010). A similar result was shown for early motor learning (Humiston and Wamsley, 2018). Additionally, Brokaw and colleagues, reported that verbal memory improvement was greater after a brief period with eyes closed, compared with an active wake condition, and increased SO activity during quiet wake was correlated with performance improvement (Brokaw et al., 2016). Given the emerging picture in aging of poor sleep, decreased SO power and sigma/SO coupling, and apparent resilience to the negative cognitive impact of sleep deprivation, it is possible that aging may give rise to plasticity mechanisms that opportunistically activate consolidation processes during non-sleep offline states. Taken together with evidence of marked deterioration in WM and frontal neural structures supporting executive functioning, in Study 2, we aimed that understanding offline mechanisms of working memory function in older adults may help slow decline by providing potential routes to interventions. Study 2 examined the effect of a nap, quiet wake (QW) or active wake (AW), on repeated within-day training in a WM task in older adults. Participants completed the Operation Span (OSPAN) task (Unsworth et al., 2005) to assess WM performance. Based on the Opportunistic Consolidation hypothesis, we predicted that across a day of training, nap and QW interventions would have similar impacts on WM improvement and would be better for WM than an AW. We additionally predicted that improvement among the nap and QW in within-day WM accuracy would be related to enhanced electrophysiological features, including activity in SO frequency band, and in SO/sigma coupling during sleep.

Materials and Methods:

Subjects: 85 (42 females) healthy, non-smoking older adults between the ages of 60 and 85 (M = 69.24, SD = 6.66) 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 6 h of total sleep per night on average. Subjects had no personal history of sleep, neurological or psychological disorders, or other chronic illnesses. The personal history of illnesses were measured two times: first, during a pre-screening questionnaire in which a general health condition report was collected over the phone and the eligibility was determined: second, eligible subjects were invited to participate in an orientation in which they were given details about the study. During the orientation, subjects were screened for cognitive impairment and dementia using Digit Span Backwards and Telephone Screening for Dementia questionnaires (referred to as TELE) (Gatz et al., 2002). In the digit span backwards which contains a multi variate length string of digits, subjects were asked to repeat the string of digits backwards after it was read to them. TELE questionnaire consists of variety of questions to identify dementia-like symptoms. All the experimental procedures were approved by the Institutional Review Board of the University of California at Riverside. Subjects with a regular sleep-wake schedule, determined during an in-person interview, were recruited and asked to maintain their schedule for one week prior to their visit, which was monitored with sleep diaries. In addition, subjects were asked to wear an actigraphy (Actiwatch Spectrum, Respironics) for one night prior to their visit. Subjects were rescheduled if they reported poor sleep quality in their sleep diary, such as having more than 2 nights of less than 6 h of sleep during the week prior to their visit, or if subjects' actigraphy data was showing less than 6 h of sleep

the night before the experimental visit. Rescheduled subjects were given another week to fill out a new sleep diary and maintain a regular sleep wake schedule prior to their visit.

Protocol: Subjects were asked to refrain from consuming caffeine, alcohol, and all stimulants for 24 h prior to and including the study day. During their visit, Test 1 began at 10:30 (**Figure 2-1**.A). Subjects first were given the Karolinska Sleepiness Scale questionnaire (KSS) (Åkerstedt and Gillberg, 1990) to assess their sleepiness. Next, subjects completed the Operation Span (OSpan) task. The task consisted of a practice phase followed by an immediate test. At 11:30, subjects were given 1hr-break in the lab and they were instructed to abstain from caffeine, alcohol, exercise and napping. At 12:30, subjects were randomly assigned to either a nap condition (NAP), a quiet wake condition (QW) or an active wake condition (AW). A high-density electroencephalogram (EEG) electrode cap was attached to the scalps of the NAP and QW groups. For the NAP group, subjects were provided a 2-hour nap opportunity and were allowed to sleep up to 90 min. In the QW conditions, subjects watched a 60-min nature documentary in a dark room lying on the bed while being monitored by lab staff to make sure they did not fall sleep. In the AW group, subjects stayed awake and played a board game with one of the lab research assistants. 30 min after the sleep intervention Test (i.e., Nap, QW or AW), around 15:00, subjects participated in Test 2 during which they were tested on the WM task for approximately 30 min. Subjects completed the KSS and PNQ questionnaire two times throughout the experimental day; at the start of each cognitive Test (i.e., Test 1 and Test 2) to report their sleepiness and mood respectively.

WM task: The WM task contained nine practice and 20 test trials. The nine practice trials were not counted towards the subjects' final score. Subjects viewed a serial visual display

of letters and math problems and then were asked to recall the string of the letters. In fact, they were asked to hold the letters in memory while simultaneously determining if the simple math problems were correct (e.g., 7 + 5 = 13). The letter strings were always 5 letters long (**Figure 2-1**.B). Subjects were tested in the WM task before (Test 1) and after (Test 2) the nap intervention. Each of the simple math equations were presented on the screen for 3000 ms and each letter was presented for 1000 ms. Subjects were instructed to press the "M" key with their right hand if the simple math equation was correct and press the "V" key with their left hand if the equation was not correct. Subjects' data were only included in the analysis if they performed equal and/or greater than 75 percent correct on the math portion of the task. After each trial, a question mark appeared on the screen to signal the response period. Subjects were required to enter the letters in the same order they were presented. The recall part of the task was not timed and subjects were not able to go to the next trial until the correct number of letters was entered. Then, a "Ready?" prompt appeared on the screen and subjects were instructed to press the space bar to start the next trial when they were ready. Four breaks were inserted throughout the task. Test 2 was identical to Test 1.

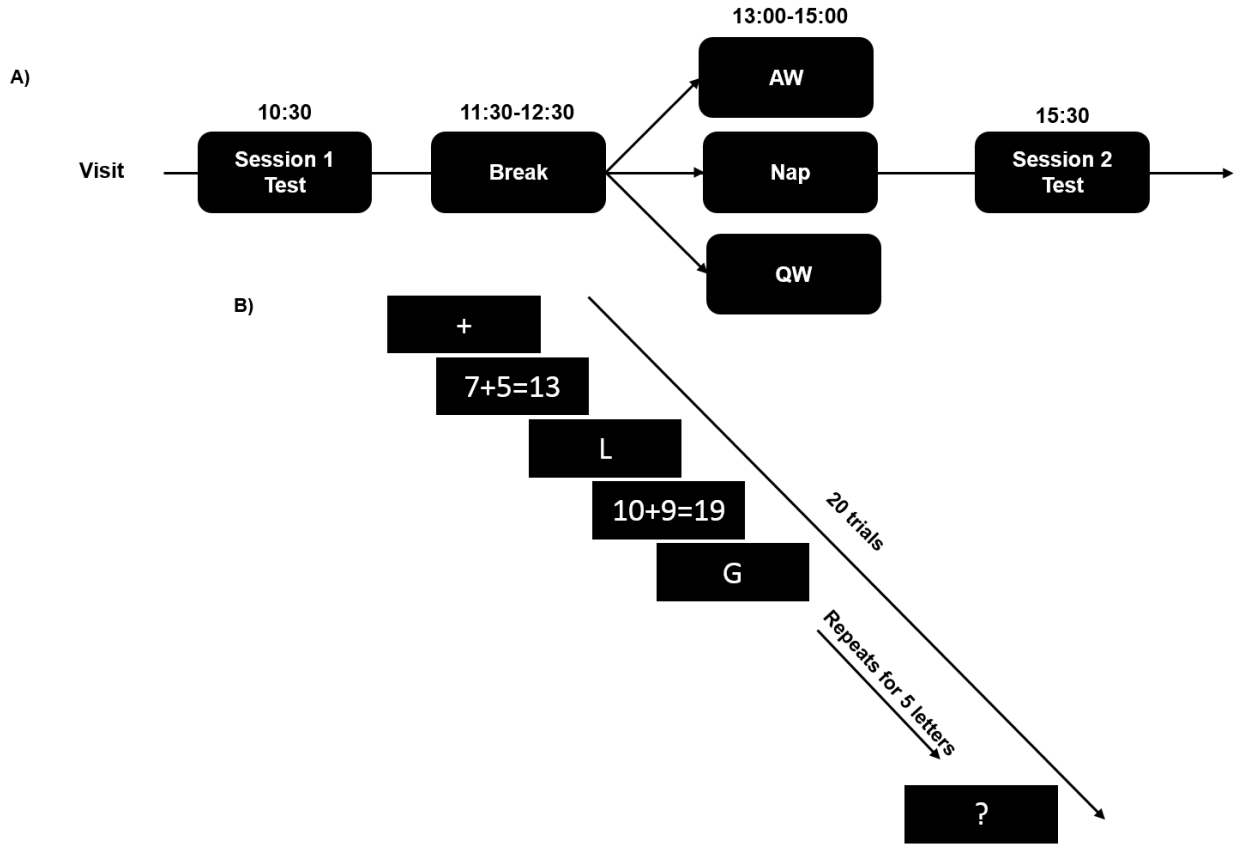

Figure 2-1: A) Experimental visit. At 10:30, subjects completed the Working Memory (WM) task at Session 1, followed by a short break. Next, subjects were randomized to one of three nap interventions (AW, QW, Nap). At 15:30, Session 2 WM testing began. B) The Operation span WM task. The WM task contained nine practice and 20 test trials. The nine practice trials were not counted towards the subjects' final score. Subjects viewed a serial visual display of letters and math problems. They were asked to hold the letters in memory while simultaneously determining if the simple math problems were correct or not. This was followed by a response period where subjects were asked to type the letters in the previously viewed order.

