The Effects of Sleep on Wellbeing and Cognition

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I, Shuman Ji, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

This thesis investigated sleep and memory in middle aged women (42-59 years old), a demographic group who is experiencing a reduction in ovarian hormones and is particularly at risk of sleep disturbances. Also, based on the findings that sleep plays an important role in cognition, I investigated the effects of sleep on memory consolidation and skill training and whether rapid eye movement (REM) during REM sleep are involved in the consolidation process.

The first chapter describes the physiology and the functions of sleep, how the circadian timing system (CTS) and sleep homeostasis influence sleep, how sleep changes across the lifespan, and how to artificially induce sleep. The second chapter describes the general methods in assessing sleep and conducting sleep experiments. The third chapter provides a descriptive account of sleep in middle-aged and menopausal women. The results show that a range of menopausal related symptoms but not menopausal status predict sleep quality. Chapter 4 addressed the question of whether there is a difference in sleep architecture between premenopausal and menopausal women during a nap and whether the nap helps to improve declarative memory performance. The results show that menopausal women performed significantly worse than premenopausal women in the memory task in both the nap and non-nap conditions, despite having had more N2 sleep. Chapter 5 investigated the facilitating effects of sleep on cognitive training that involves higher order executive functions, and the time course for cognitive training. Results show that sleep significantly facilitated the improvement in task-switching task. Chapter 6 investigated REMs during REM sleep. This study provides the first evidence that REMs during REM sleep are affected by previously learnt materials prior to sleep and these REMs are related to improved memory performance. The last chapter provides a general discussion of these experiments and future directions.

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Chapter 1: General Introduction

Allan Rechtschaffen, a pioneer in sleep research, once said, “If sleep does not serve an absolutely vital function then it is the biggest mistake the evolutionary process has ever made”. The fact that we sleep for nearly 38% of our lives, and most animals (including humans in the not so distant past) live in predatory environments where sleep impedes their responsiveness to danger, suggests that sleep must serve a vital function in our survival. Over the past 25 years, there has been a rising interest in the scientific study of the functions of sleep. Studies of sleep deprivation found that the lack of sleep increased the risk of accidents caused by human error (Dinges et al., 1995). This is because sleep deprivation results in a disruption in normal psychomotor functioning similar to the effects produced by consuming too much alcohol (e.g. reduced vigilance) (Dawson & Reid, 1997). The prevalence of traffic accidents caused by sleepiness has been estimated to be as high as accidents caused by drink-driving (Pack et al., 1995). Besides the common conception that we need sleep to revive energy and concentration, systematic literature reviews of epidemiological studies indicate that the lack of sleep is associated with a range of life-threatening diseases (Gallicchio and Kalesan, 2009; Cappuccio et al., 2010). Sleep disturbances could also trigger depression (Talor et al., 2005) as well as Schizophrenia (Phillips et al., 2012). More recently, Bellesi and colleagues (2017) studied the effects of sleep deprivation (8 hours) and chronic sleep restriction (CSR) (5 days) in mice and found 6% of astrocytes in mice with normal sleep, 8% astrocytes in mice with 8-hour sleep deprivation, and 13.5% astrocytes in mice with 5 days of CSR were active. As astrocytes are involved in pruning unnecessary synapses, this study shows that a lack of sleep results in these astrocytes going into “overdrive” mode, with an effect one might think of as similar to “eating” the brain. It is evident that sleep plays an important role in our general and mental health. However, the focus of this review is not on the recuperative functions of

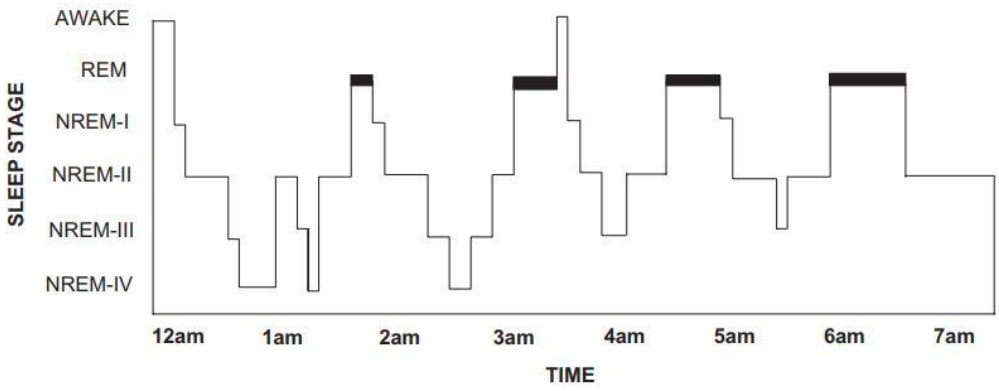
sleep or its various associations with our general or mental health, it is on the active role that sleep plays in our cognition.

1.1 Neurobiology of Sleep

There are two broad categories of sleep, rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. NREM consists of three sub-stages, N1, N2 and N3, with increasing depth of sleep as time progresses according to the new sleep scoring standards by American Academy of Sleep Medicine (Berry et al., 2012). N1 and N2 consist mainly of high frequency and low voltage theta electroencephalographic (EEG) waves. Sleep spindles and K-complexes are present in N2. N3 represents slow wave sleep (SWS), characterised by predominant delta waves, that exhibit the highest amplitude and lowest frequency in all sleep stages (1 to 3 Hz or <1 Hz). SWS is also known as the deepest stage of sleep. The synchronised slow waves during N3 has been named slow wave activity (SWA) (Amzica & Steriade, 1995). As sleep stages transit from N1 to N2 and before reaching N3, there could be an EEG arousal that results in transition to wakefulness (W) or back to N1, otherwise to N3 or REM. After N3, it slowly regresses back to N1, but this time accompanied by REM sleep. More than 60 years ago, Aserinsky and Kletman (1953) characterised REM sleep by random bursts of eye movements, vivid dreams that can be more easily recalled upon awakening than dreams occurring in other sleep stages, atonia of body muscles, and desynchronised, low-voltage brain waves that are similar to waking states. This sleep stage is also sometimes called paradoxical sleep (PS) (Jouvet and Michel, 1959). These ocular saccades are rapid under closed eyelids, peak around 5-10 minutes into REM sleep and decline significantly after 10 minutes, they are present in about 14-27% of this sleep stage (Aserinsky, 1971). Eye movements parameters during REM sleep were analysed using an automatic analyser, the mean frequency of EMs was 15.9 per minute, mean eye ball rotation was 6.27 degree, and the mean speed of rotation was 58.73 degrees per second (Takahashi and Atsumi, 1997). Each cycle of sleep from N1

to REM sleep then back to lighter sleep stages lasts approximately 90 minutes. We go through several sleep cycles each night as we sleep, but with increasing REM sleep and decreasing SWS as the night progresses (Walker, 2009).

Functional magnetic resonance imaging (fMRI) studies of the sleeping brain have found distinct differences in the cortical activation pattern between NREM and REM sleep. NREM SWS is marked by a decrease in activity in brain stem, medial temporal lobe (MTL), basal ganglia, cingulate cortex, thalamic nuclei, and prefrontal cortex (PFC) compared to wake (Maquet et al., 1997; Braun et al., 1997). On the other hand, REM sleep is marked by an increase of activity in thalamic nuclei, mediobasal PFC, anterior cingulate, hippocampus, amygdala, occipital lobe and pontine tegmentum, and a decrease of activity in dorsolateral PFC, parietal cortex and posterior cingulate compared to wake and SWS (Maquet et al.,1997, 1996; Braun et al., 1997; Maquet et al., 1997). Figure 1 shows an example of the transition of sleep stages throughout the night and a summary of characteristics of different sleep stages. Figure 2 shows the sleep architecture represented by different EEG sleep waves during the first 70 minutes of sleep.



Sleep Stage	Electrophysiology	Neurochemistry	Functional anatomy
NREM: Stage I Stage II *SWS* { Stage III Stage IV	- Loss of -EEG - Spindles/k-complex - Slow wave synchronous EEG	Aminergic to Cholinergic ratio HIGH	Activity in pons, thalamic, limbic, frontal, temporal regions
REM:	- Increased EEG frequency - PGO waves - Muscle atonia	Cholinergic to Aminergic ratio HIGH	Activity in lateral pre-frontal cortex, activity in visual, medial frontal, limbic system, anterior cingulate.

Figure 1. The transitions of sleep stages throughout a night with higher proportion of SWS during the first half of the night and increasing REM sleep and decreasing SWS duration as the night progresses. Sleep N1 is represented by stage I, stage N2 is represented by stage II, and N3 is represented by the combination of stage III and IV, according to the earlier sleep scoring standard (Rechtschaffen and Kales, 1968). It also shows a summary table of characteristics of different sleep stages. Taken from Walker (2005).

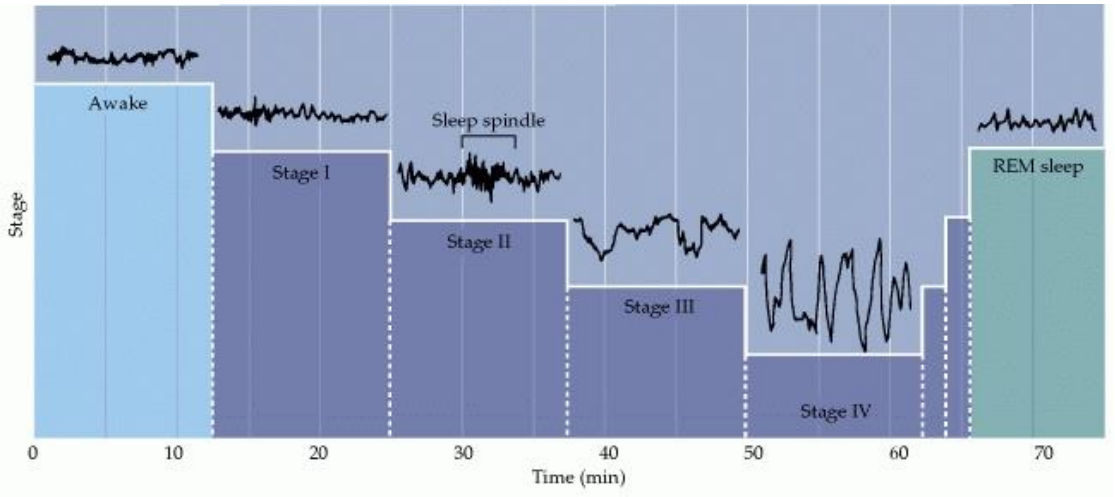


Figure 2. EEG recording of sleep during different sleep stages across the first 70 minutes of sleep. When we are awake, EEG waves show mainly alpha and beta activity. Stage I represents N1 that comprises of mainly theta activity. Stage II represent N2 that comprises of theta activity, sleep spindle and k complex. Stage III and IV represent N3 SWS that comprises of mainly high amplitude, low frequency delta activity. REM sleep comprises of theta and beta activity similar to the waking state. Taken from Hobson 1989.

1.2 Functions of Sleep

1.2.1 Sleep and memory

During the past 25 years, the study of sleep has come to the consensus that sleep plays an important and active role in learning and memory consolidation. Two types of memories have been widely studied, declarative and nondeclarative memory. Declarative memory is acquired information such as knowledge, facts, or experience that can be described. Nondeclarative memory, also called procedural memory, is learnt skills such as motor skills, playing an instrument, or playing a sport. One popular theory posits that declarative memory formation happens in the sequence that newly encoded memories are incorporated, organized, and stored into long-term memory (Alvarez and Squire, 1994). Memory is first encoded and temporarily stored in MTL region (hippocampus) as short term memory, consolidation helps to transfer the newly learnt materials to neocortex, and be incorporated into existing knowledge to form long term memory. Learning and consolidation of procedural memory involve a more diverse network of both cortical and subcortical regions (Yotsumoto et al., 2008;

Furmanski et al., 2004; Schwartz et al., 2002). More recently, a group of researchers from Massachusetts Institute of Technology (MIT) found evidence that both hippocampus and cortex are involved in initial memory formation but consolidation strengthens the memory in the cortex over time (Kitamura et al., 2017). Thus, we are still scratching the surface in understanding the underlying mechanisms of how memories are formed over time but the important role sleep plays for memory consolidation is beginning to be appreciated.

Sleep is important for memory encoding. Studies found memory encoding is significantly affected after sleep deprivation (Harrison and Horne, 2000; Harrison, 1998; Wimmer et al., 1992; Morris et al., 1960). Using a temporal memory paradigm, Harrison and Horne (2000) found that participants performed significantly worse than control after 36 hours of sleep deprivation, this effect persisted in a subgroup of participants who were given caffeine. Sleep deprivation also resulted in a lack of insight about their memory encoding difficulty. Impairment in memory encoding has been attributed to impairment in executive control as sleep deprivation affects executive functions such as attention, concentration and working memory (Harrison & Horne, 2000; Kribbs & Dinges, 1994; Kleitman, 1963). On the other hand, fMRI studies of learning found that PFC showed greater activation, and MTL showed reduced activation after sleep deprivation (Chee and Choo, 2004; Drummond et al., 2000). Also, sleep deprivation led to the engagement of parietal cortex when compared to controls (Drummond et al., 2000). These results suggest sleep deprivation not only affects executive control but also MTL dependent memory encoding, increased activation in PFC and the engagement of parietal cortex may serve as a compensatory mechanism when MTL function is affected.

Sleep has also been found to promote both declarative (Seehagen et al., 2015; Lahl et al., 2008; Rasch et al., 2007; Marshall& Born, 2007; Tucker et al, 2006; Gais & Born, 2004) and nondeclarative memory consolidation (Walker et al., 2002; Fischer et al.,

2002; Stickgold et al., 2000; Plihal and Born, 1997), with no opposing finding that indicates sleep contributes to forgetting (Crick & Mitchison, 1983). Memory consolidation once was considered a process that happens with the simple passage of time but later studies have emphasised the role played by consolidation during sleep. Lahl and colleagues (2008) tested free word recall after a 60 minutes nap, 6 minutes nap, and staying awake for the same period of time as the nap, they found that both long and short nap groups performed significantly better than the no nap group. This shows that even a short nap can help to promote memory consolidation. The beneficial effect of sleep on memory consolidation is especially pronounced for emotional memory (Javadi et al., 2011; Wagner et al., 2006). Overnight sleep (8 hours) and napping can both contribute to memory enhancement (Nishida & Walker, 2007; Tucker et al., 2006; Mednick et al., 2003). However, the longer the sleep the better the enhancement especially for non-declarative memories (Walker et al., 2003; Stickgold et al., 2000).

Many studies have found that SWS contributes to the consolidation of hippocampal dependent declarative memories (Ellenbogan et al., 2006; Tucker et al., 2006; Smith, 2001; Plihal & Born, 1997). For example, using a nap paradigm, Tucker and colleagues (2006) found a nap containing only NREM sleep (as subjects were woken up at the onset of REM sleep) promoted declarative but not nondeclarative memory performance. Plihal and Born (1997) investigated the differential effects of early and late nocturnal sleep and found that early nocturnal sleep containing mainly SWS contributed more to declarative memory consolidation whereas late nocturnal sleep containing mainly REM sleep contributed more to procedural memory consolidation. Also, more synchronised slow wave activity (SWA) was observed during SWS after declarative memory learning (Molle et al., 2004). This shows that there is a two-way interaction between declarative memory learning and SWS as SWS not only promotes declarative memory consolidation, declarative memory learning also triggers physiological changes during

SWS. Furthermore, using direct current electrical stimulation (tDCS), Marshall and colleagues (2006) artificially induced SWA at the onset SWS which led to enhanced declarative memory consolidation compared to control group. Auditory stimulation has also been found to be successful in inducing SWA which led to superior declarative memory consolidation (Ngo et al., 2013). These studies suggest that SWA during SWS is important for declarative memory consolidation.

REM sleep has been found to promote non-hippocampal dependent nondeclarative memory consolidation (procedural learning) (Mednick et al., 2003; Fischer et al., 2002; Plihal & Born, 1997, 1999). For example, Mednick and colleagues (2003) found that a nap containing both SWS and REM sleep promoted procedural learning whereas a nap containing only NREM sleep did not lead to procedural learning. Using a finger sequencing tapping task, Fischer and colleagues (2002) found that procedural learning was significantly correlated with the duration of REM sleep. The absence of REM sleep due to pharmacological suppression led to impairment in procedural learning (Rasch et al., 2009). Also, procedural learning led to an increase in REM density and the number of REMs (Smith et al., 2004). These results show that there is a two-way interaction between REM sleep and procedural learning, and that REM sleep is important for procedural memory consolidating.

These findings are consistent with the Dual-Process theory which suggests that the two sleep stages contribute to two distinct types of memory consolidation (Maquet, 2001). However, some studies indicate that such a functional distinction is not as strict as was originally thought. Studies have shown that SWS can enhance procedural learning (Aeschbach et al., 2008; Huber et al., 2004), and others have shown REM sleep facilitates declarative memory consolidation (Fogel et al., 2007; Rauchs et al., 2004; Walker et al., 2002; Stickgold et al., 1999; De Koninck et al., 1989). One possibility is that the stimuli used during the experiments did not strictly contain one type of memory component. On the other hand, these findings are more consistent with

the Sequential Theory which contends that both SWS and REM sleep occurring in succession is the most conducive for both declarative and non-declarative memory consolidation (Giuditta et al., 1995). Furthermore, both human and animal studies have shown that intermediate sleep stages can also contribute to memory consolidation (Nishida and Walker, 2007; Nader & Smith, 2003; Walker et al., 2002; Datta, 2000). In one study, overnight sleep unexpectedly improved nondeclarative memory consolidation even though REM sleep was pharmacologically supressed, and this improvement was associated with increased spindle activity during N2 sleep (Rasch et al., 2009). Also, Procedural memory consolidation has been found to be correlated with duration of N2 sleep or sleep spindles during N2 sleep (Nishida and Walker, 2007). These findings highlight the importance of the fundamental physiological mechanisms underlying different sleep stages that mediate various types of memory consolidation as some functional mechanisms may cross over between stages and the question of how memory is consolidated during sleep remain elusive. The idea of memory replay may help to illuminate how memory is consolidated. Studies have found that waking experiences are often replayed during REM sleep as dream imagery (Kusse et al., 2012; Fosse et al., 2003; Schwartz, 2003; Stickgold et al., 2000; Domhoff. 1996; Dement et al., 1965), and dream enactment of prior waking experience in a group of sleepwalkers was related to improved memory performance after sleep (Oudiette et al., 2011). Also, regions of the brain that were activated during learning when awake were reactivated again during sleep, and this led to task improvement after sleep (Maquet et al., 2000; Peigneux et al., 2000; 2003; Haxby et al., 1991). These studies suggest that memory replay in the form of dreams may be involved in memory consolidation. Collectively, these findings highlight the importance of sleep in preserving our memory function. Figure 3 shows an example of the beneficial effect of a nap containing only NREM sleep on declarative memory consolidation.

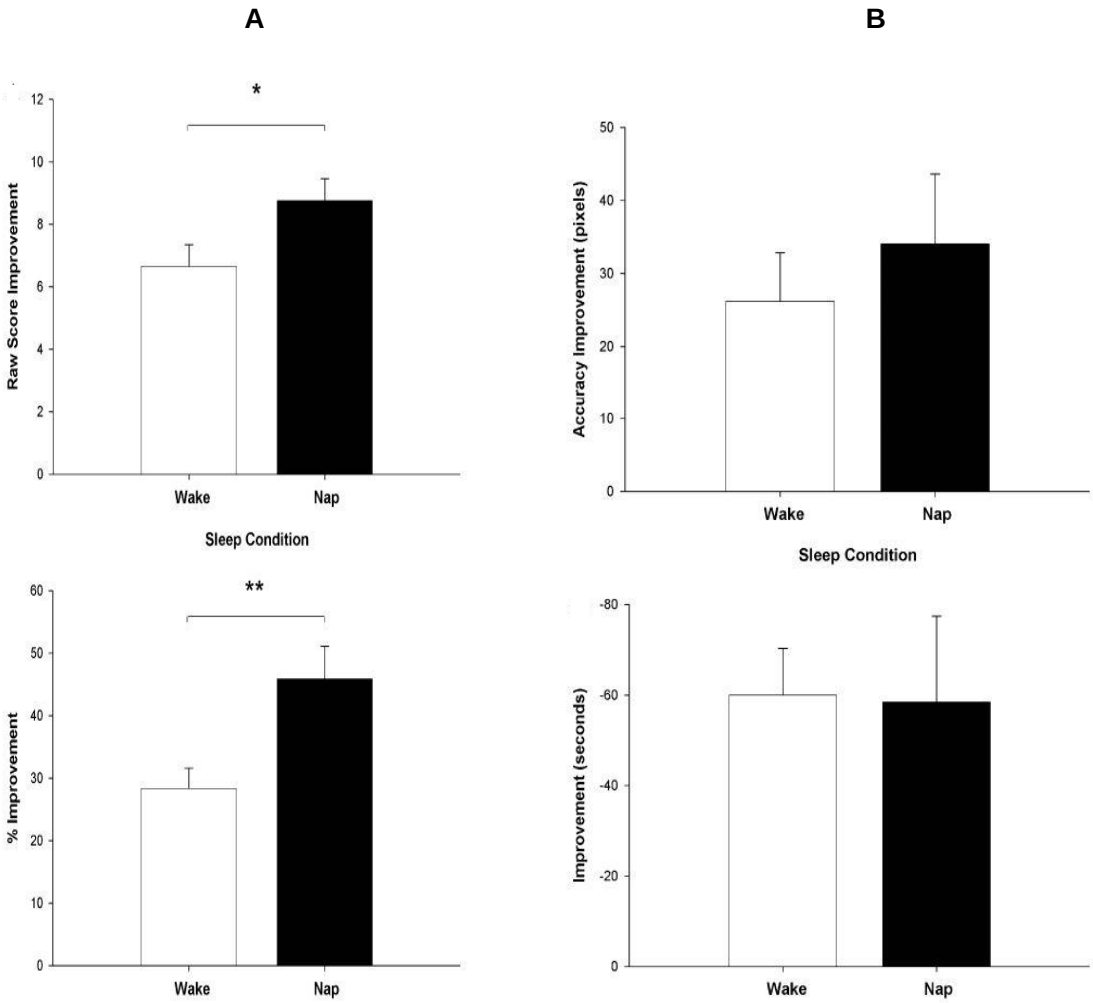


Figure 3. A shows that performance (raw scores and % improvement) of a declarative memory (paired-associative) task is significantly better after a nap containing only NREM than staying awake for the same period of time. B shows that there is no significant difference in performance (improvement in accuracy and speed) of a procedural task (mirror tracing) between nap (containing only NREM sleep) and wake condition. This shows that NREM sleep selectively promote declarative memory consolidation. Taken from Tucker and colleagues (2006).

1.2.2 Sleep and integration of information

Sleep has also been found to facilitate integration of information (Durrant et al., 2012; Lau et al., 2011; Cai et al., 2009; Ellenbogen et al., 2006; Wagner et al., 2004; Sternberg & Davidson, 1995). Using a number reduction task, Wagner and colleagues (2004) tested participants on a series of number reduction trials following a hidden abstract rule. Participants had to work through eight numbers by sequentially processing the numbers pairwise before getting the final answer in each trial. They were not told that the answer for the second pair was always the same as the final answer in each task. It's possible to skip working out the rest of the numbers to get to the final answer by just working out the answer of the second number pair (Figure 4). After a night of sleep, half of the participants in the sleep group realized the rule and the other half who did not realize the rule improved on the speed of answering these questions. The sleep group (trained in the evening and tested in the morning after a night of sleep) improved significantly compared to the wake group (trained in the morning and tested in the evening following wake period) in two ways, in terms of realizing the hidden abstract rule as well as improvement in reaction time, although not at the same time. Also, Cai and colleagues (2009) investigated the effect of sleep on word puzzle solving. Participants were shown three words and they were to come up with the fourth word that linked all the words. The results show that after a 90 minutes nap, performance of the word puzzle solving task was significantly better than staying awake for the same period of time. These results suggest that reactivation of learnt information during memory consolidation in sleep also facilitates integration of information that can inspire insights and creativity.

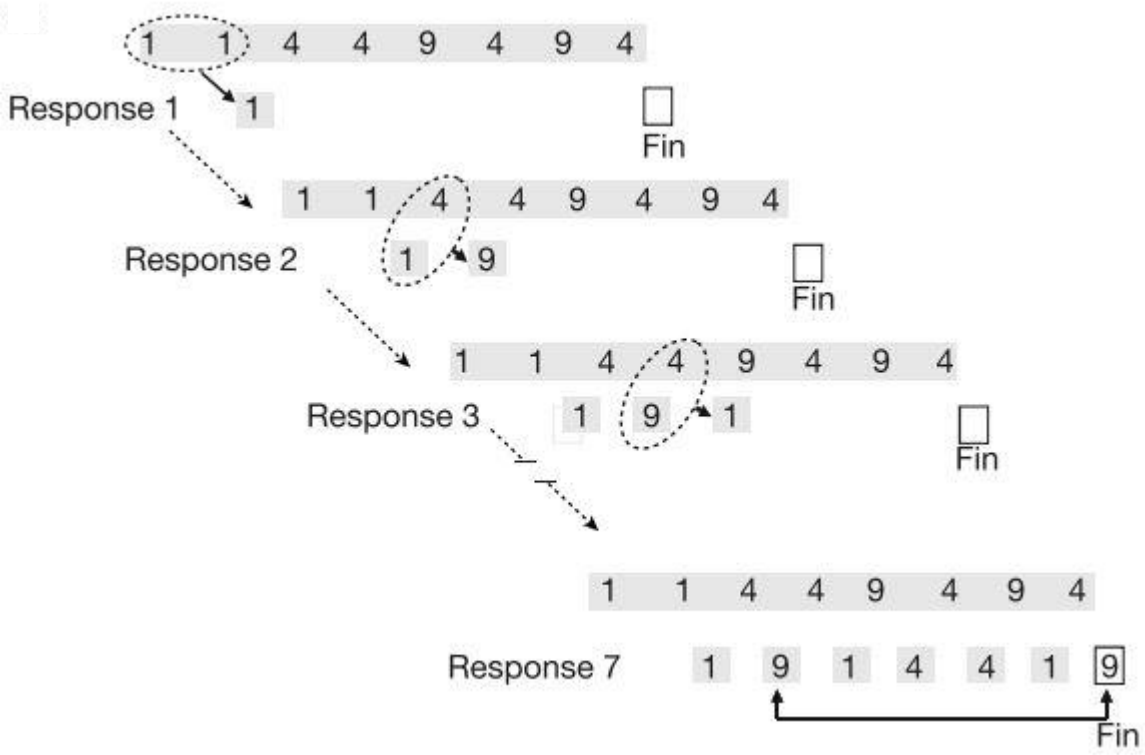


Figure 4. An example trail of the number reduction task. Each trial includes 8 numbers including the number '1', '4' or '9'. Participants have to work through these numbers in a pair-wise sequential way to get to the final answer in the box 'Fin'. The answer for two identical number is the same, and the answer for two different numbers is always the third number. For example, the answer for '1' and '1' is always '1', the answer for two different numbers (e.g. '1' '4') is always the third number (e.g. '9'). They were instructed that only the final answer matters and they can answer the final answer any time by pressing a different key. However, participants were not told about the hidden rule that the second response is always the same as the final answer. It is possible to skip through the rest of the number to get to the final answer by just solving the second number pair. The realisation of this rule requires insights. Taken from Wagner and colleagues (2004).

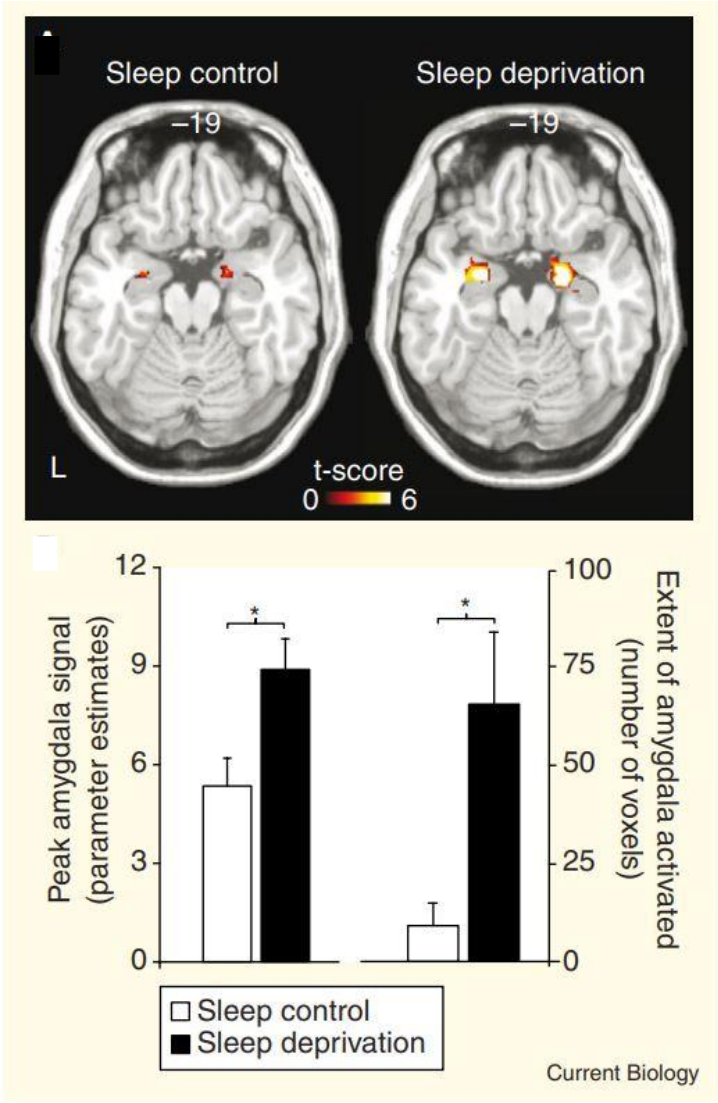
1.2.3 Sleep and emotion

The impact of sleep and sleep loss on emotional regulation have gained more interest in the past two decades with the discovery that almost all neurological and psychological disorders always occur with sleep abnormalities concurrently which suggests a close relationship between sleep and emotion. Subjective reports have consistently shown that a lack of sleep is associated with emotional volatility and irritability (Horne, 1985). Dinges and colleagues (1997) investigated subjective reports of mood using a partial sleep deprivation paradigm and found that 5 hours of sleep a night led to cumulative increase in emotional disturbances and difficulties throughout the week. Zohar and colleagues (2005) found that sleep loss amplified negative emotion in reaction to disruptive daytime events whereas positive emotion was diminished following goal-enhancing events in a group of medical residents. An overnight sleep deprivation led to greater negative emotions such as anger, anxiety and stress when exposed to mild-stressors (Minkel et al., 2012), and neutral stimuli being perceived more negatively (Daniela et al., 2010) when compared to the control group. Furthermore, sleep deprivation led to poorer emotional regulation (Mauss et al., 2013) and reduced inhibition in reactivity to negative stimuli which led to increased impulsivity (Anderson and Platten, 2011). This can lead to serious consequences as impulsivity and sleep disruptions have been found to be significantly associated with aggression and suicidal tendencies (Bernert and Nadorff, 2015; Kamphuis et al., 2012; Plutchik, 1995).

fMRI studies of the brain after sleep deprivation provide more direct evidence that sleep disruption leads to dysregulation of the emotional brain reactivity (Motomura et al., 2013; Yoo et al., 2007). In an overnight sleep deprivation study, Yoo and colleagues (2007) presented a series of pictures ranging from neutral to negative emotionality to both sleep deprivation and control (allowed to sleep normally) groups while having an fMRI scan. Significant amygdala activation was present for both groups while viewing

pictures of increasing negative emotionality, but there was a marked +60% greater magnitude of amygdala activation and a three-fold increase in the volume of the activated amygdala in the sleep deprivation group compared to the control group (Figure 5A). Also, relative to control group, sleep deprived subjects exhibited significantly weaker connectivity between amygdala and medial PFC (mPFC), a region known to play an important role in top down inhibitory control of emotions (Sotres-Bayon, 2004) (Figure 5B). Motomura and colleagues (2013) showed similar patterns of greater amygdala and reduced mPFC activation in a study of partial sleep deprivation after 5 nights with 4 hours of sleep per night. This study has more ecological validity as the partial sleep deprivation pattern resembles the sleep problems currently faced in our society. Thus, sleep loss leads to hyper activity of the limbic system represented by the amygdala in reaction to negative stimuli, as well as weakened connectivity with mPFC, signalling a weakened top down inhibitory control of emotions. Sufficient nocturnal sleep seems to be important for the functional integrity of the limbic and inhibitory control system for the regulation of emotional reactivity.

A


Sleep control
Sleep deprivation
−19
−19
L
t-score
0
6
Peak amygdala signal (parameter estimates)
Extent of amygdala activated (number of voxels)
12
9
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3
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100
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Sleep control
Sleep deprivation
Current Biology

B

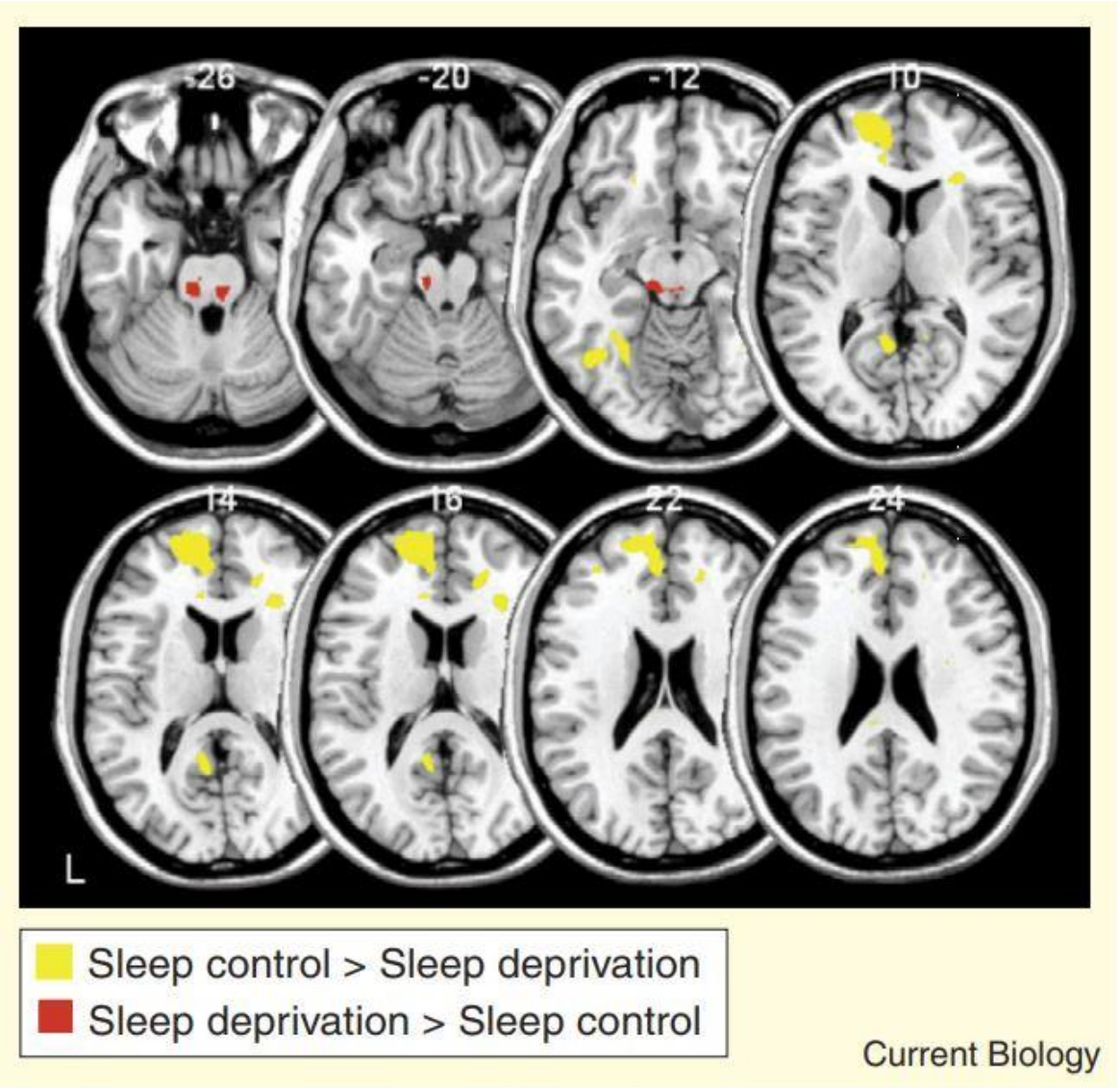


Figure 5. A shows Amygdala activation in sleep deprivation and control groups. There was significant amygdala activation in both sleep deprivation and control groups, but there was a +60% higher magnitude of activation and a three-fold increase in the volume of the activated amygdala recruited in the sleep deprived group compared to the control group (average ± SEM of left and right amygdala, $p < 0.001$). B shows functional connectivity between amygdala and mPFC. There was significantly greater connectivity with mPFC in control group than sleep deprivation group (green) ($p < 0.001$). There was significantly greater connectivity with autonomic brain stem regions in sleep deprivation than the control group ($p < 0.001$). Taken from Yoo et al., 2007.