Data reduction: In this study, if subjects were not comfortable during any part of the experimental day, they were compensated for the portion that was completed and were exempt from finishing the day (2 subjects decided to drop out after Test 1 both from AW group). In addition, three subjects were dropped because they did not pass the math criterion (i.e., 75 percent correct) (1 AW, and 2 QW).

Electroencephalography (EEG): EEG data were acquired using a thirty two-channel cap (EASEYCAP GmbH) with Ag/AgCI electrodes placed according to the international 10–20 System (Jasper, 1958). Electrodes included 24 scalp, two electrocardiogram (ECG), two electromyogram (EMG), two electrooculogram (EOG), 1 ground, and 1 on-line common reference channel. EEG signals were recorded at a 1000 Hz sampling rate and referenced on-line to the common reference channel. After data acquisition, EEG signals were re-referenced: the right side of the scalp were re-referenced to the left mastoid and the electrodes on the left side of the scalp were re-referenced to the right mastoid. 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).

Electrophysiological data: NAP and QW Raw EEG signals were digitally band-pass filtered between 0.3 and 35 Hz. All epochs of the filtered data with artifacts and arousals were identified by visual inspection and rejected. Next, the EEG data were scored using Hume, a custom MATLAB toolbox. The records were scored in 30 seconds epochs using eight scalp electrodes: Frontal (F3, F4), Central (C3, C4), Parietal (P3, P4), and Occipital (O1, O2). Sleep stages epochs were exported for further analysis in MATLAB 2011b (MathWorks, Natick MA). The MATLAB output files from Hume were first passed to BrainVision Analyzer 2.0

(BrainProducts, Munich Germany) for pre-processing. Next, the data was passed to two other MATLAB based algorithms to measure SO Power and SO/Sigma coupling (developed by Sleep and Cognition Lab (SaC lab) at University of California, Irvine). For both the nap group, the SO power spectral analysis and SO/Sigma coupling analysis were conducted within each sleep stage separately. For EEG power spectrum, we used the Welch method (4 second Hanning windows with 50% overlap) (Campbell, 2009). The SO power was calculated for each sleep stage (i.e., Stage 2, SWS and REM). In addition, given that, SOs show the strongest relative amplitude at frontal electrode cites (Massimini et al., 2004; Murphy et al., 2009), we made the a priori decision to use F3 and F4 electrode cites for our analysis of slow oscillations for both nap and QW data. SO/Sigma coupling was obtained by means of Modulation Index (MI). First, slow oscillations were detected automatically as described by Massimini and colleagues (2004). Filtered EEG data with negative to positive zero crossings separated by 0.5 to 1.5 second were detected. The detected zero crossings were labeled as SOs if the following criteria were met: a minimum width of 1 second a maximum negative peak width of 10 second and a minimum amplitude of −80 uV. Next, transient coupling between the phase of slow wave oscillations (SO) and sigma power (12–15 Hz) during stage 2 and SWS stages was measured as described by Canolty and colleagues (2006). Assuming an EEG signal (x[n]) sampled at times t_n, n = 1,2,…,N was then bandpass filtered into the two frequency bands of interest, sigma and SO bands. Applying Hilbert Transform to these two filtered signals allowed us to form the composite complex-valued signal (analytic signal) giving us the amplitude of the sigma and the phase of the SO. The absolute value of the mean of Z[n], Z [n] = aSigma [n]exp (i SO [n]) the so-called MI, provides the coupling between the sigma-amplitude and SO-phase (Canolty et al.,

2006). If we assume a uniform distribution of SO-phase, any departure of the distribution of Z[n] from symmetry will show a dependence of the sigma amplitude (sigma-amplitude) on the SO phase. Hence, a non-zero value of MI (here we call it MI_raw) indicates some amount of phase-amplitude coupling (Penny et al., 2008). To take into account the possible over-estimate of MI due to non-white noise in the signal, we normalized MI_raw by comparing it to the possible modulation indexes found in specifically generated surrogate data generated by introducing an arbitrary time lag between sigma-amplitude and SO-phase. Using many different lags, a distribution of surrogate MI values was generated, with mean μ and standard deviation σ and the normalized MI was computed as follows: $M_{norm}=(M_{raw}-\mu)/\sigma$. Further, given that sigma frequency band shows the most power over central regions (Malerba et al., 2018), for our MI analysis, we made the a priori decision to use C3 and C4 which will likely capture a more accurate representation of SO/sigma activity.

Statistical analysis: Performance was assessed by calculating the following variables for each test of the WM task: Accuracy and Reaction Time (RT). Accuracy represents the total number of correctly remembered letters. RT represents the time spent providing the correct sequence of letters. We used a Univariate ANOVA with Test 1 as the dependent variable and sleep condition as the fixed factor to test for baseline differences in accuracy and RT across the three groups. In addition, to assess performance change related to sleep, we calculated a difference score (Test 2 – Test 1), with positive difference scores indicating an improvement in WM accuracy throughout the day, and positive RT difference scores indicating a deterioration in speed throughout the day. We first used a 2 × 3 repeated measure ANOVA with the dependent variables Test 1 and 2 and the fixed factor sleep

condition (i.e., nap, QW and AW). To examine changes in performance throughout the day within each group, we next used paired sample t-test. Finally, we used bivariate correlations to assess the relationships between WM performance and sleep physiology events (i.e., sleep architecture, SO power and normalized MI) for the nap group. In addition, we used bivariate correlations to assess the relationships between WM performance and SO power during QW. Further, to control for multiple comparisons for correlations between WM performance and SO power at different electrodes (i.e., F3 and F4) we used Bonferroni method, meaning that p-values are considered significant if less than/equal 0.025 and trending if greater than 0.025 and less than/equal 0.05. Similarly, we corrected for multiple comparisons for correlations between MI at different electrodes (i.e., C3 and C4) and WM performance.

Results:

Working Memory Performance: We found no baseline differences between groups in accuracy [Test 1: $F(2,77) = 0.34$, $p = 0.71$] or RT [Test 1: $F(2,77) = 1.66$: $p = 0.19$], indicating the three groups performed similarly at the start of the training. Our 2 × 3 repeated measure ANOVA, with factors Time (Test 1 and 2) and Group (Nap, QW, AW) revealed no significant interaction effects for accuracy [$F(2,77)=0.60$: $p=0.55$; RT: $F(2,77)=0.24$: $p= 0.78$] but a significant main effect of Time [accuracy: $F(2,77) = 11.7$: $p = 0.001$; RT: $F(2,77) = 5.65$: $p = 0.02$]. Thus, regardless of group (i.e. nap, QW or AW), all subjects improved in performance throughout the day. Given our a priori prediction that a nap and QW would confer greater benefit to WM improvement than AW, we statistically tested the magnitude of change in each group, despite the non-significant omnibus

interaction. We used student paired t-test to examine the change in performance during the day, from Test 1 to Test 2, separately in each group. WM improvement was not shown in the AW group [accuracy: t (24) = −1.26, p = 0.22; RT: t(24) = 1.35, p = 0.19]. However, QW showed significant improvement in both accuracy and RT throughout the day [accuracy: t(20) = −2.05, p = 0.05; RT: t(20) = 2.29, p = 0.03]. In addition, the nap group showed significant improvement in accuracy [t(33) = −2.56, p = 0.01], but not RT [t(33) = 1.65, p = 0.10] (see **Figure 2-2**). These results indicate that since, all the three groups started at a similar level, any improvement from baseline is more likely related to the sleep intervention. Next, we examined the relation between
the WM performance change observed between Test 1 and 2 with sleep features during the nap and quiet wake periods.

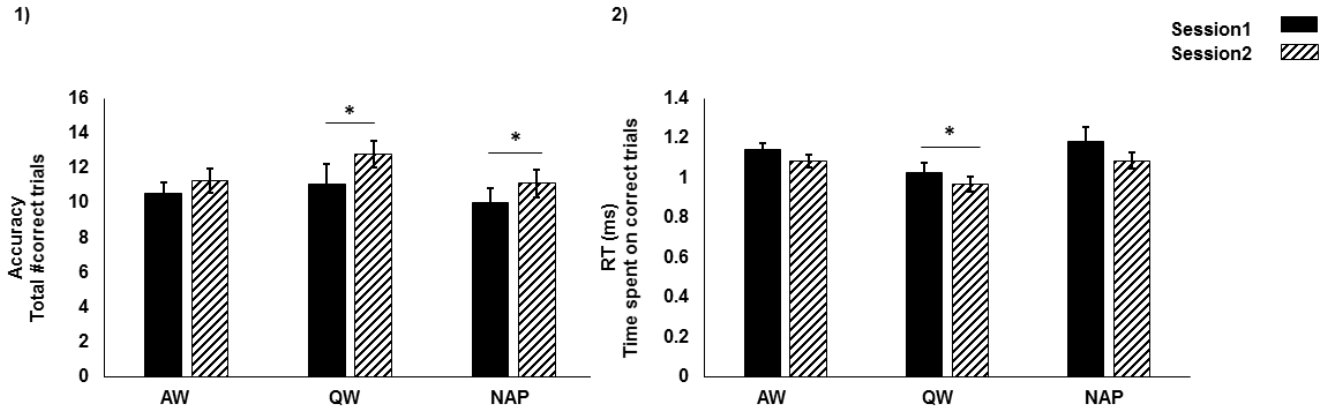

Figure 2-2: Working Memory (WM) performance across the three experimental groups. 1) WM accuracy was significantly improved from Session 1 (Black bar) to Session2 (Hatched bar) in a paired sample t-test in the Nap and QW group. 2) WM Reaction Time (RT) was significantly improved from Session 1 to Session 2 only in QW group. (* represent p-values<0.05).