Not only is sleep important for the regulation of emotion, it also plays a crucial role in emotional memory consolidation (for review, see Goldstein and Walker, 2014). Wagner and colleagues (2001) found that sleep during the latter half of the night comprised of

predominantly REM sleep enhanced emotional memory consolidation. Also, the effect of a brief three hours of sleep immediately after learning had a long-lasting effect as participants who were allowed to sleep after reading an upsetting story showed superior recall of the emotional memory compared to the wake group even after four years (Wagner et al., 2006). Other studies found that the amount of REM sleep is associated with emotional memory consolidation (Groch et al., 2013; Nishida et al., 2009; Hu et al., 2006). Sleep not only consolidates emotional memory, it selectively consolidates emotional components of memories. More recently, Payne and colleagues (2012) found that sleep immediately after learning of pictures promoted superior memory recall of the emotional objects in the pictures compared to sleep after 16 hours of wakefulness, and it was associated with the amount of REM sleep. Superior memory recall for emotional objects also corresponded with a decrease in memory recall of the neutral background of the pictures where the emotional objects were placed. This suggests that sleep selectively consolidates the most emotionally salient information (especially information with negative emotionality) and a timely sleep soon after learning is important for such consolidation (Groch et al., 2013; Nishida et al., 2009; Hu et al., 2006; Wagner et al., 2006). Thus, sleep plays an important role in emotional memory consolidation particularly during REM sleep.

1.3 Regulation of Sleep-Wake Cycle

1.3.1 Circadian Timing System

Our circadian rhythm governs a range of behavioural changes that follow a 24-hour clock such as our sleep-wake cycle and is generated and regulated by the Circadian Timing system (CTS, Moore, 1997; Dijk & Czeisler, 1995). CTS regulates the temporal organizations of our behaviours, such as sleeping, waking, feeding and reproduction, in an evolutionary adaptive manner. This is done partly by regulating a range of physiological and endocrine functions such as melatonin (Lewy & Sack, 1989), body temperature (Honma, 2013) and phagocytosis (Barriga et al., 2001) that subserve these behaviours. CTS consists of three main features - the endogenous and self-sustaining pacemaker, entrainment by photo-reception, and a feedback process (Moore, 1997). The light-dark cycle of our natural environment plays a critical role in our sleep-wake cycle. When human participants or animals are put in an environment devoid of any time cues (e.g. in total darkness or in constant artificial light), the normal sleep-wake cycle persists, but with a different period than 24 hours, this is also called a free-running state (Moore, 1997; Wever, 1979). The maintenance effect is generated by our endogenous pacemaker or clock. In order for our circadian rhythm to synchronise with the 24-hour light-dark cycle, the pacemaker must be reset regularly by the environmental stimuli (primarily light), this process is called entrainment. Dim light or darkness triggers the secretion of melatonin which provides feedback or acts as a marker for the pacemaker for the effective regulation of sleeping and waking behaviour. Thus, light is a major determinant our sleep-wake cycle.

The suprachiasmatic nucleus (SCN) has been found to form our endogenous pacemaker. Firstly, studies have shown that nearly all circadian rhythms were totally disrupted with the lesions of the SCN (Edgar et al., 1993; Meijer & Rietveld, 1989). In each case, the disruption was limited to the temporal organization of the activity under

examination. For instance, only the timing of the sleep-wake cycle was disrupted, the total amount of sleeping and waking as well as the sleep architecture remained intact (Meijer & Rietveld, 1989). Secondly, neuronal activity of the SCN continued to follow its circadian rhythm despite being separated from the rest of the brain either in vivo (Inouye & Kawamura, 1979) or in vitro (Shibata & Moore, 1998). Thirdly, animals with SCN ablations that lost their circadian rhythms had regained rhythmicity after being transplanted with fetal SCN (Lehman et al., 1987). The rhythms they gained were in accordance with the donor's rhythms (Ralph et al., 1990). Lastly, SCN has been found to be the main location to receive information from the pathway of the entrainment by light stimuli, which I will illustrate later (Moore, 1978). The hypothalamus, midline thalamus and basal forebrain are the major areas of efferent projections from SCN (Watts, 1991). Information from these brain areas is relayed to other brain regions responsible for the regulation of autonomic functions such as body-temperature, metabolism and the temporal organization of sleeping and waking behaviours (Moore, 1996).

Before the discovery of the SCN, scientists first studied how light information was relayed from the eyes which results in the entrainment of the pacemaker. Initially, studies found that circadian rhythms of the animals continued to function normally even after they were completely blinded by the transection of all their optic pathways leaving the optic chiasm (Moore, 1978). This prompted investigations of another visual pathway that could relay the light information from the retina. It was found that a small hypothalamic cell group alongside the third ventricle and located close to the optic chiasm is responsible for the direct projection of light information from the retina to the SCN, this pathway was then termed the retinohypothalamic tract (RHT) (Moore, 1973; Moore & Lenn, 1972). Also, it was found that transection of the RHT pathway totally disrupted entrainment by light stimuli, without affecting any other visual processing (Johnson et al., 1988). Thus, the RHT pathway is known to be solely responsible for

photic entrainment. The mode of transportation for the RHT pathway is glutamate (Shirakawa & Moore, 1994; Ding et al., 1994). It works with different types of receptors (mainly NMDA) to influence the working of pacemaker (Rea et al., 1993). Generally speaking, our CTS is very sensitive to light. A phase response curve (PRC) has been used to describe the effect of light (Khalsa et al., 2003; Minors et al., 1991). Bright light given at the onset of the night time and offset of day time moves the circadian rhythm of sleeping later (phase delay), and bright light given at the onset of the day time and offset of night time moves the circadian rhythm of waking earlier (phase advance) (Khalsa et al., 2003; Minors et al., 1991). Furthermore, it has been found that light is not the only stimulus that can influence the entrainment of the pacemaker and there is a non-photic pathway that combines information from different stimuli to project to SCN. Physical activity can be another stimulus that induces phasic changes in the pacemaker (Reebs & Mrosovsky, 1989; Turek, 1989), and damage to the intergeniculate leaflet (IGL) pathway abolishes the effect of the physical activity on entrainment of the SCN (Johnson et al., 1989). Thus, IGL is considered as the non-photic pathway for entrainment (Moore & Card, 1994).

Lastly, melatonin secretion from the pineal gland is under the control of the pacemaker (Fuller et al., 2006; Moore, 1996). It is almost absent during the day time but rises significantly near bedtime, stays relatively constant for the first half of the night, then declines gradually and the eventual low dose of melatonin signals the onset of the waking time (Cajochen et al., 2003; Dijk et al., 1997). Evidence has shown that exogenous administration of melatonin during participants' day time increased daytime sleepiness and shifted the circadian rhythm earlier (Rajaratnam et al., 2004; Reid et al., 1996; Cajochen et al., 1996). Also, pharmacological suppression of melatonin shifted the circadian rhythm later (Santhi et al., 2012). Taken together, melatonin secretion is not only regulated by CNS, it also provides feedback for the pacemaker, to be entrained by the melatonin level in the body. Melatonin secretion can also be

influenced by light. Studies have found that even artificial light exposure such as room light before sleep, which has much weaker intensity than natural light suppresses melatonin secretion which in turn delays sleep (Santhi et al., 2011; Gooley et al., 2010; Figueiro et al., 2011). It has become evident that light plays a crucial role in our sleep-wake pattern.

1.3.2 Homeostatic sleep process

Sleep homeostasis is another process that regulates sleep and wake behaviours and it is thought to be largely independent of the CTS. Simply put, this process can be described as the sleep pressure that builds up as the duration of waking increases and sleep pressure decreases as the duration of sleep increases. SWS and EEG SWA have been used as standard markers for sleep homeostatic process. Studies have shown that high sleep pressure characterised by a large amount of SWA at the beginning of a night time sleep episode dissipated rapidly as the night progresses, characterised by decreasing SWA during SWS (Daan et al., 1984; Borbely, 1982; Borbely et al., 1981). Also, the amount of time we stay awake predicts the amount of SWA that occurs during the SWS of our subsequent sleep, proportional to the amount of waking time, and independent of the circadian rhythm (Akerstedt et al., 1998; Dijk et al., 1990; 1987; Feinberg, 1974). Sleep deprivation also resulted in a bout of increases in the duration and intensity of SWS during subsequent recovery sleep (Djik et al., 1993). Furthermore, in a rodent study, the increase in SWA during SWS as a result of sleep deprivation was not affected by the ablation of SCN (Tobler et al., 1983). Thus, CTS and sleep homeostatic process seem to work independently to influence sleeping and waking behaviours.

On the other hand, EEG delta and theta waves during wakefulness can also be used as markers for homeostatic sleep pressure. The amount of high frequency EEG activity during wakefulness increases as the duration of wakefulness increases independent

of circadian phases (Finelli et al., 2000; Cajochen et al., 1999a; Aeschbach et al., 1997). Cajochen and colleagues (2001) studied these activities when multiple naps were introduced, and found that the normal increase of these low frequency activities during wakefulness as time progresses changed. This finding is similar to the study of SWA in which a nap during the day reduced the number of SWA during subsequent night time SWS sleep (Werth et al., 1996). Hence, both SWA during sleep and low frequency EEG during wakefulness are useful markers for the sleep homeostatic process. Moreover, the changes in these EEG waves are mostly found in the frontal regions of the brain (Finelli et al., 2001; 2000; Cajochen et al., 1999a; 1999b).

Although these two processes (CTS and sleep homeostasis) work independently, nevertheless they interact with one another to influence sleep and wakefulness.

1.4 Sleep changes across the life span

1.4.1 Sleep during adolescence

Studies have found that sleep patterns change during the first great hormonal change in life, adolescence (Giannotti et al., 2002; Laberg et al., 2001; Szymczak et al., 1993). Self-report studies revealed that adolescents (between 10 to 20 years old) go to bed later and wake up later during the weekends (average of 1-2 hours) when they do not have to comply with the school rules than on the weekdays, and the delay in sleep and rise time is more pronounced for older adolescents (Wolfson & Carskadon, 1998; Manber et al., 1995; Carskadon, 1990). Other studies also looked at the sleeping patterns of adolescents during school holidays. One study reported that adolescents' sleeping time was delayed for an average of 1.5 hours during vacation than term weekdays (Hansen et al., 2005). Another study has also shown delayed sleep and rise time for adolescents during school holidays (Crowley et al., 2006). Thus, the natural sleep and wake time is delayed in adolescents. Some researchers attributed the sleep phase delay in adolescents to various environmental factors such as reduced parental

control (Carskadon, 1990), engagement in extra-curricular activities (Carskadon, 1989-1990) or a part-time job (Carskadon, 1990). However, day-time sleepiness was reported in 61% of high school students during weekdays (White et al., 1980). A longitudinal survey showed that 63% of adolescents reported feeling tired waking up in the morning for school (Strauch & Meier, 1988). A survey by U.S. National Sleep Foundation (2006) found that 70% of teenage students needed parental assistance in waking up in the morning. Roenneberg and colleagues (2003, 2004) offered a genetic explanation of this phase delay. On a more extreme scale, Delayed Sleep Phase Syndrome (DSPS), a sleep disorder characterised by chronic phase delay in natural sleep and rise time and excessive day-time sleepiness when forced to comply with social clock time, has a typical onset during adolescence (Thorpy et al., 1988; Weitzman et al., 1981). It is more likely that natural causes such as hormonal changes, rather than other environmental factors that play a major role in the sleep phase delay in adolescents. Delayed sleep time during school terms resulted in a deficit relative to the number of hours of sleep required for a night of restful sleep for teenagers (Wolfson & Carskadon, 1998). This in turn has detrimental effects on learning and school performances (Wolfson & Carskadon, 2003; Fallone et al., 2001). Thus, it is proposed that schools' start times should be delayed for adolescents and such changes have been made in some North-American and Israeli schools (Louzada et al., 2008).

1.4.2 Sleep during menopause

Menopause marks the second great hormonal change in women's lives. Due to an aging population, an increasing number of women are experiencing the transition into menopause and its related problems. There was an estimate of 470 million post-menopausal women in the 1990s, with a growing rate of 1.5 million per year, and by 2030, the number is expected to increase to 1.2 billion (World Health Organization, 1996). 25% to 50% of women during menopause have sleep difficulties compared to 15% of the general population (Shaver et al., 1988). Existing literature on sleep and

menopause is small and has used both subjective reports and objective measures using PSG or actigraphy to assess sleep disturbances in menopausal women. In a survey of 539 female subjects between 42 to 50 years old, post-menopausal women reported greater difficulty in falling and staying asleep compared to peri- and pre-menopausal women (Ballinger, 1976). More details will be discussed in later chapters (3 and 4) on the effects of menopause on sleep.

1.4.3 Sleep and aging

Sleep changes across the life span. Not only is the amount of sleep reduced as we age, but also sleep architecture changes over time. The amount of SWS declines as we grow older and by the age of 74 there is almost no SWS produced during sleep (Lewis, 2013; Mokhlesi et al., 2012; Van et al., 2000). The reason behind this reduction has not been explained. It may be due to a reduction in the need for SWS or that the brain is experiencing difficulty in the extensive synchronisation of the neural activity. If the latter explanation is true, then it is possible that the reduction in SWS is associated with a range of aging-related cognitive problems including neural atrophy. Recently, Mander and colleagues (2013) found that prefrontal cortex atrophy in older adults was associated with a reduction in SWS and an impairment in hippocampal–dependent declarative memory consolidation. The prospect of artificially inducing slow wave oscillations, especially in people that lack SWS, may yield beneficial outcomes in the prevention and treatment of various neurocognitive impairments. It may also be beneficial for patients who suffer from insomnia and other sleeping problems (Bellesi et al., 2014). Due to the crucial role SWS plays in declarative memory consolidation, and since a lack of it affects almost all other executive functions such as attention, planning and decision making (Bellesi et al., 2014), efforts have been made to artificially induce more slow wave oscillations.

1.5 Faking sleep

1.5.1 tES and SWA

Transcranial Electrical Stimulation (tES) is a form of transcranial electrical stimulation, it is a non-invasive and safe brain stimulation technique that delivers constant low electrical current to the scalp to induce long-term cortical excitability (anodal stimulation) or cortical depression (cathodal stimulation). Recent studies have shown promising results in increasing SWA during SWS through application of tES. Marshall and colleagues (2006) have successfully induced an increase in SWA at the emergence of SWS by applying pulsed square wave transcranial direct current stimulation (tDCS, a type of tES) over prefrontal cortex at a frequency of 0.75 Hz, with 5-minute stimulation intervals separated by 1 minute resting periods. Furthermore, both stimulation and sham stimulation groups performed better after sleep in a memory retrieval task than before sleep, and the stimulation group recalled more words than the sham stimulation group. On the other hand, no declarative memory facilitation effect was found when the current was applied during REM states. The outcomes suggest that SWA in SWS plays a critical role in declarative memory consolidation. These results have also been extended to clinical studies. For example, using a similar tES protocol increased the duration of slow wave sleep and reduced the duration of stage 1 sleep in patients suffering from insomnia, suggesting improved sleep efficiency (Saebipour et al., 2015). Also, tDCS increased SWA in children suffering from attention deficit hyperactivity disorder (ADHD) (Prehn-Kristensen, 2014). People with ADHD have abnormally low SWA during SWS and problems with sleep related memory consolidation. Encouragingly, this increase in SWA results in an improvement in memory consolidation comparable to healthy controls. However, the effect of tES may be hard to evaluate due to several limitations. For one, tES causes marked electrical artifacts in the EEG signal which make the accurate evaluation of EEG readings difficult. Also, although tES produces widespread regional neural activation, it also results in a

complex web of activated and deactivated brain regions which may mask its effect on SWA (see review Bellesi et al., 2014). Thus, the beneficial effect of tES on SWA is difficult to replicate.