Quiet Wake-SO Power and WM Performance: SO power descriptive for QW can be found in Table 2.2 In the QW group, increase in WM accuracy from Test 1 to Test 2 was positively associated with SO power at F4 ($r = 0.58$, $p = 0.02$) (See **Figure 2-3**). This result indicates that higher SO activity during a quiet period relates to greater gain in WM performance among the participants. SO power did not reveal significant association with RT ($p>0.08$).

3.3. Nap Architecture and WM Performance Associations Sleep architecture can be found in Table 2.1. No significant association was found between WM accuracy and sleep architecture variables (all $ps>0.09$). RT at Test 2 was negatively associated with time spent in SWS (minutes: $r = -0.45$, $p = 0.007$; percentage: $r = -0.40$, $p = 0.02$) indicating that more time spent in SWS is associated with better RT after the nap.

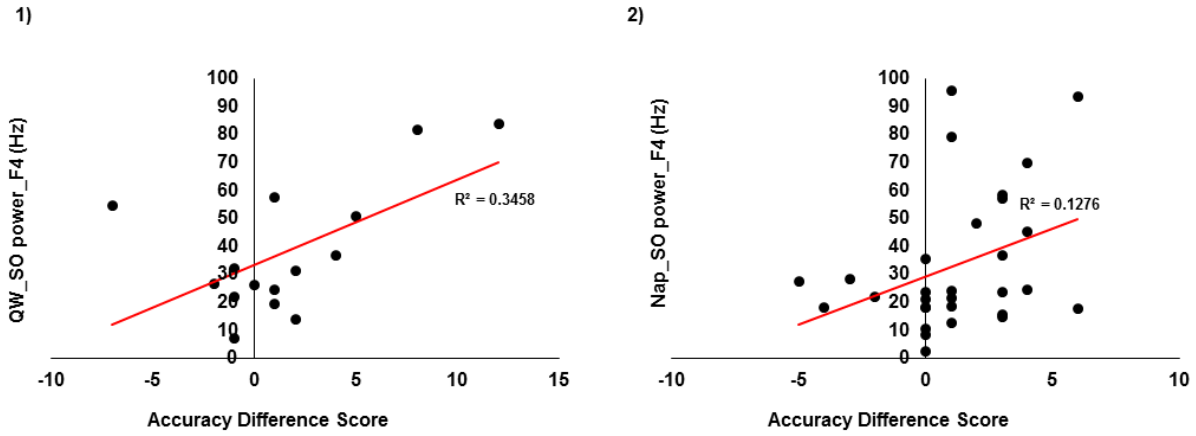

Figure 2-3: WM accuracy difference score association with 1) QW_SO power at F4 (significant) and 2) Nap_SO power at F4 (trend).

Table 2-1: Sleep summaries during nap.

Sleep Stages	S1 (min)	S2 (min)	SWS (min)	REM (min)	S1(%)	S2(%)	SWS(%)	REM(%)	WASO	SE(%)	TST
N=32	7.54 (1.11)	30.91 (2.82)	2.95 (1.05)	8.11 (1.67)	20.41 (1.63)	62.20 (2.93)	13.41 (2.53)	3.96 (1.44)	16.87 (1.81)	59.43 (3.30)	49.52 (3.93)

Notes: Data are reported as mean (SEM). SE; sleep efficiency, SWS: slow wave sleep, WASO; wake after sleep onset, TST; Total Sleep Time.

Sleep-SO Power and WM Performance Associations: Descriptive analysis of SO power for nap can be found in Table 2.2. In addition, since only 7 subjects had REM sleep in their nap, the associations between REM sleep and performance were not measured. Further, r effect sizes for all the associations between the WM improvement and brain physiology events can be found in Table 2.3. In the nap group, increase in WM accuracy from Test 1 to Test 2 had a trending positive association with SO power during stage 2 sleep at F4 ($r = 0.36$, $p = 0.05$). In addition, WM accuracy at Test 2 was positively associated with SO power during NREM sleep at F4 (Stage 2 sleep: $r = 0.42$, $p = 0.02$; SWS: $r = 0.48$, $p = 0.05$ (trend)). Further, faster RT at Test 2 was associated with higher SO power during SWS at F4 ($r = -0.51$, $p = 0.004$). Together, these results indicate that WM performance may be increased with greater offline SOs.

Table 2-2: Slow Oscillation power summaries during nap and quiet wake.

SO power	F3	F4	C3	C4
Stage 2	32.69 (4.19)	33.38 (4.51)	19.04 (2.13)	16.43 (2.41)

	SWS	81.92 (16.49)	79.11 (14.82)	55.89 (8.70)	48.09 (10.15)
	Quiet Wake	26.76 (3.45)	38.21 (5.97)	9.48 (1.09)	9.75 (1.03)

Equation 1SO power during SWS was significantly higher compare to SO power during Stage 2 sleep (all ps<0.001) and SO power during QW (all ps 0.001). Further, SO power in Stage 2 sleep was significantly higher than SO power in QW only at C3 (p = 0.004) and was similar across Stage 2 sleep and QW at C4, F3 and F4 electrode channels (all ps>0.07). * represents p- alue<0.001. Notes: Data are reported as mean (SEM).

Table 2-3: QW and nap physiology association with Working Memory performance.

	F3 (RT/Acc)	**F4 (RT/Acc)**	**C3 (RT/Acc)**	**C4 (RT/Acc)**
Stage 2 MI	-.12 / +.31	-.17 / +.27	-.12 / +.13	+.12 / +.40
SWS MI	+.19 / +.51	+.45 / +.63	-.18 / +.69*	-.03 / +.65*
Stage 2 SO	+.011 / +.17	+.17 / +.36*	+.09 / +.13	+.09 / +.05
SWS SO	+.07 / +.09	+.11 / +.20	+.06 / +.002	+.09 / +.13
QW SO	+.21 / +.26	-.008 / +.58*	+.27 / +.37	+.17 / -.04

Notes: Effect size r for the Working Memory difference score (Reaction-Time/Accuracy) and brainphysiology association is reported. Significant associations (p<0.05) are marked with asterisks.

Sleep Modulation Index and WM Performance Associations: Next, we examined the potential benefit of greater sigma/SO coupling for WM improvement by correlating

normalized MI with performance. The accuracy difference score was positively correlated with MI in SWS [C3: r = 0.69, p= 0.006; C4: r = 0.65, p = 02.] (See **Figure 2-3**). In addition, Test 2 WM accuracy was positively correlated with MI in SWS (C4: r = 0.65, p = 0.02). Further, faster RT at Test 2 had a trending association with MI in SWS at C4 (r = −0.59, p = 0.03). Change in RT did not show any association with MI during sleep (all ps>0.09). Thus, increased phase amplitude coupling between sigma and SO during SWS was related to better WM accuracy. MI in Stage 2 sleep was not associated with WM performance (all ps>0.38 s). (**Figure 2-4**). 3.6. Self-reported Sleepiness and WM Performance We also examined the extent to which sleepiness in each group may have predicted performance differences. Using One Way ANOVA here, we found that the amount of self-reported sleepiness (Karolinska Sleepiness Scale (KSS)) at the beginning of Test 1 (KSS-am) was similar across our three groups ($F(2,67) = 1.047$, $p = 0.36$). However, at the beginning of Test 2 (KSS-pm), after the sleep intervention, we found a significant difference in self-reported sleepiness between the groups ($F(2,69) = 11.55$, $p <= 0.001$). Post hoc analysis with Bonferroni corrections, revealed that the amount of sleepiness was not different between AW and QW ($p = 0.21$), but significantly lower in the nappers compared with both AW ($p<0.001$) and QW ($p = 0.04$). In addition, both KSS-am and KSS-pm were was not associated with WM performance at Test 1 and Test 2 respectively in any of the groups [accuracy: all ps>0.37; RT: all ps>0.27]. Together, these results suggest that even though the amount of self-reported sleepiness was lower among the nappers compared to both wake groups, considering gain in WM accuracy in both nap and QW and the lack of association between self-reported sleepiness and WM performance among all the three

groups, self-reported sleepiness may not have directly contributed to the reported performance changes.

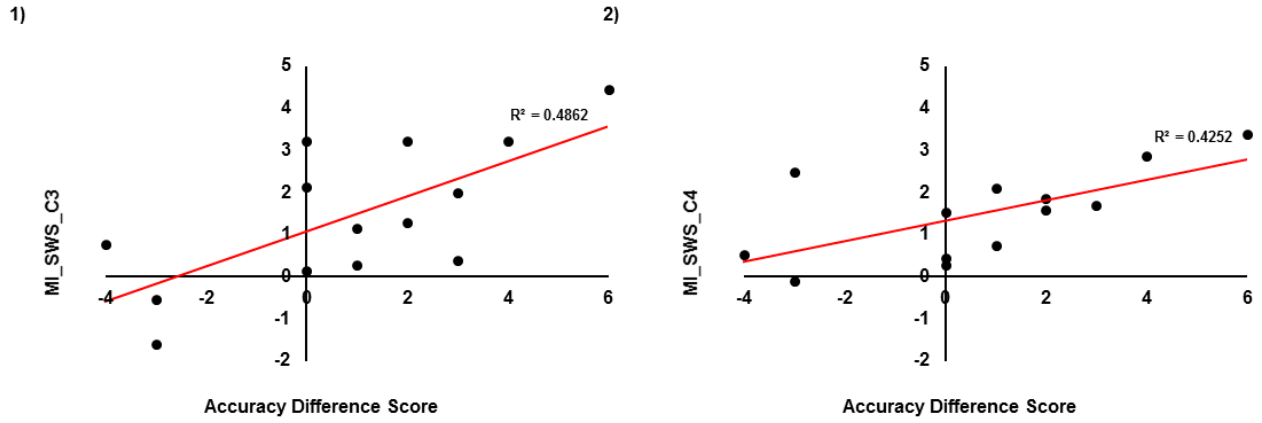

Figure 2-4: WM accuracy difference score association with 1) MI during SWS at C3 (significant) and 2) MI during SWS at C4 (significant).

Discussion:

We investigated the impact of a nap, quiet wake and active wake on within-day training on a working memory (WM) task in older adults. We found that WM improved within a day of practice among our three groups, with significant levels of improvement shown only after offline periods containing naps and quiet wake, but not active wake. Furthermore, offline slow oscillation power in both the nap and quiet wake was associated with gain in WM performance. The nap provided additional benefit to WM as performance improvement was also correlated with SO/sigma coupling during SWS. Together, these findings suggest that experience-dependent changes in WM in older adults may benefit

from specific neural activity shared across quiet wake and deep sleep. WM, which is critical for a wide variety of cognitive abilities and real-world activities (Baddeley, 2003), declines in late adulthood (Bopp and Verhaeghen, 2005; Payer et al., 2006; Borella et al., 2008). These decreases have been associated with broad cognitive impairments in older adults (Park et al., 2002), including reading comprehension, decision making, problem solving, and vocabulary learning (Engle and Kane,2004). In addition, this decline may impact daily life functioning, such as medication adherence (Raz, 2000). Therefore, investigating the possibilities of improving WM functioning across the lifespan has been a primary focus of many cognitive training studies (for reviews, see Klingberg, 2010; Shipstead et al., 2010; Takeuchi et al., 2010a, 2010b; Morrison and Chein, 2011), with many reporting gains (Mahncke et al., 2006; Buschkuehl et al., 2008; Li et al., 2008; Dahlin et al., 2008; Borella et al., 2010; Schmiedek et al., 2010; Richmond et al., 2011; Kuriyama et al., 2008; Kuriyama et al., 2011). For example, Li and colleagues (2008) examined younger (20–30 years old) and older (70–80 years old) adults in a 45-day practice period on a 2-back WM task and reported substantial performance gains in both age groups compared to the age-matched control. Similarly, young and older adults who practiced a WM task three times a week for five weeks (11 h of training in total) showed significant WM improvement that remained significant at 18-month follow-up testing, compared with controls (Dahlin et al. 2008). Here, we showed the possibility of improvement in WM within a day of practice. Importantly, WM training has been shown to yield broad cognitive benefits as well (reviewed in Morrison and Chein, 2011). For example, training older adults on a complex WM span for 20 tests across four weeks resulted in significant improvement on attention, verbal learning and reading span task (Richmond, 2011). In addition, a sample of 80-year-

old adults who underwent WM training twice weekly over 3 months, showed increased visual and episodic memory performance immediately after training completion, compared to the control group (Buschkuehl et al., 2008). In our sample although, WM increased among the participants within a day of practice, the increase was only significant when a period of rest occurred between training sessions. Taken together, these findings indicate that improvement and transfer effects of cognitive training engages neural processes that change slowly over many days of training, and suggests that daily rest that provides the opportunity for slow oscillatory brain rhythms to emerge may be critical (Orban et al., 2006). An important question to be understood is what mechanisms underlie WM improvement and transfer to other cognitive domains. To date, a handful of neuroimaging studies have attempted to characterize the neural changes associated with WM training (Brehmer et al., 2009; Dahlin et al., 2008; Hempel et al., 2004; McNab et al., 2009; Olesen et al., 2004; Takeuchi et al., 2010a, 2010b; Westerberg and Klingberg, 2007; Wager and Smith, 2003). Results have indicated that cognitive training improves processing efficiency, with changes in recruitment of task-related brain areas including the prefrontal cortex (Heinzel et al., 2016), striatum and hippocampus (Flegal et al., 2018), see Salmi et al., 2018 for a recent meta-analysis. Thus, improvement in working memory may reflect greater efficiency of local neural networks that are associated with both working and long-term memory formation. Interestingly, sleep, in particular SWS, may be critical for restoring prefrontal executive control functions that relate to memory retrieval (Wilckens et al., 2012; Tse et al., 2011). In fact, SOs, which are the fundamental cellular phenomenon underlying EEG activity in SWS may play a role (Steriade et al., 1993; Mölle et al., 2011). While it is well established that improved memory is associated with SOs during sleep (Huber et al., 2004;

Marshall et al., 2006), Brokaw and colleagues 2016, showed that, after a period of quiet rest, increased memory for a short story was also associated with increased SO activity in young adults. Similarly, here, we showed that sleep or quiet wake, but not active wake, benefited performance and the gain was associated with SO activity during deep sleep and quiet wake respectively. Taken togetherwith the recent cognitive training literature, greater efficiency in hippocampus-prefrontal cortex dialog may occur during quiet rest and NREM sleep, potentially mediated by SOs, resulting in enhancement of both working and long-term memory. Like sleep, quiet rest is characterized by a dramatic reduction in sensory processing, prevalence of hippocampal "sharp-wave ripples" (Axmacher et al., 2008; Clemens et al., 2011), and decreased levels of the acetylcholine (Marrosu et al., 1995), a neurotransmitter hypothesized to set the appropriate neural dynamics for consolidation by regulating the balance of processing of external and internal signals (Hasselmo et al., 2006). In line with this thinking, the Opportunistic Consolidation Hypothesis posits that the core condition favoring consolidation may not be sleep per se, instead consolidation may be facilitated during any offline state with limited encoding and plasticity, which will reduce retroactive interference and permit SO-driven replay processes to emerge (Mednick et al., 2011). This may be particularly important in aging as individuals are faced with a reduction in sleep across many measures. Therefore, along with SO-rich NREM sleep, quiet wake may also facilitate memory by creating favorable conditions (i.e. reduced interference) for consolidation. Future studies should examine whether these shared neural features of the sleeping and resting brain, as compared to non-resting brain, underlie performance improvements from cognitive training. Age-related deterioration in sleep quality, efficiency and continuity is well-known (Pace-Schott

and Spencer, 2011; Dijk et al., 2010), as well as declines in specific electrophysiological events during sleep (Westerberg et al., 2015; Landolt et al., 1996). In general, older people tend to experience less deep sleep (Bliwise, 1993, Ohayon et al., 2004; Yetton et al., 2018), decreased amplitude of slow waves (0.5–1 Hz) (Carrier et al., 1997), lower total sleep time, higher sleep latency, and a more fragmented sleep. Importantly, these changes in sleep have also been associated with age-related medial prefrontal cortex gray-matter atrophy and abnormal hippocampal-neocortical dialogue (Mander et al., 2013). Compared with youngers, older adults may also experience changes in spindle/SO coupling with lower coupling over the frontal site (Helfrich et al., 2018). Interestingly, Helfrich et al. (2018) reported that post-sleep declarative memory improvement predicted by the spindle/SO coupling in both young and older adults. In the present work we reported positive associations between WM accuracy improvement and coupling of SO/sigma in SWS in older adults. Taken together, it appears that thalamocortical communication is important for memory improvement, and interventions that boost thalamocortical activity during NREM sleep may be helpful in improving both working and long-term memory in both young and older adults. There are some limitations in the current work. In the current study, we did not examine EEG frequency patterns during the active wake state preventing examination of what brain activity in quiet vs active wake led to large WM increases in the former and only small increases in the latter. We hypothesize that though the majority of active wake is spent engaged in processing sensory input and executing behavioral responses, there are short bouts of inward mind-wandering during which the brain may experience increases in slower frequency activity (Braboszcz and Delorme, 2011; Aeschbach et al., 1997; Smallwood and Schooler, 2006; Mason et al., 2007). Prior work has reported that delta

activity is present and increases across prolonged periods of wakefulness (Aeschbach et al., 1997; Braboszcz and Delorme, 2011). Aeschbach and colleagues (1997) recorded EEG at half-hourly intervals during ~40 h of sustained wakefulness where EEG power density in the 0.75–9.0 Hz range exhibited a global increasing trend, as well as local increases in the delta (0.75–4.0 Hz), theta (4.25–7.0 Hz) and lower alpha band (7.25–9.0 Hz). In addition, in mind-wandering episodes; periods of task-unrelated thoughts that result in attention drifting away from the task at hand (Smallwood and Schooler, 2006; Mason et al., 2007), slower frequencies such as delta (2–3.5 Hz) and theta (4–7 Hz) EEG activity increase, compared with alpha (9–11 Hz) and beta (15–30 Hz) frequencies (Braboszcz and Delorme, 2011). Together, these results support the hypothesis that the actively waking brain is speckled with episodes of low frequency brain activity that indicate inward reflection and mind wandering. However, the impact of this jostling between active and quiet wake on cognitive improvement needs further study. Second, since spindles are not present during QW, we only measured MI during sleep. As a result, the extent to which QW is mirroring sleep mechanisms in memory formation remains unclear. In conclusion, we show that improvements in WM across a day of training may be more facilitated by a mid-day nap or a quiet period compared to wake. In addition, we hypothesize that, similarities between sleep and resting brain's electrophysiology events such as slow oscillations may play a role in this process. Additionally, our data suggest that WM improvement may benefit from similar sleep-dependent mechanisms as long-term memory consolidation (e.g., coupling of sigma and SOs). Therefore, promoting more and better sleep quality in older adults could improve their WM, especially in the context of brain training.