1.5.2 TMS and SWA

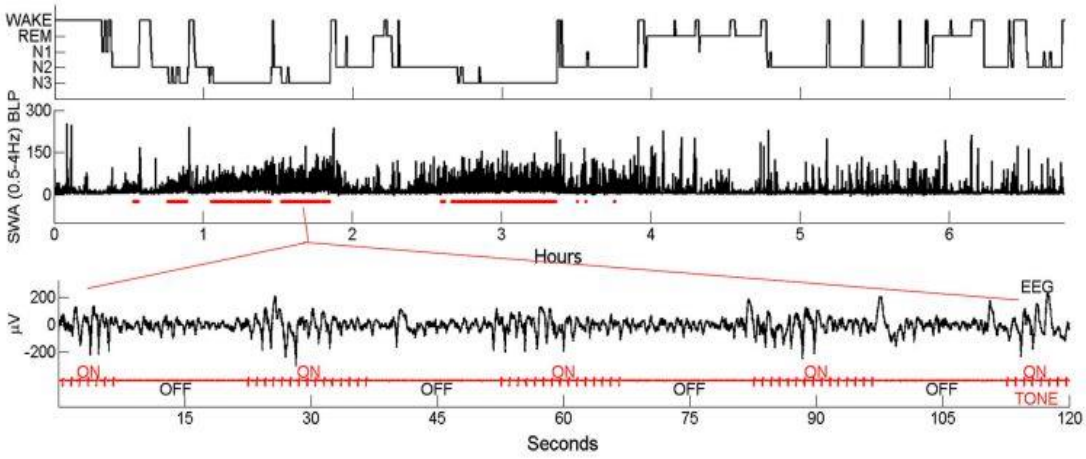
SWA can also be induced by transcranial magnetic stimulation (TMS) (Saeki et al., 2013; Huber et al., 2007; Graf et al., 2001). TMS is widely used as a safe, non-invasive brain stimulation technique that stimulates nearby neurons at the site of stimulation, which can be used to assess neuro excitability when paired with electroencephalogram (EEG) recording. Physiology studies with no-task protocol have yielded promising results in successfully generating slow waves and increasing SWA during SWS. By using repetitive TMS (rTMS) prior to sleep at a frequency of 20 Hz over dorsolateral prefrontal cortex (DLPFC), Graf and colleagues (2001) have yielded a small increase in SWA during subsequent SWS in DLPFC. Another study (Saeki et al., 2013) using a similar protocol but with 10 daily rTMS sessions yielded a more marked increase in SWA during subsequent SWS in DLPFC. Despite having clear evidence that TMS is able to induce an increase in SWA during SWS, few TMS studies have used tasks that examined whether the increase in SWA caused by TMS leads to cognitive enhancement after sleep. In one rodent study, Estrada and colleagues (2015) examined the effects of TMS on cognitive functions in a sleep deprivation (SD) paradigm. Rodents were handled gently to keep them awake while having their brain stimulated by TMS. The results showed that the group with TMS stimulation made significantly fewer errors in the behavioural tasks that examined spatial and working memory after SD than the control group. However, this study did not measure whether slow waves were induced by TMS stimulation. Also, the long-term effect of TMS stimulation on SWA is unknown. Hence, future research should combine TMS-EEG with tasks that measures cognitive abilities in TMS-EEG studies as well as investigate

the long-term effect of TMS stimulation to form a more conclusive view about the efficacy of TMS in inducing SWA and subsequent cognitive enhancement.

1.5.3 Auditory stimulation and SWA

Auditory stimulation offers a more practical way of inducing SWA as it is safe, non-intrusive and easy to control. Recent studies have provided encouraging results in both stimulating SWA and its related enhancement in learning. Using intermittent tone stimulation in blocks of 15s with stimulation free intervals during deeper stages of NREM sleep (N2 and N3), Riedner and colleagues (2012) were able to generate a greater number of slow waves of larger amplitude during stimulation than adjacent stimulation free intervals (Figure 6). Another study with the aim of establishing the role of sleep in learning new information administered auditory stimulation during both REM and NREM sleep and found increased SWA during NREM sleep stimulation (Arzi et al., 2012). Using continuous rhythmic auditory stimulation with tones of 0.8 Hz starting from 2 minutes before lights off lasting for 90 minutes, Ngo and colleagues (2012) found significant increased and entrained SWA during the 90 minutes stimulation period, despite participants taking longer to fall asleep. Furthermore, in their other experiment, Ngo and colleagues (2013) found that closed-loop auditory stimulation in phase with the up states of SWA increased the amplitude of SWA but not during the down states of SWA. This also led to improved declarative memory performance when auditory stimulation was in phase with the up states of SWA compared to stimulation with down states of SWA as well as a no stimulation group. These results suggest SWA can be enhanced by auditory stimulation which can lead to subsequent improvement in declarative memory performance. However, care must be taken with the volume, frequency, and timing of the tones as they can induce unwanted arousal or difficulty in initiating sleep (Arzi et al., 2012; Riedner and colleagues 2012; Ngo and colleagues 2012).

Despite promising results from these stimulation methods, results seem to indicate that stimulation benefits SWA by enhancing existing SWA. It remains unknown whether these stimulation methods would produce beneficial results in people who lack SWA. It would be of great interest for future studies to examine the effects of these stimulation methods in people characterised by decreased SWA such as older adults.



Figures 6. The effect of intermittent auditory stimulation in blocks of 15s during N2 and N3 sleep. Tones were delivered and adjusted for volume and timing with ongoing EEG assessment of sleep stages. Each tone was played for 50ms with 1s interstimulus interval during each block. Hypnogram of sleep stages and Band limited power (BLP) with the timing of stimulation marked in red are shown. SWA appears to be more numerous and higher in amplitude during stimulation compared to adjacent stimulation free intervals. Taken from Bellesi and colleagues (2014).

Chapter 2: General method for assessing sleep

Abstract

This chapter reviews the experimental techniques used to assess sleep architecture, sleep quality and sleep-wake pattern. Polysomnography (PSG) is the most common sleep electroencephalogram (EEG) used in sleep research that records the brain oscillations during sleep and is used in conjunction with electromyography (EMG) as well as electrooculography (EOG) to record other sleep parameters such as muscle tone, and eye movements. Sleep stages can then be scored and analysed, and sleep quality can be assessed. Actigraphy is another practical tool to measure the sleep-wake patterns over days or longer period of times as well as aspects of sleep quality. Chapter 3 of this thesis used actigraphy technique to assess sleep-wake patterns as well as sleep quality. Chapter 4 and 6 of this thesis used PSG to assess sleep architecture and eye movements during sleep.

1. EEG

1.1. A brief history of EEG

The History of EEG traces back to the discovery of the electrical activity of the brain from exposed brain hemispheres of monkeys and rabbits by an English physician practicing in Liverpool, Richard Caton in 1875 (Swartz, 1998). 15 years later, by measuring the electrical activity from the surface of the brain, Polish physiologist Adolf Beck published work on the rhythmic oscillation of the brain from studies of animals, his results led to the discovery of brain oscillations (Coenen et al., 2014). In 1913, Russian electrophysiologist Vladimir Pravdich-Neminsky published the first work about EEG and evoked potentials from the study of dogs (Pravdich-Neminsky, 1913). Later, German psychiatrist Hans Berger expanded work from earlier animal studies and published the first human EEG study and invented the method to record brain waves and named it electroencephalogram (EEG) in 1924 (Millet, 2002). His discovery was initially met with doubts and scepticism and it took five years for his study to be published. The validity of human EEG was later confirmed by British electrophysiologists Edgar Douglas Adrian and B. H. C. Matthews in 1934 which led to general acceptance and development of EEG technology. Berger's invention of EEG has been described as "one of the most surprising, remarkable, and momentous developments in the history of clinical neurology" (Millet, 2002).

1.2. What is EEG?

EEG is an electrophysiological monitoring technique that records physiological events and electrical activity generated by a population of neurons with safe and non-invasive recording. The EEG signals are generated by the post-synaptic potentials of synchronously active neurons called pyramidal neurons with perpendicular orientation in relation to the scalp. It measures the difference in electrical voltage between any electrode and the reference electrode. EEG can be used to study a range of

neurological disorders or cognitive functions as it offers millisecond temporal resolution. For example, studies have shown that N400 evoked response potentials (ERPs) are related to semantic processing (Nigam et al., 1992; Kutas and Hillyard, 1984). ERPs are generated by time-locked responses to cognitive processes. On the other hand, EEG is also a useful tool in the evaluation of sleep architecture. In this case, continuous recording of brain oscillations by PSG (a combination of EEG, EMG and EOG for the assessment of sleep) is assessed and scored for sleep stages instead of ERPs.

The advantage of EEG over other neuroimaging techniques is that EEG offers high temporal resolution (ms) which makes the investigation of real time processing possible. It is also cost effective for running experiments as only initial purchase of equipment is needed. However, EEG has inherent poor spatial resolution which means it is difficult to determine the location of the cognitive process that takes place. Advanced computational method is needed for source localisation but it is still impossible to localise intracranial source of activation as electrical signals are picked up from the surface of the scalp. Also, EEG recording requires minimal eye and muscle movements as they generate artefacts that can distort the data. Skin and scalp need to be cleaned and prepped for electrode placement and electrode gel needs to be applied which may irritate sensitive skin. The benefit for sleep EEG recording is that only brain oscillations are of interest so high spatial resolution is not necessary, participants close their eyes and relax their muscles while sleeping which minimises signal artefacts.

1.3. Sleep scoring

For almost fifty years, sleep researchers have used the Rechtschaffen and Kales (1968) standardised scoring system for the scoring of sleep stages. Their sleep stages include wakefulness, stage 1, stage 2, stage 3, stage 4 and REM. Stage 3 and 4 are markers of SWS. A new scoring standard by American Academy of Sleep Medicine (AASM, Berry et al., 2012) has now been widely used in sleep research. The new

scoring system includes W (wakefulness), N1 (stage 1), N2 (stage 2), and N3 (combines stage 3 and 4) representing SWS, as well as R (REM).

Stage W represents wakefulness and it is comprised of more than 50% of alpha waves (8-13Hz). Figure 1 shows an example of brain oscillations during stage W.

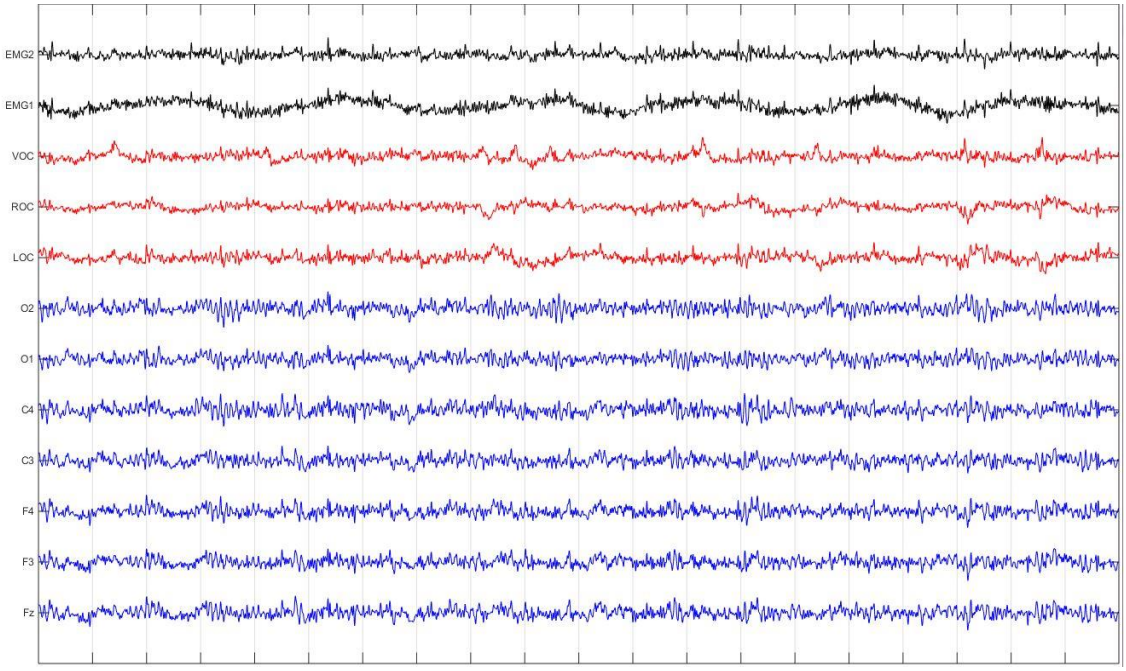


Figure 1. An example of a stage W epoch from my own work. Stage W comprises of predominately low amplitude, high frequency alpha waves.

Stage N1 indicates the onset of sleep which is the lightest stage of sleep that comprises of predominantly low amplitude mixed frequency theta waves (4-7 Hz). Figure 2 shows an example of brain oscillations during N1 sleep.

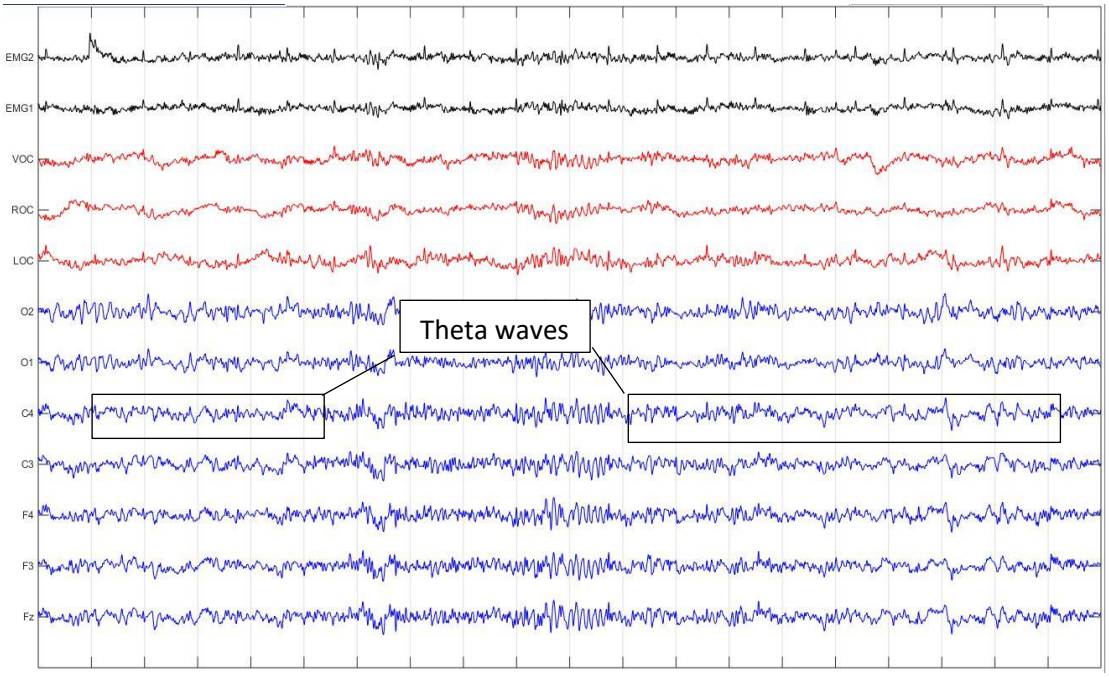
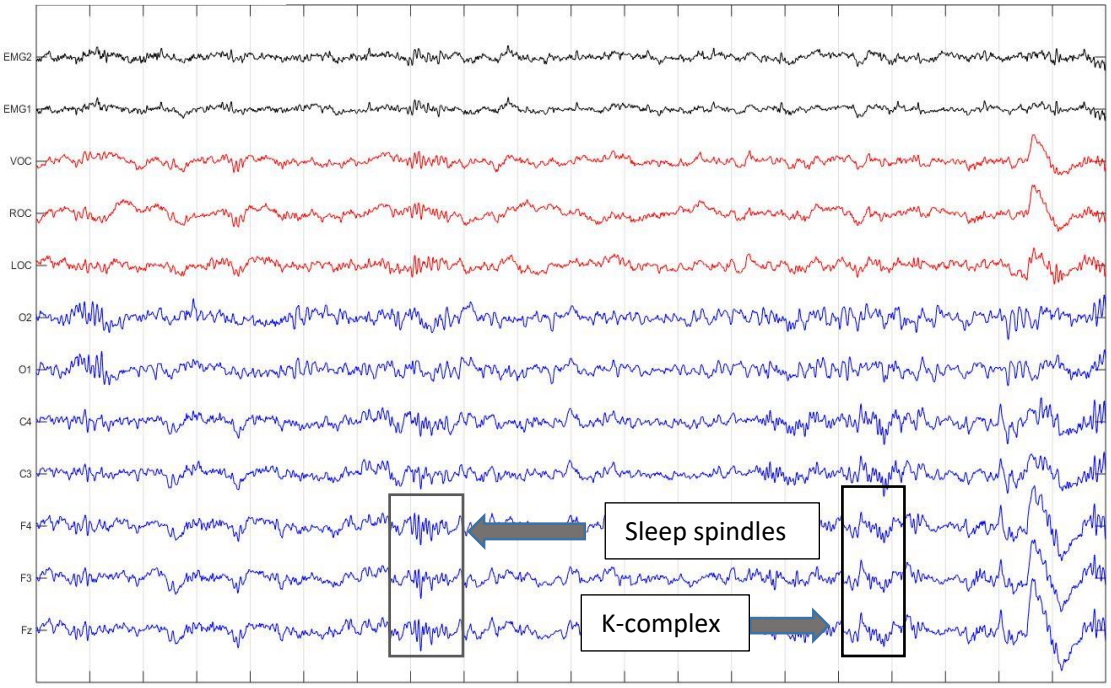


Figure 2. An example of a stage N1 epoch from my own work. Stage N1 comprises of predominately low voltage mixed frequency theta waves.

Stage N2 comprises of mostly theta waves interspersed with sleep spindles and K-complexes. Sleep spindles are trains of distinct waves (11-16Hz) that last at least 0.5seconds. K-complex is a negative sharp wave followed by a positive component that last at least 0.5 seconds. Figure 3 shows an example of brain oscillations during N2 sleep.