CHAPTER 3

The role of working memory in age-related emotional memory bias

Aging is associated with changes across a range of cognitive and physiological domains, including memory. Older adults frequently describe deterioration in memory (Hohman et al., 2011), and objective measures validate these reports with decreases in both long-term memory (LTM) and working memory (for review see Reid & MacLullich, 2006) across the lifespan. Specifically, declines in performance have been shown in hippocampus-dependent, episodic memory (Miller and O'Callaghan, 2005; Park and Reuter- Lorenz, 2009), spatial navigation (Barnes, 1979; Gage et al., 1984; Markowska et al., 1989) and associative learning (Behrends et al., 2007). WM (working memory), the ability to hold information in mind for a short period, also decreases with age, and is thought to contribute to a range of cognitive impairments in older adults (Park et al., 2003), such as reduced language learning, decision making, problem solving, and reading comprehension (Engle and Kane, 2004), which may be related to decreases in daily life functioning (Raz, 2000). Associations between WM and LTM performance has been shown among younger adults. Lugtmeijer and colleagues (2019) tested both younger and older adults on WM and episodic LTM tasks and found that WM and LTM were positively related only among younger adults. In addition, studies reported an overlap between brain regions associated with WM and LTM processing among 19 to 40 years old subjects (Ranganath et al., 2003), specifically in the pre-frontal cortex (PFC; Jetter et al., 1986; McAndrews and Milner 1991; Eslinger and Grattan 1994; Moscovitch and Winocur 1995). Together, these studies suggest that WM may support LTM

processing and declines in LTM performance among older adults may be associated with a similar decline in WM capacity.

Aging is also associated with a shift in memory functioning from an enhanced negative memory bias in young adults towards better retention of neutral and positively valenced memory, compared to negative, in older adults. Cognitive models have posited that the change in the emotional memory bias across the lifespan may to be due to the youthful prioritization of knowledge acquisition because young adults perceive their future to be unlimited, whereas the prioritization of emotional well-being (or reduced negative bias) in older adults may be due to a perception that the future is relatively limited (Carstensen, 2006; Carstensen et al., 1999) (Jones et al., 2018). This emotional memory bias may be further influenced by WM capacity as well. Mather and colleagues (2005) measured older adults' LTM memory for positive and negative pictures as well as their WM, and reported that older adults with superior WM recalled a higher proportion of positive pictures and older participants with inferior WM recalled less positive pictures (Mather et al., 2005). These findings suggest that WM influences LTM performance and may be one mechanism by which older adults' emotional memory bias persists (Mather et al., 2005).

Another potential candidate for memory modulation across the lifespan is sleep. It has been shown that sleep benefits memory in young adults (Stickgold, 2005; Rasch and Born, 2013), with this effect particularly pronounced for negatively valenced representations (Mather et al., 2005, meta-analysis; Lipinska et al., 2019). Sleep's benefits to memory also change with aging (Scullin, 2011, Sattari et al., 2019). Jones and colleagues (2018) showed that recognition of negative and neutral pictures was not different between sleep and wake

groups among middle-aged subjects. Taken together, this suggests there is an age-related decline in the relative influence of sleep compared to wake on emotional memory.

The goal of the current study is to investigate the role working memory plays in emotional memory formation in young and older adults. We tested a group of older and younger subjects on both WM and LTM in the morning. After finishing the cognitive tasks, half of the subjects took a daytime nap to see if sleeping between encoding and test would amplify the emotional memory bias. In the afternoon, all subjects took a recognition memory test for the word pairs. We predicted that older adults would show worse memory for negative word pairs, compared with neutral pairs, whereas younger adults would show better memory for the negative compared to neutral word pairs. We also tested emotional reactivity (measured by change in valence and arousal rating) during encoding and recognition, to test the prediction that emotional reactivity would be associated with the emotional memory bias. Lastly, we predicted that WM will be correlated with both negative and neutral word pair memory in younger, but not older adults.

Materials and Methods:

Subjects: 93 Younger adults, (41 females) between the ages of 18 to 39 (M=21.02, SD=2.91) and 121 older adults (58 females) ages of 60-85 (M=72.5, SD=6.05) gave informed consent to participate in the study. Inclusion criteria required adults to be healthy, non-smoking adults with a regular sleep schedule (defined as 6 to 9 hours of sleep per night on average). Subjects had no personal history of sleep, neurological or psychological disorders, or other chronic illnesses. Medical history was assessed twice. First, a general health condition report was collected over the phone (or internet survey) during pre-screening and eligibility was

determined. Second, at orientation, older subjects were given details about the study and screened for cognitive ability using the Digit Span Backwards (DSB) and dementia using Telephone Screening for Dementia questionnaires (referred to as TELE) (Gatz et al., 2002), respectively. The DSB task contains a varying length of digit strings that subjects were asked to repeat backwards after it was read to them. All the experimental procedures were approved by the Institutional Review Board of the University of California, Riverside.

Eligible subjects were asked to maintain a regular sleep schedule (6-9 hours per night) for one week prior to their visit, which was monitored with sleep diaries. In addition, subjects were asked to wear an actigraph (Actiwatch Spectrum, Respironics) for one night prior to their visit to ensure they received adequate sleep. Subjects were rescheduled if they reported poor sleep quality in their sleep diary, such as having more than 2 nights of less than 6 hours of sleep during the week prior to their visit, or if subjects' actigraphy data detailed less than 6 hours of sleep the night before the experimental visit. If subjects' sleep did not meet this criterion, they were given another week to fill out a new sleep diary and maintain a regular sleep/wake schedule prior to their visit. Subjects were asked to refrain from consuming caffeine, alcohol, and all stimulants for 24 h prior to and including the study day.

Protocol: Subjects arrived at the Sleep and Cognition (SaC) lab at 11AM for Session 1. Working memory was tested using the Operation Span task (OSPAN). Word pairs were also encoded and emotional reactivity (valence and arousal) for each word pair was provided by the participant (**Figure 3-1**). Task order was counterbalanced across subjects and within sleep/wake group. At 12:30 PM, subjects were randomly assigned to either a nap, or a wake

condition. For the nap, subjects were provided a 2-hour nap opportunity and were allowed to sleep up to 90 minutes. In the wake group, subjects could remain in the lab and engage a range of activities from playing board games with a lab research assistant, watching TV, reading in the lab, or they were permitted to leave and return for Session 2. All wake subjects were instructed to abstain from caffeine, exercise and napping during their break and were asked to report back to the lab at 3:30PM for Session 2. Subjects activity levels were also tracked with actigraphy during their breaks to ensure they did not nap. During Session 2, subjects completed recognition for the word pair task and again rated the valence and arousal of each word pair.

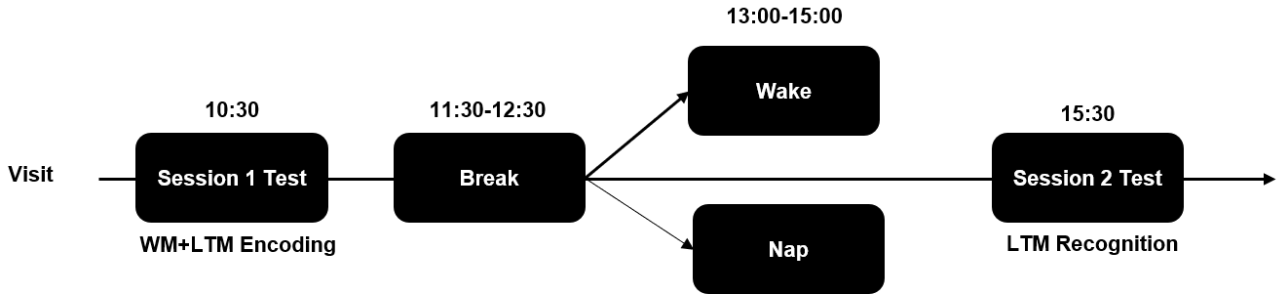

Figure 3-1: Subjects were tested on a WM task and encoded word pairs in the morning at Session 1. Task order was counterbalanced. After the break, subjects were randomly assigned to either take a Nap or stay awake. At Session 2 subject's LTM was tested in a recognition task.