A



20 seconds

B

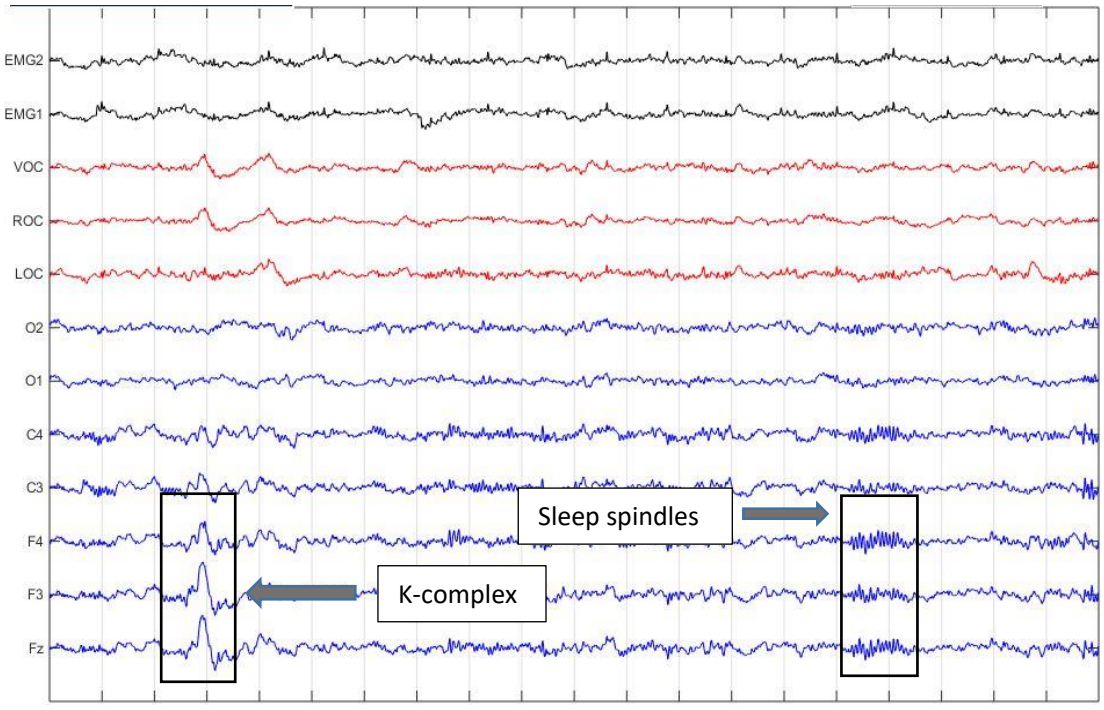


Figure 3 A and 3 B. Examples of N2 epochs from my own work. Stage N2 comprises of predominately low voltage mixed frequency theta waves interspersed with sleep spindles and K-complexes.

Stage N3 is the deepest sleep stage which comprises of high amplitude, low frequency delta waves also called slow waves (0.5-4 Hz). A sleep epoch is scored as N3 if slow waves occupies at least 20% of the epoch. Figure 4 shows an example of brain oscillations during N3 sleep.

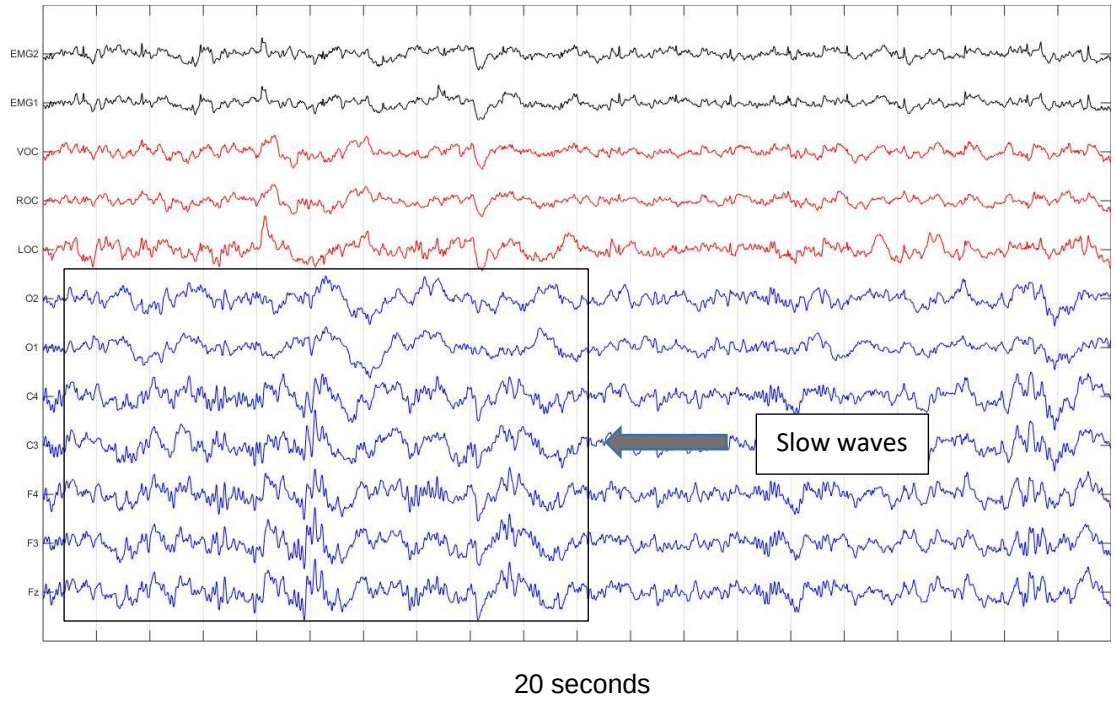


Figure 4. An example of a stage N3 epoch from my own work. Stage N3 comprises of at least 20% of high amplitude, low frequency slow waves.

Stage R is similar to wakefulness, it comprises of theta, alpha, and sawtooth waves, sometimes accompanied by rapid eye movement. Figure 5 shows an example of brain oscillations and rapid eye movements during REM sleep.

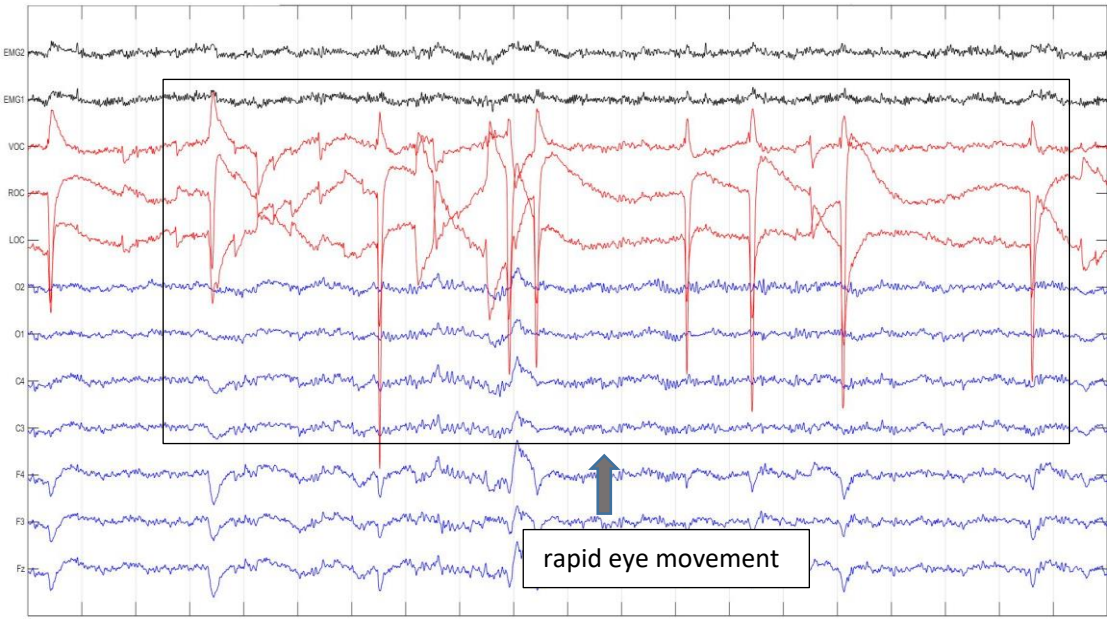


Figure 5. An example of a stage R epoch from my own work. Stage R comprises of theta, alpha and sawtooth waves sometimes accompanied by rapid movements of the eyes, but facial muscle tone is low as can be seen from stable EMG recording.

1.4. Method

10-20 EEG placement is the standard protocol in EEG electrodes placement. Four skull landmarks namely Nasion, Inion, left Pre-auricular point, and right Pre-auricular point are used as references, electrodes are placed 10% and 20% from the landmarks (Figure 6). AASM recommends at least 3 EEG derivatives to record activity from frontal, central and occipital regions as frontal regions are conducive to pick up slow waves, central regions are conducive to pick up sleep spindles, and occipital regions are conducive to pick up alpha waves. Other markers of sleep stages are also taken into consideration when it comes to sleep EEG recording. Eye movements are measured with electrooculography (EOG) technique by placing electrodes on the sides of the eyes and just below the left or right eye. Facial muscle movements are measured with electromyography (EMG) by placing electrodes on the left and right sides of the chin..

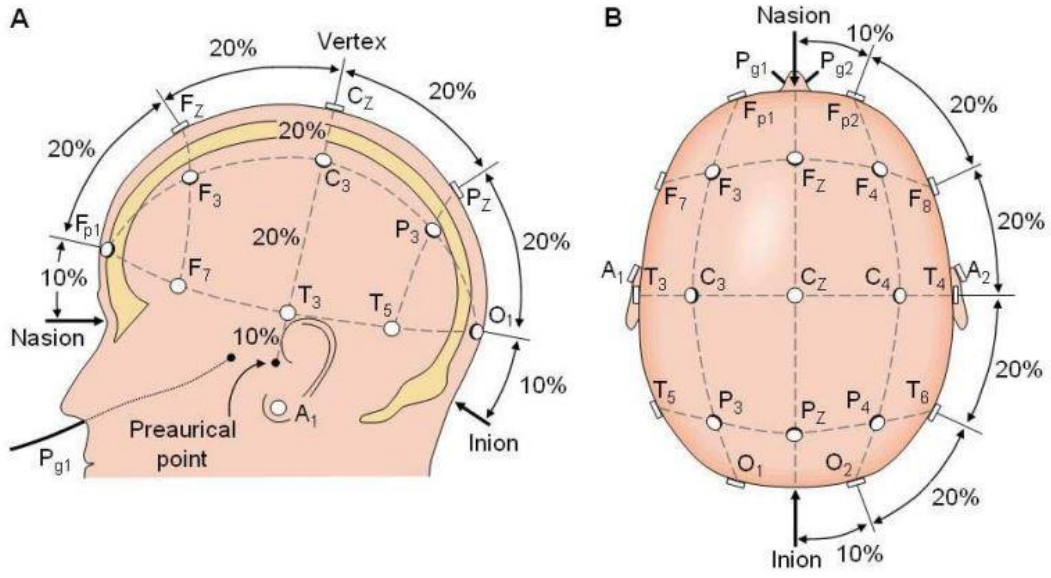


Figure 6. 10-20 EEG placement. F stands for frontal, T stands for temporal, C stands for central, P stands for parietal and O stands for occipital. Longitudinal distance from left Pre-auricular point to right Pre-auricular point are divided into sections of 10% and 20%, T_3, C_3, C_z, C_4, and T_4 can be found along the line. Longitudinal distance from Nasion to Inion are also divided into sections of 10% and 20%, F_{pz}, F_z, C_z, P_z, and O_z can be found along the line. Distance from the sides of the head from F_{p1} to O_1 includes F_7, T_3, and T_5. Distance from F_{p2} to O_2 includes F_8, T_4, and T_8. F_3 is in between F_7 and F_z, C_3 is in between T_3 and C_z, P_3 is in between T_5 and P_z, F_4 is in between F_8 and F_z, C_4 is in between T_4 and C_z, and P_4 is in between T_6 and P_z. (Taken from Malmivuo and Plonsey, 1995)

The process of EEG electrodes placement starts with prepping the sites. Alcohol wipes are used to remove grease and abrasive gel (e.g. Nuprep) is used to scrub the surface of the scalp to remove dead skin and debris which helps to reduce skin impedance for better signals. Electrodes are then filled with EEG conductive paste (e.g. Ten20) and pasted onto the scalp. Disposable medical tape is then used to secure the EEG electrodes. Once all electrodes are placed, an impedance check is performed to make sure the impedance for all electrodes are lower than 5 kΩ. If the impedance for any electrode site is too high, the electrode is removed and repasted after cleaning the site. Once all electrodes have passed the impedance check, participants are directed to lie down in a comfortable position and refrain from moving. Once they are in their sleep positions, an impedance check is performed again to make sure all electrodes are properly attached after lying down followed by recording and turning off the lights.

2. Actigraphy

2.1. What is actigraphy?

Actigraphy is another safe, non-invasive recording method for human sleep qualities as well as sleep/wake cycle. It has been used in sleep research for over 20 years. Actigraphs are small watch-like device that can be worn on the wrist or ankle. The advantage of actigraphy over sleep EEG is that it records activity over 24 hours for days or weeks in the comfort of participants' own working and sleeping environments without disturbing their normal routines, and it is cheaper and less cumbersome than setting up sleep EEG (Ancoli-Israel, 2003; Sadeh et al., 1995). Actigraphy is a useful tool for determining the general pattern of sleep qualities and sleep-wake cycle over longer period of time. For this reason, actigraphy has greater ecological validity than EEG as the recording reflects real life sleep and activity patterns, suitable for field studies.

2.2. Methods and Analysis

With technological advances, current actigraphy devices detect motion with a linear accelerometer in a single or multiple vectors (Jean-Louis, 2001). There is also a common 0.25-3 Hz band pass filtering for data storage for most single vector devices (Ancoli-Israel, 2003). Raw data are generated and stored with three methods of activity counts: time above threshold, zero crossing, and digital integration (Figure 7). Raw actigraphy data is first downloaded after recording, and converted into epochs of 60s. Different methods of data analysis are then conducted for different objectives. Chapter 3 describes its use in determining Interdaily Stability, Intradaily Variability, Relative Amplitude, M10 (activity level during the10 hours of the highest activity of a day) and L5 (activity level during the 5 hours of the lowest activity of a day). Figure 8 shows an example of the mean sleep/wake pattern of a group of participants from actigraphy recording over two weeks.

Figure 7.

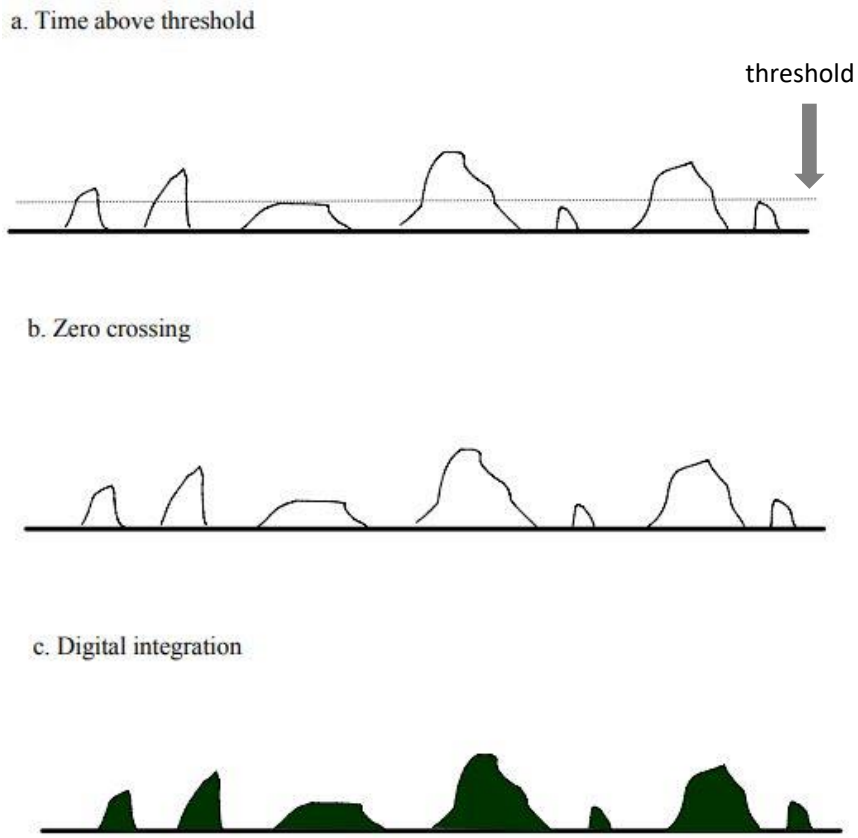


Figure 7. Methods of measurements. a. Time above threshold calculates the duration per epoch that the activity level (wave) is above a predetermined threshold (often based on previous studies or pilot data). b. Zero crossing calculates the duration per epoch that the activity level is above 0. c. Digital integration calculates the area under the curve per epoch. (Taken from Ancoli-Israel, 2003).

Figure 8.

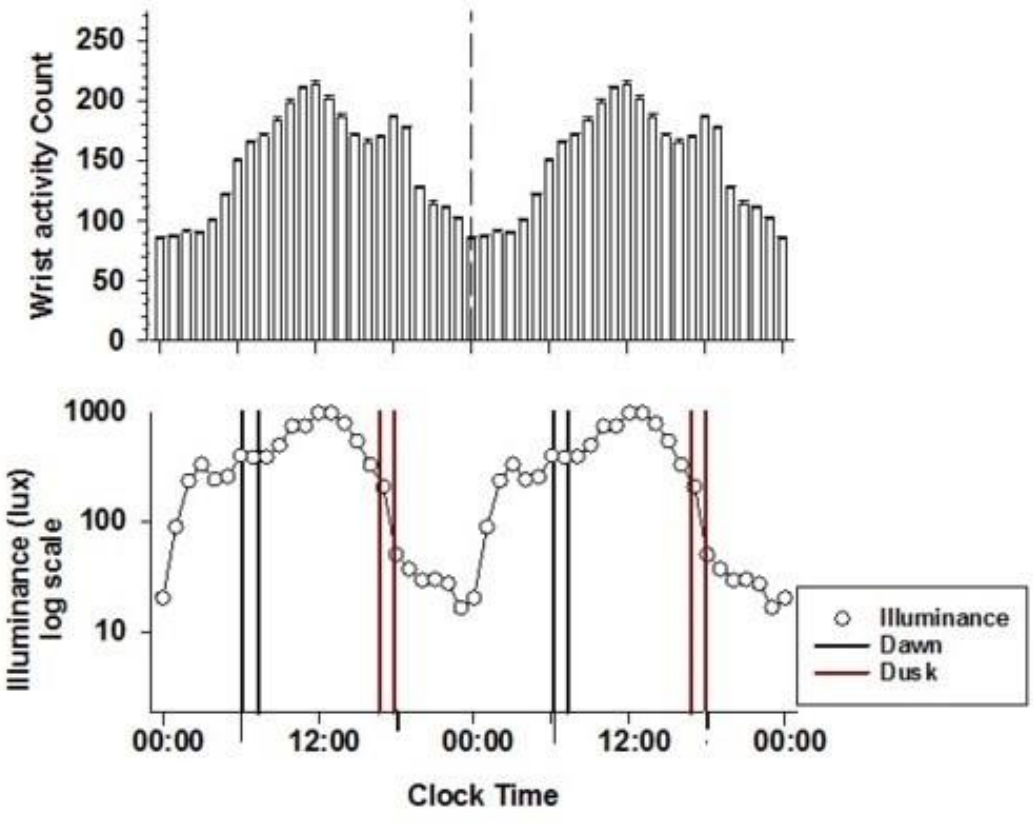


Figure 8 shows an example of the mean sleep-wake pattern and exposure to lighting of a group of participants between 42-59 years old over two weeks, double plotted (from my own work). The sleep-wake pattern coincides with the level of illuminance throughout the day. This shows that light is an important factor in the entrainment of the circadian rhythm of our sleep-activity pattern.

Chapter 3: The effects of menopause on sleep

Abstract

Objective – Most research on sleep has been carried out on men and younger adults. There is very little data about sleep quality, sleep-wake pattern, and sleep architecture of women. Also, studies have found that the first great hormonal change, adolescence, exerts a great influence on sleep. Few studies have explored sleep in the second great hormonal change, menopause. Thus, the aim of this study is to investigate whether menopause exerts an influence on sleep, independent of age, using both subjective report and actigraphy as an objective measure. We hypothesize that there will not be a significant difference between groups for various sleep measures. However, quality of sleep is significantly correlated with the severity of menopausal symptoms.

Methods - 57 participants were recruited and were allocated to three groups, premenopausal, menopausal and men. Subjects completed a range of questionnaires as a baseline measure of sleep and mood, and also the Menopausal Rating Scale (MRS) as a measure of the severity of menopausal symptoms. An actiwatch was configured for each participant to wear on his or her non-dominant wrist throughout the following two weeks while filling in a daily Karolinska Sleep Diary (KSD) and Karolinska Sleep Scale (KSS) at the participant's own environment (e.g. home). Daily text message reminders were sent around 6pm to each subject.

Results – Mixed model analyses for subjective reports of sleep quality and one-way between-subject ANOVA analyses for actigraphy measures found that there was no difference in various measures of sleep quality between groups. However, correlation analyses found significant correlations between the severity of menopausal symptoms and measures of sleep quality.

Conclusion – Sleep complaints during menopause or the transition to menopause are related to the severity of menopausal symptoms but not menopausal status.

1. Introduction

Most sleep research has been carried out on men and younger adults, mainly because the menstrual cycle adds noise to the physiological data. A meta-analysis of the sleep literature concluded that there is very little data about the sleep quality, sleep-wake pattern and architecture of sleep in women (Ohayon et al., 2004). This gap in our knowledge has significant implications as treatments or therapies that alleviate sleep disturbances based on the sleep physiology of men cannot be generalized with confidence to women. Also, both men and women go through a great hormonal change during their early life, adolescence. Studies have found that there is a marked phase delay of sleep in adolescents (Giannotti et al., 2002; Laberg et al., 2001; Szymczak et al., 1993), and this change is regulated by pubertal hormonal change (Hagenauer and Lee, 2012; Sadeh et al., 2009). However, little is known about sleep during the second great hormonal change in women, menopause. Due to an aging population, an increasing number of women are experiencing the transition into menopause and its related problems. There was an estimate of 470 million post-menopausal women in the 1990s, with a growing rate of 1.5 million per year, and by 2030, the number is expected to increase to 1.2 billion (World Health Organization, 1996). 25% to 50% of women during menopause have sleep difficulties compared to 15% of the general population (Shaver et al., 1998). Given that women experience a marked change in hormone levels, it is imperative to determine whether there are any significant differences in sleep during menopause compared to other women of similar age who have not become menopausal, as well as men. Menopause is defined as one year after the cessation of menstruation (Nowakowski et al., 2009; Moline et al., 2003). The group of women who have stopped menstruating for over a year is termed as post-menopausal or menopausal, interchangeably. However, hormonal changes and the decline in ovarian functions start several years before menopause. Some studies termed the transition period as peri-menopausal (Young et al., 2003; Rannevic et al., 2008). Other

studies generally defined the group of women who have not ceased to menstruate for over a year as premenopausal (Bixler et al., 2001; Lindheim et al., 1992). Menopause is caused mainly by the decrease of the production of certain sex hormones by the ovaries such as oestrogen and progesterone which are responsible for reproduction and sexual behaviours, at an average age of 51 (Al-Azzawi & Palacios, 2009). On the other hand, testosterone levels in healthy men decreases steadily as they age, there is no sudden disruption of production of testosterone in men to match the impact of the menopause in women (Harman and Tsitouras, 1980; Sparrow et al., 1980).

Disruption in the production of oestrogen and progesterone is associated with a range of menopausal related symptoms such as hot flushes, mood changes, and insomnia, which is indirectly related to a range of sleep complaints (Moline et al., 2003; Kripke et al., 2001). Oestrogen plays an important role in the regulation of sleep. It helps to decrease sleep latency, reduce the number of awakenings after falling asleep, and lengthen total sleep time (Nowakowski et al., 2009; Thomson and Oswald, 1977). It also plays an important role in temperature regulation (Charkoudian and Stachenfeld, 2014; Dacks and Rance, 2010). Thus, it is possible that reduction in Oestrogen results in the occurrence of hot flushes which in turn causes sleep disruption. Progesterone has direct sedative effects which help to regulate sleep (Caufriez et al, 2011; Anderson et al., 2006). It also regulates breathing (Behan and Wenninger, 2008; Bayliss et al., 1987). A reduction in progesterone may lead to obstructive sleep apnea (OSA) which is caused by breathing difficulty during sleep (Empson & Purdie, 1999). One way to test whether the reductions in hormones indeed cause sleep disruptions in menopausal women is to investigate whether hormone replacement therapy (HRT) alleviates the disruptions. Studies have found that HRT reduced hot flushes (Polo-Kantola et al., 1999; Anarte et al., 1998; Holst et al., 1989), alleviated depressive symptoms (Ditkoff et al., 1991) and lessened sleep complaints (Antonijevic et al., 2000; Polo-Kantola et al., 1999). Other studies that combined subjective reports and Polysomnography (PSG)

found that Oestrogen therapy decreased sleep onset latency, reduced the number of awakenings during sleep and improved REM sleep (Schiff et al., 1979; Thomson & Oswald, 1977). Furthermore, statistically more OSA was found in post-menopausal than pre-menopausal women, and HRT in post-menopausal women eliminated this difference (Bixler et al., 2001). Thus, restoring ovarian hormone level is effective in alleviating sleep related problems as well as menopausal related symptoms. Nevertheless, the relationship between these hormones and sleep is complicated and it remains a significant gap in our knowledge, but a marked reduction in the ovarian hormones clearly disrupts sleep in many ways.

Currently, the findings of gender differences are mixed. This may be due to small sample sizes, the use of different study designs as well as variabilities in the populations (Mong and Cusmano, 2016). However, some differences have been consistently observed across different study designs. Women have been found to have better sleep quality than men as measured by PSG (Bixler et al., 2009; Goel et al., 2005; Voderholzer et al., 2003; Dijk et al., 1989). In a PSG study of 31 young adults, Goel and colleagues (2005) found that women had better sleep efficiency, longer sleep duration, shorter duration for awakenings during a night sleep, and shorter sleep onset latency (SOL). SOL is the period between trying to fall asleep and actually falling asleep. These findings were also observed in a large cross-sectional analysis of PSG studies, the average age of participants was 62, women had better sleep efficiency, higher percentage of SWS and REM sleep, and smaller percentage of N1 and N2 sleep compared to men (Redline et al., 2004). A number of other studies consistently found that women spent a higher percentage of time in SWS than lighter sleep stages when compared to men, which indicates that sleep intensity in women is generally better and less affected by aging than men (Latta et al., 2005; Ehlers and Kupfer, 1997; Mourtazaev et al., 1995). Paradoxically, subjective reports of sleep quality are the opposite of objective measurements. Women of different ages reported more disrupted

and insufficient sleep than men including poor sleep quality, difficulty in falling asleep and longer duration of wake after sleep onset (WASO, Zhang et al., 2006; Groeger et al., 2004; Lindberg et al., 1997; Reyner et al., 1995). The reason behind this disparity is not clear. One possible contributing factor is the desynchronization between circadian timing and sleep time. Retrospective analysis of CTS of both and women and men found that women have an earlier circadian rhythm measured by melatonin secretion level and body temperature (Cain et al., 2010) and a shorter circadian period (Duffy et al., 2011) than men. Their sleep time might have followed more closely to their male partners instead of their natural circadian timing, and this desynchronization may lead to poorer subjective sleep quality.

Existing literature on sleep and menopause is small and has used subjective reports and objective measures using PSG or actigraphy to assess sleep disturbances. Studies of subjective reports of sleep found that menopausal women had poorer sleep than premenopausal women (Freeman et al., 2015; Hung et al., 2014; Cheng et al., 2008; Ballinger, 1976). Also, higher menopausal symptoms were associated with poorer sleep quality. For example, psychological symptoms such as depression were found to be associated with difficulty initiating sleep and waking up earlier than desired (Vousoura et al., 2015), sleep fragmentation (Woods and Mitchell, 2010), and lower global sleep quality (Regestein, 2004), whereas vasomotor symptoms such as hot flushes were associated with sleep fragmentation (Vousoura et al., 2015; Woods and Mitchell, 2010; Ensrud et al., 2009) and lower global sleep quality (Pien et al., 2008; Regestein, 2004). An early survey of 539 female subjects between the age of 42 to 50 years old, post-menopausal women reported greater difficulty in falling and staying asleep compared to peri- and pre-menopausal women (Ballinger, 1976). Another study examined 521 menopausal women of the same age range and found that 42% of them reported some types of sleep disturbance, and after three years of follow-up, premenopausal women who became menopausal reported significant increase in

sleep disturbances (Owens & Mattews, 1998). More recently, Chedraui and colleagues (2010) investigated daytime sleepiness (Epworth Sleepiness Scale) in a group of women with an average age of 47.6 and found that menopausal status, as assessed by Menopause Rating Scale (MRS), is positively associated with daytime sleepiness, and is likely the result of night time sleep disturbances. Arakane and colleagues (2011) found a positive correlation between menopausal status (MRS) such as hot flushes severity and insomnia score (insomnia severity index). Monterrosa-Gastro and colleagues (2013) also found positive correlations between the scores of MRS somatic, psychological subscale, and insomnia scores (Athens Insomnia Score). A 14-year longitudinal study of middle aged women (Freeman et al., 2015) found that sleep quality during premenopausal period strongly predicted sleep quality during menopause, which means only poor premenopausal sleepers became poorer sleepers during menopause. Further, hot flushes were significantly related to sleep quality regardless of baseline sleep quality. Thus, post-menopausal women reported more sleep disturbance than peri- and pre-menopausal women, and the sleep disturbance is related to the severity of menopausal symptoms. However, these population-based studies did not exclude participants who may have health related issues such as obesity, anxiety, depression, or the use of HRT. It is unknown whether it is the natural decline in the production of oestradiol hormones that results in the worsening of sleep quality, or if it is the prevalence of other problems during menopause that affect sleep.

Other objective studies that used PSG to measure sleep architecture and sleep-wake cycle of menopausal women have yielded different results from self-reports (Hachul et al., 2015; Kalleinen et al., 2008; Young et al., 2003). Young and colleagues (2003) conducted a large epidemiologic study and found subjective report of poor sleep quality was moderately related to menopausal status, but objective PSG recording showed that menopausal women had more slow wave sleep (SWS) and longer total sleep duration than premenopausal women. SWS is an indicator of deep sleep as well as

good sleep quality, this study showed that menopausal women had better sleep quality than premenopausal women which contradicts the previous studies of subjective reports. A more recent study (Hachul et al., 2015) studied women between 20-80 years old and showed similar results, they found that menopausal women spent more time in slow wave sleep (SWS) and less time in REM sleep than premenopausal women. Another study also found that subjective sleep complaints were associated with menopausal status but there was no difference in PSG measures of objective sleep quality between pre-, peri- and post-menopausal women (Kalleinen et al., 2008). Thus, there is a discrepancy between subjective reports and objective measures of sleep between premenopausal and menopausal women. A number of limitations may render these studies less informative. First, they did not recruit age-matched participants. Younger women were grouped into pre-menopausal and older women were grouped into peri- and post-menopausal or menopausal. It has been established that sleep changes as we age (Lewis, 2013; Mokhlesi et al., 2012; Van et al., 2000), so we can only measure the effect of menopause on sleep independent of age with age-matched control groups. Also, there is no age-matched male participant group to assess for gender differences in any of these studies. As men do not go through a marked change in their hormone level, they would be a good control group. Moreover, the problem with PSG is that subjects have to be attached to the machine with EEG electrodes that restrict some movements and usually allow recording for not more than 24 hours. It is a great way to study the sleep architecture, for example, the amount of SWS versus REM sleep. However, a 24-hours recording does not provide enough data to determine the sleep-wake cycle and sleep quality of the subjects over more ecologically relevant time courses and conditions.

On the other hand, actigraphy has an advantage over PSG in continuous recording 24 hours a day for several days, weeks or even longer. It is also deemed as more cost effective (Sadeh et al., 1995). It is a watch-like device that is generally worn on the

wrist to detect wrist movement. It is based on the observation that there are more wrist movements during wakefulness and less during sleep. Actigraphy has been validated as a reliable objective method in measuring sleep-wake patterns as well as sleep quality (Ancolo-Israel et al., 2003; Broughton et al., 1996; Teicher, 1995). It has been used to study insomnia (Chambers, 1994), disturbed sleep in children (Franck et al., 1999), healthy adults (Duka et al 1995), psychiatric patients (Dursum et al., 1999), older adults (Pollak et al., 1997), circadian rhythms (Pollak et al., 2001), and menopausal women (Kravits et al., 2015; Baker et al., 1997). However, only one actigraphy study (Baker et al., 1997) has been conducted for continuous recording of the daily activities of premenopausal and menopausal women for several days to determine the sleep-wake pattern and sleep quality of these women. This study grouped premenopausal and menopausal women based on menopausal symptoms experienced by the women. Women who had higher menopausal symptoms based on Oestrogen Level Assessment Questionnaire (OLA) experienced more frequent and longer night time arousals than women with lower level of menopausal symptoms. Menopausal women also reported higher levels of anxiety and lower levels of vigour than premenopausal women. However, this study did not include an age-matched male control group, had a small sample group, and one week of recording may not be sufficient.

The current study aims to address the limitations of these previous studies by using ambulatory wrist actigraphy as an objective measure and a range of questionnaires and a sleep diary as subjective measures to investigate the sleep quality and sleep-wake cycle of menopausal women in their naturalistic settings. An age-matched male control group will also be recruited. This will provide the critical first step in understanding sleep changes in middle aged and menopausal women, as well as comparing sleep between genders. As mentioned earlier, as men generally have worse sleep quality, and sleep in menopausal women and age-matched premenopausal women becomes worse, we hypothesize that there will not be a significant difference

between groups for various sleep measures. However, quality of sleep is significantly correlated with the severity of menopausal symptoms.

2. Method

2.1. Ethics and Participants

The research protocol was approved by University College London (UCL) Institute of Cognitive Neuroscience (ICN) ethics committee. Written informed consent was obtained from each participant. A total of 57 participants between the ages of 42 to 59 were recruited. This includes 20 pre-menopausal women (mean age ± SD: 47.25 ± 4.13) who were still experiencing menstruation, 18 menopausal women (mean age ± SD: 54.50 ± 2.75) whose menstruation had ceased for at least one year and no longer than 5 years, and 19 men (mean age ± SD: 48.79 ± 5.09) as an age-matched control group. The age range of women during menopause has been established by prior studies (e.g. Moline et al., 2003; Owen and Matthews, 1998).

An initial telephone screen was carried out to determine the eligibility of the participants. The BMI cut-off point was 30. Women who have had their last menstruation more than five years ago were excluded. Women having Hormone Replacement Therapy (HRT) were excluded. Participants who were taking prescribed anti-depressant medication, or have a recent history of diagnosed depression or anxiety, or suffering from any clinical sleep disorder, or taking any medication that has an effect on sleep (e.g. melatonin) were excluded from the study. There were 28 participants who were excluded due to the above reasons, two did not turn up for the study after passing the telephone screen and one dropped out after a few days of wearing the actiwatch due to skin irritation.

2.2. Measures

A range of questionnaires were used for baseline measure of sleep. Pittsburgh Sleep Quality Index (PSQI, Buysse et al., 1989) was used to assess sleep quality for the past month. Epworth Sleepiness Scale (ESS, Johns, 1991) was used to assess day-time sleepiness. Horne-Osberg Morningness-Eveningness questionnaire was used to assess whether a participant falls into a morning person chronotype or evening person chronotype (Horne & Osberg, 1976). The Menopausal Rating Scale (MRS, Schneider et al., 2000) was used to measure their symptoms or complaints associated with menopause. The Positive and Negative Affect Scale (PNAS, Watson et al., 1988) was used to measure their mood.

Karolinska Sleep Diary (KSD, Akerstedt et al., 1994) and the Karolinska Sleepiness Scale (KSS, Kaida et al., 2006) were used to record subjective measures of sleep quality, sleep-wake pattern and level of alertness before bed and upon awakening for 14 days.