WPA Task: Words were chosen from the Affective Norms for English Words (Bradley & Lang, 1999) During encoding, subjects viewed 50 unrelated, word pairs on a computer monitor. Words were presented one at a time. Each word was on the screen for 1000ms followed by a blank screen with a fixation point for 2000ms. After each pair presentation, participants were asked to rate arousal and valence of the word pairs. Valence was rated on a

scale of one to seven with one being very negative, four being neutral and seven being very positive. Arousal was rated on the same scale; one was low and seven was high arousal. For this task, words in each pair were either both neutral valence, or one of the words was negatively valenced (negative word was always presented in top position on computer screen; see **Figure 3-2**.A). Thus, each subject only encoded emotional pairs or neutral pairs. During Session 2, after the sleep intervention, subjects were given a recognition task with all the word pairs from Session 1 and 25 new pairs and were asked to determine if each pair was new or old. They were then asked to rate the level of arousal and valence again (see **Figure 3-2**.A, B).

Working Memory task (OSPAN): At Session 1, subjects were tested on the 20 trials of the OSPAN task. Subjects viewed a serial visual display of letters and math problems. They were asked to hold the letters in memory while simultaneously determining if the simple math problems were correct (e.g 7+5=13). Based on pilot data, we selected letter strings that would equate performance differences between younger and older subjects. For older adults, the letter strings were between 3 to 5 letters long, and for youngers, the strings were 4 to 6 letters long (see **Figure 3-2**.C). Each math equation was on the screen for 3000ms and each letter was presented for 1300ms. During the trial, subjects were instructed to press designated keys on the keyboard to indicate equation accuracy. At the end of each trial, a question mark appeared on the screen to signal the participant's response. Subjects were required to enter the letters in the same order they were presented. Subjects' data were only included in the analysis if they performed equal and/or greater than 75 percent correct on the math portion. Recall was not timed and subjects were not able to go to the next trial until the correct number of letters was entered. Four breaks were equally spaced throughout the

task. All subjects were provided three test trials at the start of the task to ensure task comprehension. To this end, some subjects required extra practice trials. The practice trials were not counted towards the subjects' final score.

Data reduction: In this study, if subjects were not comfortable during any part of the experimental day, they were compensated for the portion that was completed and were exempt from finishing the day (among the older subjects 2 decided to drop out after the Encoding session). In addition, for sleep analysis 5 subjects (2 older and 3 younger adults) were not included due to missing data because of technical computer problems. Further, one younger and two older adults were excluded from the WM analysis due to not meeting the math criterion.

Electroencephalography (EEG): EEG data were acquired using a 32-channel cap (EASEYCAP GmbH) with Ag/AgCI electrodes placed according to the international 10-20 System (Jasper, 1958). Electrodes included 24 scalp, two electrocardiogram (ECG), two electromyogram (EMG), two electrooculogram (EOG), 1 ground, and 1 on-line common reference channel. EEG signals were recorded at a 1000 Hz sampling rate and referenced on-line to the common reference channel. Next, EEG signals were re-referenced. The electrodes on the right side of the scalp were re-referenced to the left mastoid and the electrodes from the left side of the scalp were re-referenced to the right mastoids. 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).

Z

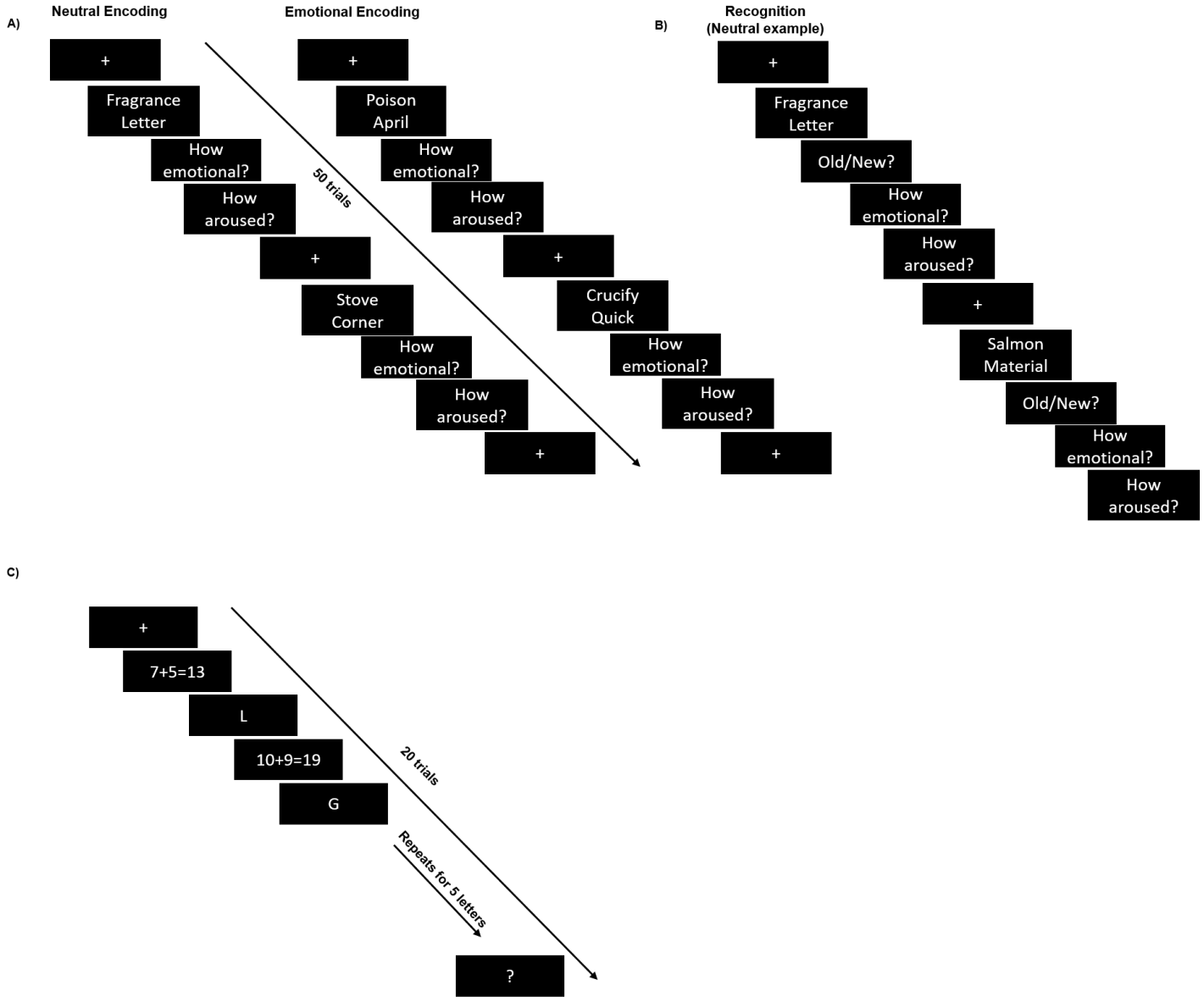

Figure 3-2: Memory tasks. A) WPA encoding for both neutral and emotional word pairs. B) WPA recognition test for the neutral condition. C) WM task.

Statistical Analysis: Memory performance for the WPA at Session 2 was assessed by calculating the following variables: hit rate, false alarm rate and d-prime (Zhit rate – Zfalse alarm rate; where Z is the inverse of the cumulative distribution function and a measure of

memory discriminability). We used a multivariate analysis of variance (ANOVA) with memory measures (e.g., dprime) as the dependent variable and Sleep, Age and Word-Type (emotional, neutral) as the fixed factors. In addition, we examined the change in arousal and valence rating in a difference score (Session 2-Session 1). We included these variables in a univariate ANOVA with the dependent variables Arousal change and Valence change and fixed factors Sleep, Age and Word-Type. Further, student's *t*-test was used for comparisons within each group. Next, one-sample *t*-tests were used to compare change in arousal and valance across the day to zero (no change) in each group. WM capacity was assessed by calculating the accuracy (total number of correct recalls). The accuracy for WM performance was averaged across the three difficulty levels (i.e., 3, 4 and 5 letter length) for bivariate correlation tests. Finally, we used bivariate correlations to assess the relationship between WPA performance and OSPAN as well as performance with Arousal and Valence change.

Results:

Nap vs Wake on LTM Performance: We first examined the impact of Age and Sleep on recognition memory performance. We did not find a main effect of Sleep on recognition memory [dprime: $F(1,208)=1.13$, $p=.29$, $\eta^2=.006$], hit rate: $F(1,208)=0.53$, $p=.46$, $\eta^2=.003$, false alarm $F(1,208)=3.76$, $p=.054$, $\eta^2=.02$]. In addition, no significant interactions were found for SleepXAgeXWord-Type (all ps>.17), SleepXAge (all ps>.39), or for SleepXWord-Type (all ps>.18).