Wrist actigraphy was measured by GENEActive Standard Device (Activeinsight Ltd), which continuously recorded wrist movement from the non-dominant wrist and exposure to lighting for 14 days.

2.3. Procedures

Eligible subjects were invited to UCL ICN to fill in the baseline questionnaires. On the same day, an actiwatch was configured for each participant to wear on his or her non-dominant wrist throughout the following two weeks while filling in a daily KSD and KSS at the participant's own environment (e.g. home). As the device is water-proof, participants were instructed to try not to take off the actiwatch at any time and fill in a daily form to indicate the times and durations when they were not wearing the actiwatches in an emergency. A daily text message reminder to fill in KSD and KSS was sent every day at 6pm. For female subjects, they were required to fill in an

additional MRS on day 7 and day 14, additional text reminders were sent on those days. After two weeks, Subjects returned the actiwatches, KSS, and KSD to UCL ICN and received a formal debrief.

2.4. Statistical Analysis

2.4.1. Baseline and demographic data

Premenopausal, menopausal and male subjects' demographic and baseline sleep characteristics were analysed using IBM SPSS Statistics (Version 22.0) one-way unrelated ANOVA, If Levene's test of homogeneity of variance is violated, non-parametric tests (Wilcoxon) were conducted.

2.4.2. Assessment of rest-activity variables from actigraphy data

Raw data were first extracted using GENEActive software, and were converted with 60s epoch. All non-parametric analyses were conducted using 'nparACT' package for R (2.14.0, Blume, Santhi and Schabus, 2016). The parameters computed include interdaily stability (IS), intradaily variability (IV), the average activity of the ten consecutive hours with the highest activity level (M10), the average activity of the five consecutive hours with the lowest activity (L5), relative amplitude (RA), M10 start time, and L5 start time. These measures are widely used to determine sleep efficiency (Gonçalves et al., 2014; Oosterman et al., 2009; Van Someren et al., 1999). Daily values were first averaged across days for each participant. One-way unrelated analyses of variance (ANOVAs) were then conducted for comparisons between groups (premenopausal, menopausal and men).

Interdaily Stability (IS)

IS measures how well the rest-activity rhythm is synchronised with 24-hour zeitgebers, which are environmental cues such as light that entrains our biological rhythms to the earth's 24 hour light-dark cycle. It ranges from 0 to 1, the higher the number the better

the synchronisation. Studies have shown that IS is a good measure of sleep quality, as it is associated with less sleep fragmentation (Bromundt et al., 2011; Witting et al., 1990). The computation formula is shown below

$$IS = \frac{n\sum_{h=1}^{p}(\overline{X}_h - \overline{X})^2}{p\sum_{i=1}^{n}(X_i - \overline{X})^2}$$

where n is the total number of data, p is the number of data per day, $\bar{x}_h$ are the hourly means, $\bar{x}$ is the grand average of all data, and x_i is the activity value from each data point.

Intradaily Variability (IV)

IV measure the fragmentation of the rest-activity rhythm, which can be caused by daytime naps due to daytime sleepiness as well as nocturnal arousals. IV has been found to be a good measure of sleep quality (Bromundt et al., 2011; Huang et al., 2002). It ranges from 0 to 1, the higher the number, the more fragmented the rest-activity rhythm is. The computation formula is shown below

$$IV = \frac{n\sum_{i=2}^{n}(X_i - X_{i-1})^2}{(n-1)\sum_{i=1}^{n}(X_i - \overline{X})^2}$$

where n is the total number of data and p is the number of data per day, X is the grand average of all data and Xi is the activity value from each data point.

Relative Amplitude (RA)

RA shows the relationship between M10 and L5. It can be calculated from the formula below:

$$RA = \frac{(M10 - L5)}{(M10 + L5)}$$

2.4.3. Assessment of sleep diary variables

Sleep diary variables were analysed using mixed model analysis for repeated measures (Brown and Prescott, 2015) with **SAS® 9.4** software, that allowed assessment of fixed effect, Group (premenopausal, menopausal and men), and Day type (weekday and weekends), controlled for random effects represented by each subject. Upon visual inspection of the residual plot for each variable, if a non-Gaussian distribution was found, transformations (e.g. log and Arcsine transformation) were applied to the dependent variables so that the residuals become normally distributed. 2 standard errors of the skewness and kurtosis parameters were selected as cut off points for normality (Tabachnick & Fidell, 2007).

2.4.4 Assessment of menopausal symptoms

The averages of the MRS scores were first obtained. A series of independent t-tests was conducted to see whether there were significant differences in the score of psychological, somatic, urogenital, or combined symptoms between menopausal and premenopausal women. Pearson's correlation tests were then used to examine the relationship between menopausal symptoms and actigraphy variables, and between menopausal symptoms and sleep diary variables (averaged for each subject). These analyses were done on IBM SPSS Statistics (Version 22.0).

3. Result

3.1. Demographic and baseline descriptive data (*table 1*)

The groups did not differ in the baseline measures of sleep variables and mood. However, menopausal women (mean ± SD: 54.5 ± 2.75) were significantly older than premenopausal women (mean ± SD: 47.25 ± 4.13), $p < .05$.

Table 1.

Baseline demographic and descriptive characteristics

Variable	premenopausal	menopausal	men	*F* (2, 53)	*p*
Daytime sleepiness	5.75 ± 3.42	7.33 ± 4.70	5.89 ± 2.83	1.02	.37
Morningness-eveningness	54.75 ± 10.31	55.83 ± 9.33	51.22 ± 8.85	1.16	.32
Positive affect	32.90 ± 7.99	31.22 ± 8.20	34.89 ± 6.95	1.01	.37
Negative affect	17.50 ± 8.21	20.50 ± 7.43	16.94 ± 7.60	1.10	.34
Sleep quality (past month)	4.70 ± 2.43	7.06 ± 3.95	5.56 ± 2.62	2.87	.07
Age	47.25 ± 4.13	54.5 ± 2.75	49.11 ± 5.04	15.83	.00**

Table 1 summarizes the baseline descriptive and demographic data from questionnaires, which revealed that there was no significant difference between groups for daytime sleepiness, morningness-eveningness, positive affect, negative affect, and sleep quality. However, there was a significant difference between groups for age**,** F (2, 53) = 15.83, p < .05. Post hoc analyses using Tukey's HSD test indicate that menopausal women (mean ± SD: 54.5 ± 2.75) were significantly older than premenopausal women (mean ± SD: 47.25 ± 4.13) p < .05.

3.2. Actigraphy data (*Table 2*)

IS, IV, M10, L5, RA, M10 start time, and L5 start time were first obtained for each subject, then a series of one way unrelated ANOVAs were conducted. A summary of the means, standard deviations, degree of freedom, F statistic, and p values for variables IS, IV, M10, L5, RA, M10 start time, and L5 start time of the three groups (premenopausal, menopausal and men) is shown in table 2. Of note, men (mean ± SD: 57.42 ± 17.03) had a near significant higher level of activity during L5 than menopausal women (mean ± SD: 44.77 ± 11.42), p = .055.

Table 2.

One-way between-subject ANOVA results for actigraphy data

Analysis method	premenopausal	menopausal	men	*F* (2, 53)	*p*
IS	0.23 ± 0.05	0.22 ± 0.05	0.20 ± 0.06	1.61	.21
IV	0.37 ± 0.87	0.37 ± 0.80	0.36 ± 0.28	0.09	.91
M10	227.78 ± 48.51	208.79 ± 54.38	228.99 ± 84.79	0.57	.57
L5	49.67 ± 17.01	44.77 ± 11.42	57.42 ± 17.03	3.07	.055
RA	0.65 ± 0.08	0.59 ± 0.19	0.59 ± 0.10	1.25	.30
M10 start time	8:41 ± 1:15	9:22 ± 1.35	9.32 ± 2.17	1.25	.29
L5 start time	3:35 ± 6:54	1:19 ± 1:13	4:11 ± 6:35	1.32	.28

Table 2 summarizes the findings from the actigraphy data, which revealed that there was no significant difference between groups for **IS**, **IV**, **M10**, **RA**, **M10 start time**, and **L5 start time**. However, there was a near significant difference between groups for **L5** F (2, 53) = 3.07, p = .055. Post hoc analyses using Tukey's HSD test indicate that men (mean ± SD: 57.42 ± 17.03) had higher activity level during the 5 consecutive hours in a day with the least activity than menopausal women (mean ± SD: 44.77 ± 11.42) p = .055.

3.3. Sleep Diary analysis (*Table 3-5*, and *Figure 1*)

Mixed model analyses were conducted for sleep diary variables. There was no significant difference between groups. Of note, wake time (p = .05), WASO (p < .05), and number of awakenings (p < .05) were significantly different between weekdays and weekends. Wake time (min from 0700) was near significantly earlier during the weekdays (mean ± SD: 37.87 ± 102.55) than weekends (mean ± SD: 56.15 ± 95.56). WASO (min) was significantly shorter during weekdays (mean ± SD: 19.04 ± 38.2) than weekends (mean ± SD: 22.07 ± 38.1). Number of awakenings were significantly lower during the weekdays (mean ± SD: 1.13 ± 1.14) than weekends (mean ± SD: 1.27 ± 1.18). There was also a significant interaction effect between group and day type for time spent in bed (min) (p < .05), Men spent significantly more time in bed during the weekdays than weekends, whereas menopausal and premenopausal women spent significantly more time in bed during the weekends than weekdays.

Table 3.

Sleep diary variables estimated from mixed models.[a.b]

Variables	Group (3)			Daytype (2)			Daytype*Group		
	Den DF	F Value	*p* value	Den DF	F Value	*p* value	Den DF	F Value	*p* value
Bed time (min from midnight)	49.8	2.97	0.06	50.2	3.01	0.09	50.2	0.91	0.41
Wake time (min from 0700)	49.6	2.22	0.12	49.6	3.87	=0.05	49.6	1.68	0.20
SOL (min)[c]	49.7	1.72	0.19	50.1	1.28	0.26	50.1	0.92	0.41
Time spent in bed (min)	49.9	1.50	0.23	50.2	1.47	0.23	50.2	3.58	0.035*
Total sleep time (min)	50.1	1.27	0.29	50.3	0.06	0.81	50.3	1.71	0.19
Sleep efficiency (%)[d]	50.3	1.89	0.16	50.6	3.56	0.06	50.6	0.24	0.79
WASO (min)[c]	56.8	0.21	0.81	676	6.36	0.01*	676	0.32	0.72
Sleep quality[e]	50	1.60	0.21	50.5	2.77	0.10	50.5	1.72	0.19
Number of awakenings	48.4	0.01	0.99	675	5.07	0.02*	675	0.77	0.46
KSS evening	50.1	1.60	0.21	49.8	0.00	0.99	49.8	0.40	0.67
KSS morning	50	2.90	0.06	50.4	1.96	0.17	50.4	1.77	0.18

Table 3 summarises the results of sleep diary variables from mixed model analysis.
a. variables in original units.
b. values based on two weeks of data collection
c. log (x+1) transformation used for statistics
d. Arcsine transformation used for statistics
e. higher values indicate worse sleep quality

Table 4.

Descriptive statistics for sleep diary variables between weekday and weekends.

	Weekday		Weekend	
Variables	Mean	Standard deviation	Mean	Standard deviation
Bed time (min from midnight)	-23.41	95.04	-10.32	94.83
Wake time (min from 0700)	37.87	102.55	56.15	95.56
SOL (min)	17.56	25.39	17.51	27.22
Time spent in bed (min)	489.67	93.09	500.49	96.62
Total sleep time (min)	425.01	98.79	428.29	99.21
Sleep efficiency (%)	87	12	86	12
WASO (min)	19.04	38.2	22.07	38.1
Sleep Quality[a]	4.71	1.75	4.49	1.62
Number of awakenings	1.13	1.14	1.27	1.18
KSS evening	6.07	1.94	6.05	1.96
KSS morning	5.27	1.89	5.11	1.75

Table 4 summarises the means and SDs of sleep diary variables between weekdays and weekends.

a. higher values indicate worse sleep quality

Table 5.

Descriptive statistics for sleep diary variables between groups

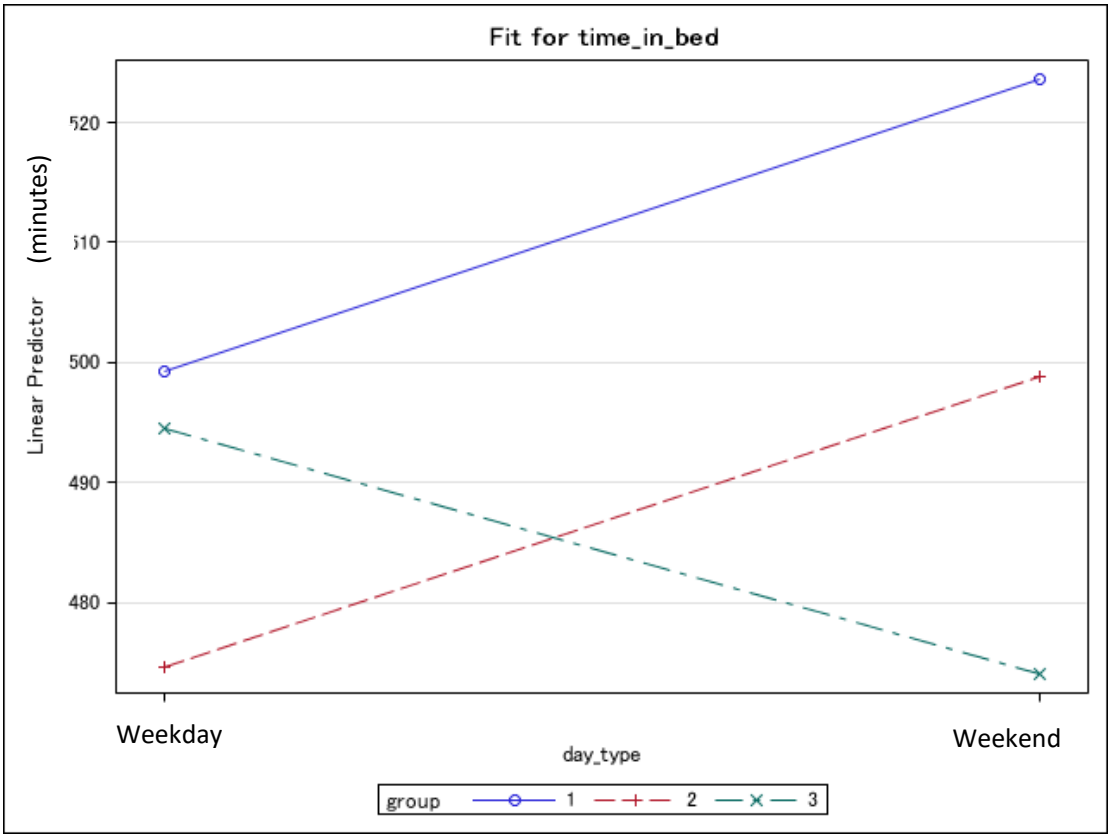
	Premenopausal women		menopausal women		men	
Variables	Mean	SD	Mean	SD	Mean	SD
Bed time (min from midnight)	-44.7	83.44	-18.64	75.5	11	116.94
Wake time (min from 0700)	33.95	94.78	31.51	93.15	67.73	112.12
SOL (min)	14.62	20.48	18.44	34.34	20.29	20.56
Time spent in bed (min)	505.8	100.86	481.56	79.22	488.58	98.83
Total sleep time (min)	451.51	99.59	407.59	76.68	413.61	112.21
Sleep efficiency (%)	89	9	85	12	84	15
WASO (min)	16.24	29.78	20.23	36.58	24.24	47.85
Sleep Quality[a]	4.7	1.68	4.77	1.85	4.44	1.61
Number of awakenings	1.16	1.12	1.31	1.17	1.02	1.17
KSS evening	6.07	1.83	6.68	1.67	5.39	2.14
KSS morning	5.08	1.63	5.73	2.01	4.85	1.81

Table 5 summarises the means and SDs of sleep diary variables between groups.

a. higher values indicate worse sleep quality

Figure 1.

Interaction between group and day type.



Group 1 (premenopausal), 2 (menopausal) and 3 (men).

Figure 1 –Post-hoc analysis of the group by day type interaction effect using Tukey-Kramer shows that men spent less time (min) in bed during the weekends (mean ± SD: 474.02 ± 83.52) than weekdays (mean ± SD: 494.67 ± 104.22) whereas menopausal and premenopausal women spent more time (min) in bed during the weekends (mean ± SD: 498.78 ± 90.72; 523.41 ± 106.39) than weekdays (mean ± SD: 474.67 ± 73.29; 498.74 ± 97.94).

3.4. Menopausal symptoms (*Table 6*, *Figure 2-8*)

Independent t-tests revealed that menopausal women reported significant higher levels of somatic symptoms (mean ± SD: 4.63 ± 2.31) than premenopausal women (mean ± SD: 3.05 ± 2.42), $t(36) = -2.05$, $p < 0.05$, higher level of urogenital symptoms (mean ± SD: 4.55 ± 3.05) than premenopausal women (mean ± SD: 1.47 ± 2.03), $t(29.11) = -3.63$, $p < 0.05$, and higher levels of combined symptoms (mean ± SD: 13.76 ± 7.40) than premenopausal women (mean ± SD: 7.65 ± 6.05), $t(36) = -2.80$, $p < 0.05$ (see Figure 2).

Figure 2.