We found a significant main effect of Age on memory, with young adults showing better recognition performance [dprime: $F(1,208)=27.64$; $p<.001$, $\eta^2=.12$; hit rate: $F(1,208)=22.34$, $p<.001$, $\eta^2=.10$, and false alarm: $F(1,208)=12.59$; $p<.001$, $\eta^2=.06$]. Also, we

found a main effect for Word-Type in hit rate [$F(1,208)=5.48$, $p=.02$, $\eta^2=.02$), such that memory was higher for negative, compared to neutral word pairs. This negative-bias was not present in dprime [$F(1,208)=0.45$, $p=.50$, $\eta^2=.002$] or in false alarm [$F(1,208)=0.11$, $p=.74$, $\eta^2=.06$]. We did find a significant interaction for AgeXWord-Type in dprime [$F(1,208)=8.74$; $p=.003$, $\eta^2=.04$] and false alarm [$F(1,208)=4.42$; $p=.04$, $\eta^2=.02$], but not hit rate [($F(1,208)=0.54$, $p=.46$, $\eta^2=.02$] where younger adults showed better memory for negative word pairs, compared to neutral word pairs [dprime:$F(1,208)=5.97$, $p=.01$; hit rate: $F(1,208)=4.07$, $p=.04$; false alarm:$F(1,208)=1.42$, $p=.23$ (non-significant)]. In contrast, older adults had less false alarms for neutral compared to negative word pairs [false alarm: $F(1,208)=4.03$, $p=.04$]. No differences in dprime [$F(1,208)= 2.85$, $p=.09$] or hit rate [$F(1,208)= 1.40$, $p=.23$] emerged (see **Figure 3-3**). These results align with prior findings that have found an age-specific valenced memory bias (Joens et al., 2016).

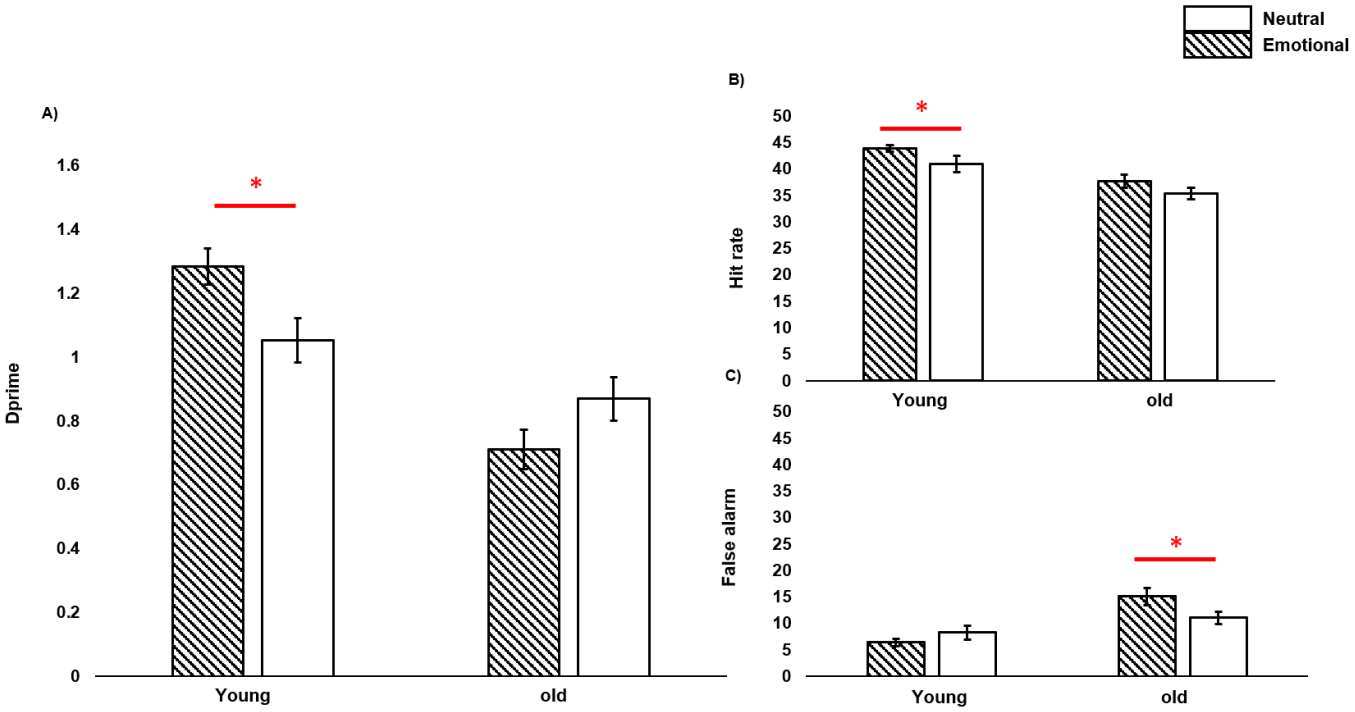

Figure 3-3: Long-term memory measured in dprime (A), hit rate (B) and false alarm (C) for both emotional (striped) and neutral (white) words in young and older adults. Error bars represents SEM.

Subjective Emotional Reactivity: Due to the lack of a sleep effect, we collapsed across the sleep and wake groups and examined the changes in valence and arousal ratings across the day (difference scores) among younger and older adults. Positive difference scores represent increased positivity in valence and increased arousal. For Arousal, a significant main effect of Age emerged such that younger adults reported higher arousal [$F(1,178)=6.13$; $p=.01$, $\eta^2=.03$]. All participants reported higher valence ratings for negative compared to neutral word pairs [$F(1,178)=7.10$; $p=.008$, $\eta^2=.04$]. No Age differences presented for Valence [$F(1,178)=0.11$; $p=.74$, $\eta^2=.001$] and no WordType differences were present for Arousal [$F(1,178)=0.22$; $p=.64$, $\eta^2=.001$]. We found a significant interaction of AgeXWord-Type for

Valence [F(1,178)=5.81; p=.02; η^2=.04] but not for Arousal [F(1,178)=0.06; p=.81, η^2=.001]. Using one-sample t-tests, we compared both Valence and Arousal scores to zero (no change) and found no significant change in ratings for both negative [Valence: t(52)=0.62, p=.54; Arousal: t(52)=1.20, p=.24] and neutral word pairs [Valence: t(34)=0.33, p=.74), Arousal: t(34)=1.66, p=.10] in young adults. On the other hand, older adults rated word pairs more positively across the day for both negative [Valence: t(47)=2.44, p=.02;] and neutral word pairs [Valence: t(49)=2.12, p=.04]. No differences in arousal were present [negative: Arousal: t(47)=-1.61, p=.11(non-significant); neutral: Arousal: t(49)=-1.29, p=.20 (non-significant)]. These results indicate that along with a positivity bias in memory, older adults also show greater positivity in subjective ratings of valence across the day, whereas younger adults remained stable in their ratings.

LTM and Emotional Reactivity Association: Next, we examined the associations between the change in Valence with LTM recognition performance. In younger adults, we found no significant associations between recognition and change in Valence in either neutral (all ps>.39) or negative word pairs (all ps>.54). However, in older adults, change in Valence across the day was related to greater neutral memory performance [dprime: r=.31, p=.03; false alarm: r=-.28, p=.045; hit rate=.26, p=.06 (trend)]. In addition, among older adults, change in Valence of negative words was related to higher dprime (r=.37, p=.009) but not to false alarm or hit rate (all ps>.14). No correlations were present for Arousal (all ps>.27). These results indicate that increased positivity may support better memory in older adults.

LTM and WM Associations: Figure 3-4 presents the effect size r for the correlations between WM and dprime, false alarm and hit rate of the WPA performance by Age and Word-

Type. In younger adults, better WM performance was related to higher hit rate (r=0.39, p=.01) and dprime (r=.38, p=.02) for neutral word pairs, and higher hit rate for negative word pairs (r=0.34, p=.02) (see **Figure 3-4**). However, in older adults, we did not find significant associations between WM and WPA performance (all ps>.08). Additionally, no significant relations were found between WM and Valence or Arousal of word pairs for older or younger adults (all ps>0.07). These results suggest that WM and LTM may share related processes (Ranganath et al., 2003), yet the robustness of this relation may fade with age.

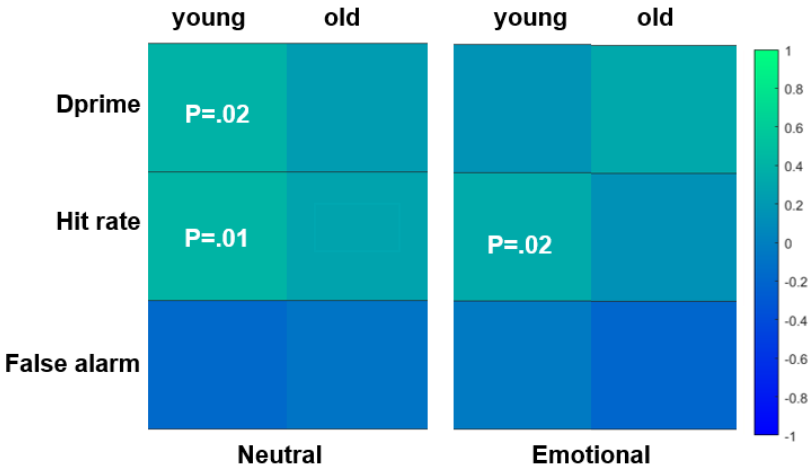

Figure 3-4: WM and LTM (dprime, hit rate and false alarm] associations in Young and Old adults for neutral (left) and Emotional (right) word types. Color represents the effect size r with blue shows negative, and green shows positive associations. P-value is reported for significant (P<.05) and trending (P>=.05 and <=.06) significant associations.

Discussion:

Our study sought to measure the contribution of working memory and emotional salience to long-term memory across a period of sleep or wake in younger and older adults. Similar to prior results, younger adults had better overall memory compared to older adults

and showed a negativity bias with greater memory for negative pairs, whereas older adults showed worse memory for neutral pairs. In young adults, emotional reactivity, measured by the change in valence, remained stable over time and did not predict later memory. However, older adults showed decreased negativity that was correlated with better long-term memory performance. Further, working memory showed positive associations with LTM in younger, but not older adults, suggesting that there may be overlapping benefits afforded to both domains that may fade with aging. We did not find an effect of sleep on recognition memory in either age group, however the study was not designed for this purpose, as we did not include an immediate test that would have provided a measurement of change in memory across the day.

Long-Term Memory and Aging: LTM refers to the ability to hold information in mind indefinitely (Cowan, 2008). Like many other cognitive domains, LTM, specifically associative learning, declines with age (Behrends et al., 2007; Wingfield et al., 2002; Koen and Yonelinas, 2013). The Associative Deficit Hypothesis (ADH) suggests older adults may exhibit a disproportionate decrement in memory for bound, associative information, relative to memory for individual items due to problems both with binding and retrieval as we age (Chalfonte & Johnson, 1996). Here, we found lower memory performance on both neutral and negative word pairs in elders. Importantly, however, the younger adults showed better memory for negatively valenced word pairs, whereas older individuals showed worse memory for negatively valenced words-pairs. Thus, for each age group, the strength of the association between memory items depended on the emotional salience of the words.

Relatedly, the socioemotional selectivity theory (SST; Carstensen, 2006; Carstensen et al., 1999), which posits that the perception of the future can impact the relative importance placed on different types of goals, can inform the age effect seen in our data and others (Jones et al., 2018). This theory hypothesizes that young adults may perceive their futures to be relatively open-ended, and therefore prioritize learning and novel experiences, which may include valuing negative vs neutral or positive experiences. Alternatively, older adults, who perceive their futures to be relatively limited, prioritize well-being and as such are biased to remember positive events. Consistent with SST hypothesis, our older adults showed lower performance for negative memories.

Long-Term Memory and Working Memory: WM is a key determinant of several higher-order cognitive functions (Engle, 2002; Borella et al., 2010; Nettelbeck and Burns, 2010), including LTM (Burgess and Hitch, 2005). Similar to other cognitive domains, WM capacity declines with age (Wingfield et al., 2002). It has been shown that WM and LTM are more tightly associated among younger adults (Lugtmeijer et al., 2019; Yonelinas, 2013). Lugtmeijer and colleagues (2019) tested 30 younger and 30 older adults on an N-back WM task and an object location LTM task and reported that, compared to younger adults, older individuals had a decline in both WM and LTM performance. In addition, performance in the WM and LTM tasks were correlated among younger, but not older adults. Similarly, here we found a reduction in LTM in older compared to younger adults with no relation between WM and LTM performance among older individuals regardless of the emotional component of the word pairs. However, WM was related to better LTM performance for both emotional and neutral word pairs among younger adults. Interestingly, Mather and Knight (2005) reported an age-related positivity bias for older adults where higher WM performance among older

individuals predicted better memory for positively valenced pictures in comparison to negatively valenced stimuli. Additionally, the prefrontal cortex has been implicated in the emotional memory bias (Gong et al., 2014) with higher activation reflecting greater recruitment of emotion regulation or control processes against negative memories in older adults. Together, these findings suggest a role for cognitive control in age-related emotion regulation goals. Here, although we did find such an effect in our younger adults, we did show that as WM declines in older subjects it may play less of a role in LTM.

In conclusion, we found an emotional bias in both memory and emotional reactivity, with decreased emotional reactivity associated with better memory in older adults. We found a robust relation between WM and LTM in younger but not older adults. Our findings are consistent with the socioemotional selectivity theory that posits that aging is associated with a relative suppression of negative information, suggesting that this bias is more related to the saliency of the stimuli rather than with top-down working memory processes. In contrast, robust WM functioning may play an important role in processing LTM in young adults, a relation that may fade with decreased WM processing as we age.

Summary and Conclusions

Here, I present a novel investigation into the role of sex and aging, the two major factors for Alzheimer disease, on sleep-related memory formation. I presented three experimental studies. The first study examined the role of sex and sex hormone's fluctuations on sleep-dependent LTM consolidation among younger adults. From this study, we can glean three main points, 1) performance on word-pair association is altered by sex (i.e., women performed better than men at baseline) and 2) women's performance, post sleep, differed based on their phase in menstrual cycle (i.e., perimenses women showed more forgetting compared to non-perimenses) and 3) men and women in different phases of their menstrual phase appeared to rely on different sleep-related consolidation mechanisms. In this study, I showed women benefit from slow oscillations during non-perimenses, whereas when they were in their perimenses phase of their cycle, women showed to benefit only from sleep spindle events. Men however, showed benefit from the temporal coupling of spindles and slow oscillations (i.e., spindle/SO coincidence) as well as spindles. Study 1 suggests that sex and sex hormones may specifically modulate sleep-dependent memory consolidation via changes in thalamocortical communication.

In the second experimental study, it was determined that WM training among older adults can benefit from both sleep and a period of quiet rest. Interestingly, older adults, who are known to experience decline in their sleep quantity and quality, showed sleep-related similar mechanistic benefits of quiet-wake (i.e., SOs), an idea that is supported by Opportunistic Consolidation Hypothesis (Mednick et al., 2013). This hypothesis posits that human's brain opportunistically seek for *no* or *low* interference situations to form memory.

Together with evidence of age-related deteriorations in sleep's quality and quantity and WM, study 2 proposed that offline mechanisms of WM function in older adults may help slow age-related decline by providing potential routes to interventions while designing WM training protocols. Taking these two studies in concert suggests that biological factors such as sex and aging, may mediate sleep and/or quiet rest related memory formation highlighting the importance of these two factors while studying age-related cognitive decline.

While these data support a possible role for sex and sex hormones' fluctuation on sleep-related LTM processes and potential benefits that older adults may receive for WM improvement from similar mechanisms during sleep and quiet rest, a possible role for WM on LTM was discovered in the third study among older and younger adults. In study 3, I unpacked a possible role for WM on emotional LTM processes that only appeared among younger adults. Similar to prior findings, regardless of sleep and memory valence, younger adults had better overall memory compared to older adults and showed a negativity bias, whereas older adults showed worse memory for negative pairs. In young adults, emotional reactivity, measured by the change in self rated valence, remained stable throughout the day and did not predict later memory. However, older adults showed decreased negativity in their rating that was correlated with better long-term memory performance. Interestingly, in Study 3, WM was positively related with LTM in younger, but not among older adults, suggesting that there may be overlapping benefits afforded to both domains that may fade with aging.

In summary, behavior and brain function are sexually dimorphic (Astur, et al., 1998,Cahill, 2006,Canli, et al., 2002,Lewin, et al., 2001,McDevitt, et al., 2014,Voyer, et al., 1995,Voyer, et al., 2016)). There is also a marked sex difference in risk for neurodegenerative conditions associated with memory and learning problems, like Alzheimer's disease. In fact, women have a 2-fold greater risk for Alzheimer's disease after the age of 75 years (Hamson, Roes, & Galea, 2016). Although the underlying mechanisms for these sex differences are still unclear, sex hormones and aging likely play a role, (Brinton, Yao, Yin, Mack, & Cadenas, 2015; Engler-Chiurazzi, Brown, Povroznik, & Simpkins, 2017; Henderson, 2009; Merlo, Spampinato, & Sortino, 2017; Pike, 2017). In addition, like many other cognitive functions, memory, both WM and LTM, decline with age (for review see Reid & MacLullich, 2006). However, WM, that plays an important role in daily functioning, can improve with practice and this improvement has been shown to generalize to other cognitive domains such as LTM improvement (Karbach and Verhaeghen, 2014). Therefore, WM training among older adults has been the focus of brain training protocols. Since WM training occurs across multiple days, sleep may play a role. Importantly, sleep that has been extensively shown to be important for memory processes, loses its quality and quantity with aging (Pace-Schott and Spencer, 2011; Dijk et al., 2010). This age-related diminishment in sleep electrophysiological features is thought to contribute to age-related decline in memory (Helfrich, Mander, Jagust, Knight, & Walker, 2018; Mander et al., 2013). On the other hand, sleep has been shown to be altered between men and women (Van den Berg et al., 2009; Collop et al., 2004) and also among women , sleep is influenced by sex hormones' fluctuations (Armitage and Hoffmann, 2001; Carrier, Land, Buysse, Kupfer, & Monk, 2001; Dijk, Beersma, & Bloem, 1989; Redline et al., 2004; Carrier et al., 2001).

Further, midlife and older women, during the transitioning to menopause and post-menopause are more likely to experience sleep difficulties (Baker, de Zambotti, Colrain, & Bei, 2018; Joffe, Massler, & Sharkey, 2010) as well as memory complaints (Maki, 2013; Mitchell and Woods, 2001). Therefore, given the cooccurrence of sleep and cognitive decline with aging, and the possible role of sex hormones' fluctuations in the interaction of sleep and cognition, it is important to study biological factors' effects on the well-known relation of sleep and memory formation which may inform new line of treatments to prevent the most severe manifestation of cognitive decline, i.e. Alzheimer's disease.

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