Severity of menopausal symptoms

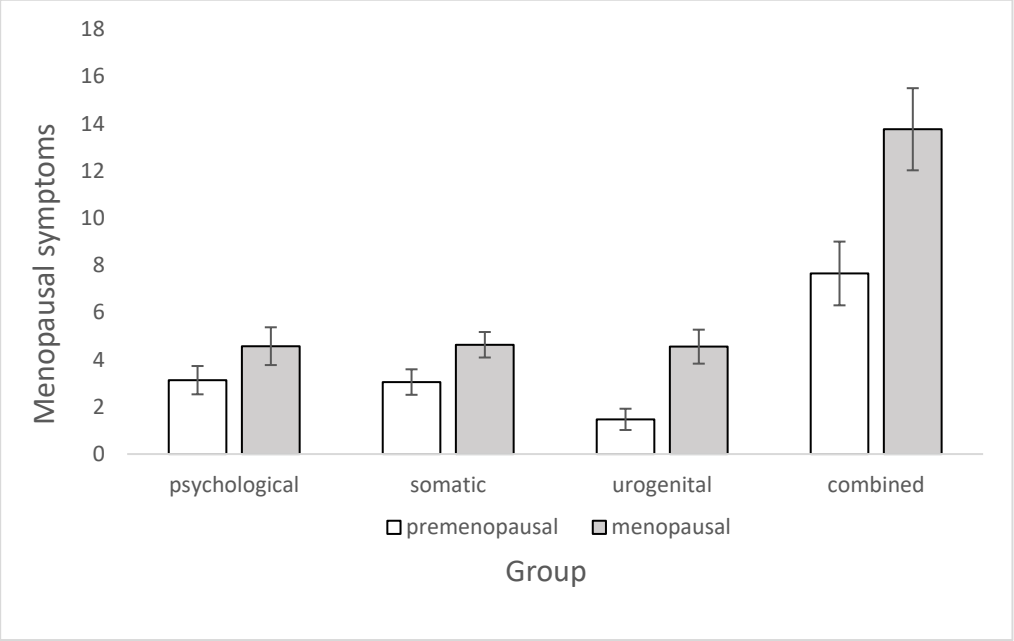


Figure 2 shows reported menopausal symptoms between premenopausal and menopausal women.

A series of correlation analyses was run, between menopausal symptoms and actigraphy and sleep diary sleep variables (see Table 6-7).

Table 6.

Correlations between MRS variables and actigraphy variables.

MRS variables	actigraphy variables	n	*r* value	*p* value
Psychological symptoms	IS	38	-.08	.63
	IV	38	.15	.36
	M10	38	-.09	.59
	L5	38	-.18	.28
	RA	38	.15	.37
	L5 start time	38	-.13	.45
	M10 start time	38	.01	.97
Somatic symptoms	IS	38	.06	.74
	IV	38	.04	.83
	M10	38	-.25	.14
	L5	38	-.33	.04*
	RA	38	.10	.55
	L5 start time	38	-.27	.10
	M10 start time	38	.02	.93
Urogenital symptoms	IS	38	- .04	.80
	IV	38	.01	.96
	M10	38	-.21	.20
	L5	38	-.28	.09
	RA	38	.10	.55
	L5 start time	38	-.14	.40
	M10 start time	38	.14	.40
Combined symptoms	IS	38	- .03	.85
	IV	38	.07	.66
	M10	38	-.21	.21
	L5	38	-.30	.07
	RA	38	.15	.36
	L5 start time	38	-.20	.22
	M10 start time	38	.07	.70

Table 6 summarises the correlations between MRS variables and actigraphy variables.

There was a significant negative correlation between somatic symptoms and L5 (r = -.33, N = 37, p < .05, two-tailed), 11 % of variance was explained. The scatter plot (Figure 3) shows that data points are reasonably well distributed along the regression line, in a linear manner with some outliers.

Figure 3.

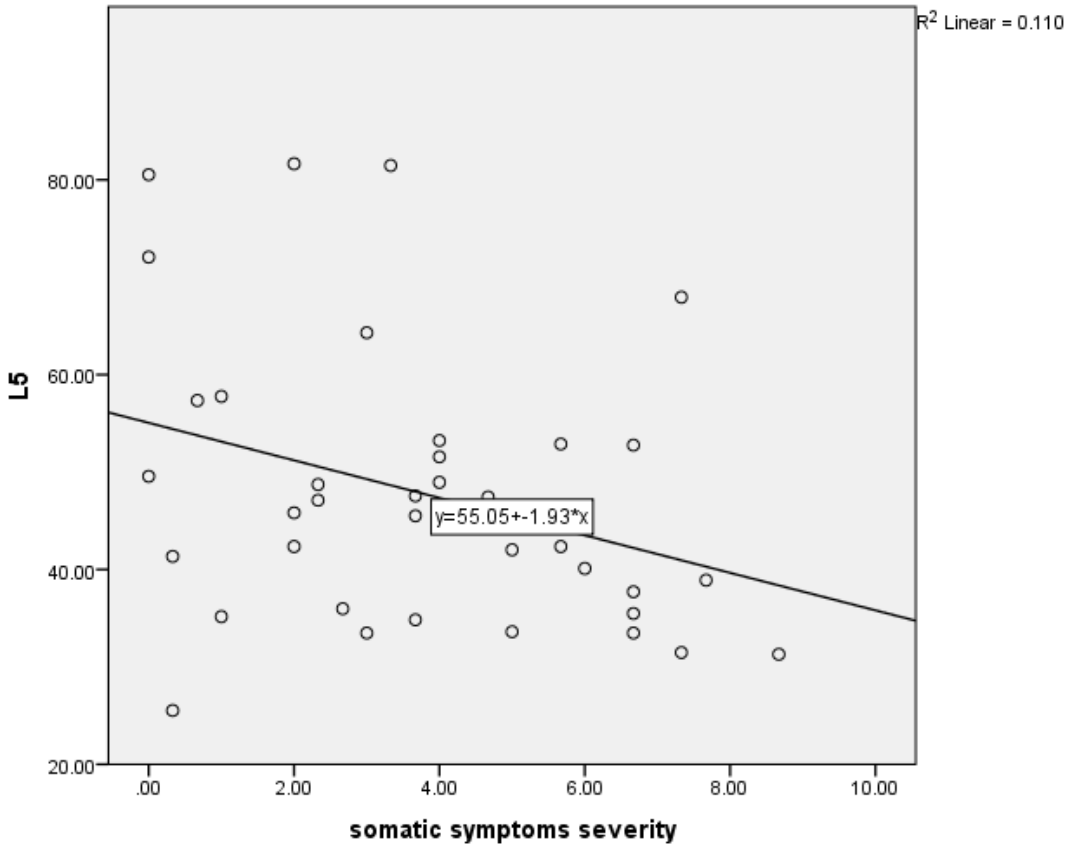


Figure 3. Somatic symptom severity plotted against L5.

Table 7.

Correlations between MRS variables and sleep diary variables.

MRS Variables	Sleep diary variables	n	*r* value	*p* value
Psychological symptoms	Bed time	37	.01	.95
	Wake time	37	-.08	.62
	SOL	37	.04	.80
	Sleep quality[a]	37	.32	.051
	Sleep efficiency (%)	37	-.14	.41
	Time in bed (min)	37	-.26	.12
	Total sleep time (min)	37	-.32	.06
	WASO (min)	37	.07	.67
	Number of awakenings	37	.34	.04*
	KSS evening	37	-.02	.89
	KSS morning	37	.12	.47
Somatic symptoms	Bed time	37	.07	.67

	Wake time	37	-.17	.30
	SOL	37	.17	.33
	Sleep quality[a]	37	.25	.13
	Sleep efficiency (%)	37	-.37	.03*
	Time in bed (min)	37	-.12	.50
	Total sleep time (min)	37	-.31	.06
	WASO (min)	37	.30	.07
	Number of awakenings	37	.40	.02*
	KSS evening	37	-.22	.18
	KSS morning	37	.16	.35
Urogenital symptoms	Bed time	37	.05	.76
	Wake time	37	.03	.84
	SOL	37	.02	.89
	Sleep quality[a]	37	.22	.19
	Sleep efficiency (%)	37	-.23	.18
	Time in bed (min)	37	-.21	.22
	Total sleep time (min)	37	-.31	.06
	WASO (min)	37	.17	.33
	Number of awakenings	37	.32	.06
	KSS evening	37	.04	.80
	KSS morning	37	.25	.14
Combined symptoms	Bed time	37	.05	.77
	Wake time	37	-.08	.64
	SOL	37	.08	.62
	Sleep quality[a]	37	.31	.06
	Sleep efficiency (%)	37	-.27	.10
	Time in bed (min)	37	-.23	.17
	Total sleep time (min)	37	-.36	.03*
	WASO (min)	37	.20	.24
	Number of awakenings	37	.41	.01*
	KSS evening	37	.08	.63
	KSS morning	37	.20	.23

Table 7 summarises the correlations between MRS variables and sleep diary variables.

a. higher values indicate worse sleep quality

There was a near significant positive correlation between psychological symptoms and global sleep quality (r = - .37, N = 37, p = .05, two-tailed), 11% of variance explained. The scatter plot (Figure 4) shows that data points are reasonably distributed along the regression line, in a linear manner with some outliers.

Figure 4.

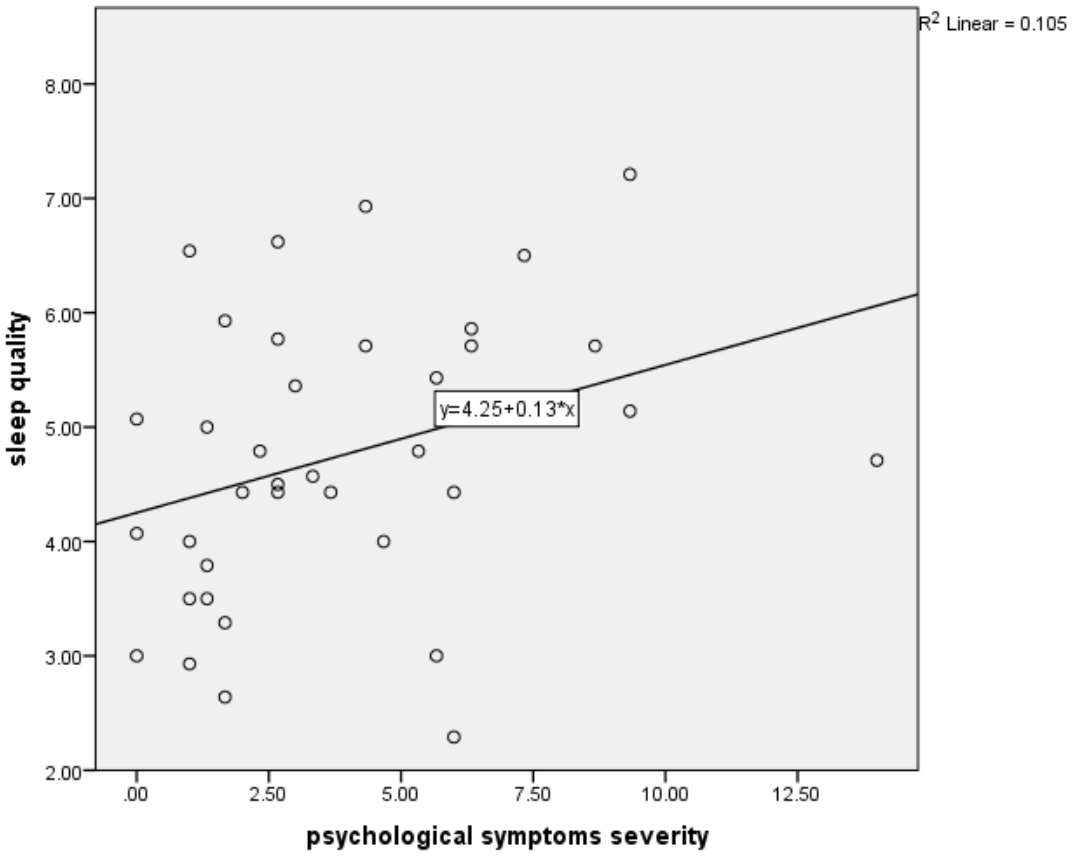


Figure 4 psychological symptom severity plotted against global sleep quality.

There was a significant positive correlation between psychological symptoms and number of awakenings (r = - .34, N = 37, p < .05, two-tailed), 12% of variance explained (figure 5).

Figure 5.

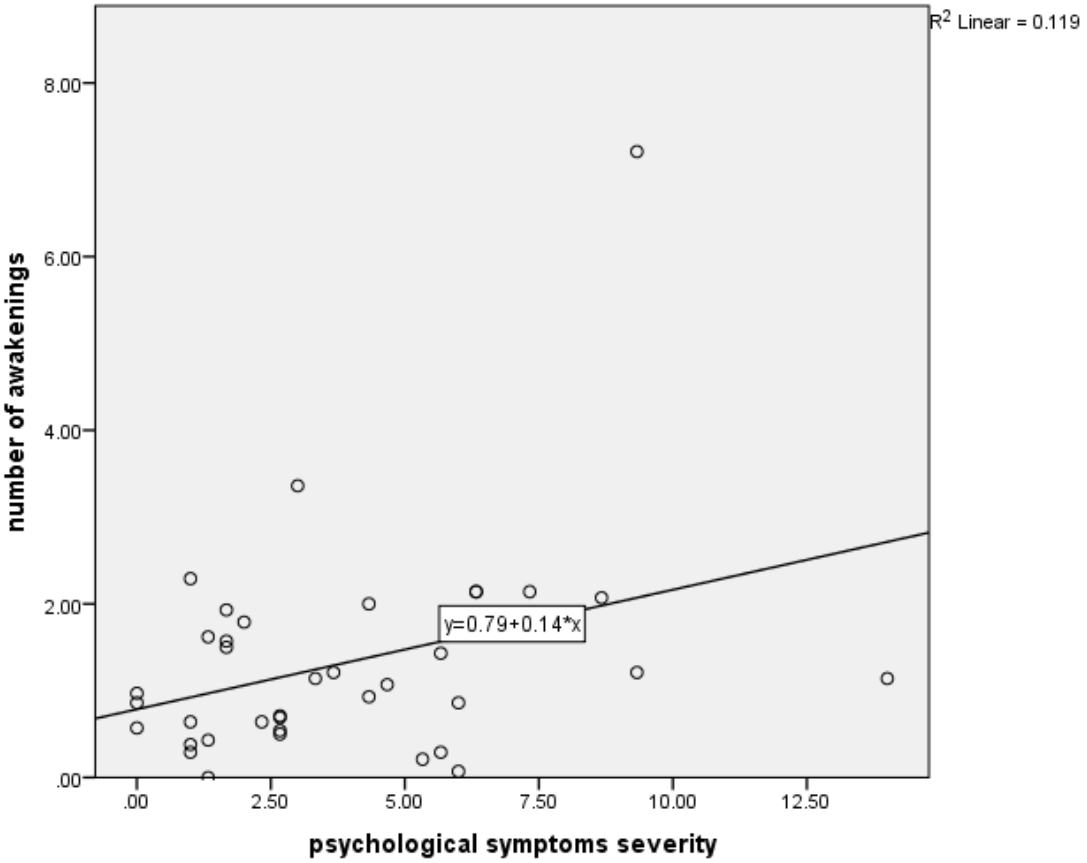


Figure 5 psychological symptom severity plotted against number of awakenings.

There was a significant negative correlation between somatic symptoms and sleep efficiency (r = - .368, N = 37, p < .05, two-tailed), 14 % of variance was explained (figure 6).

Figure 6.

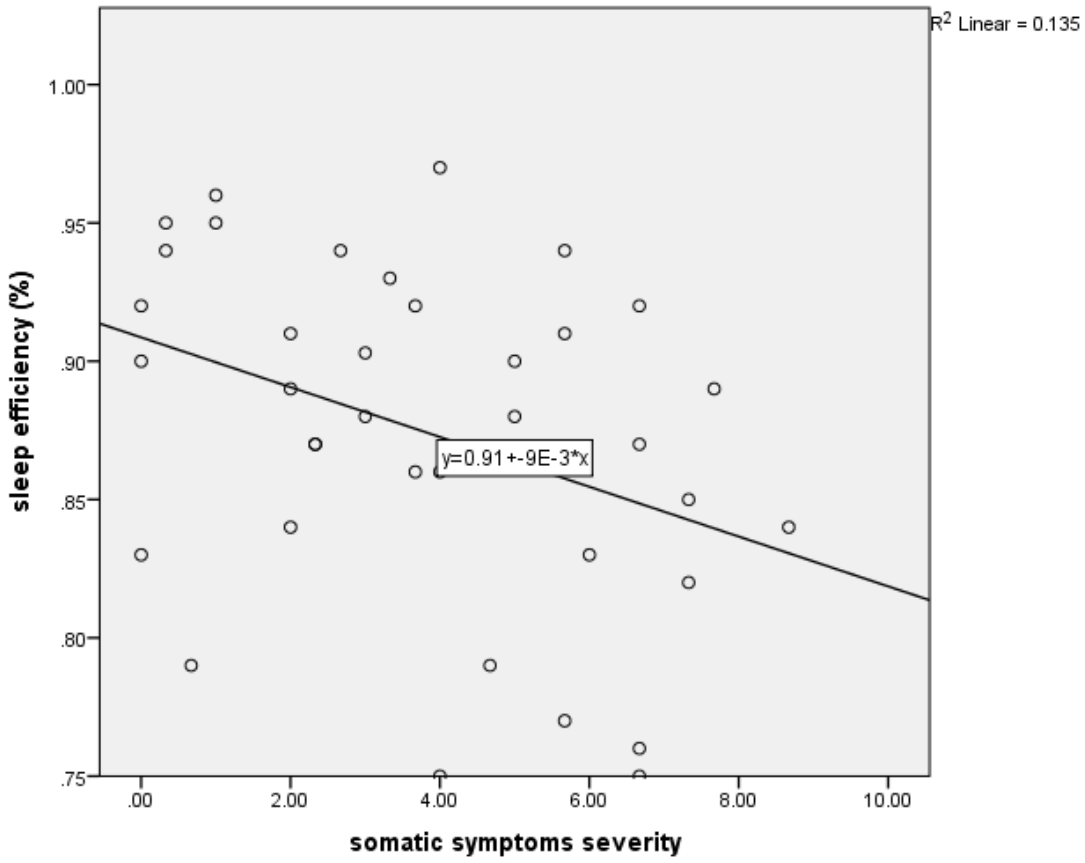


Figure 6 Somatic symptom severity plotted against sleep efficiency.

There was a significant positive correlation between somatic symptoms and number of awakenings (r = .40, N = 37, p < .05, two-tailed), 16 % of variance was explained (figure 7).

Figure 7.

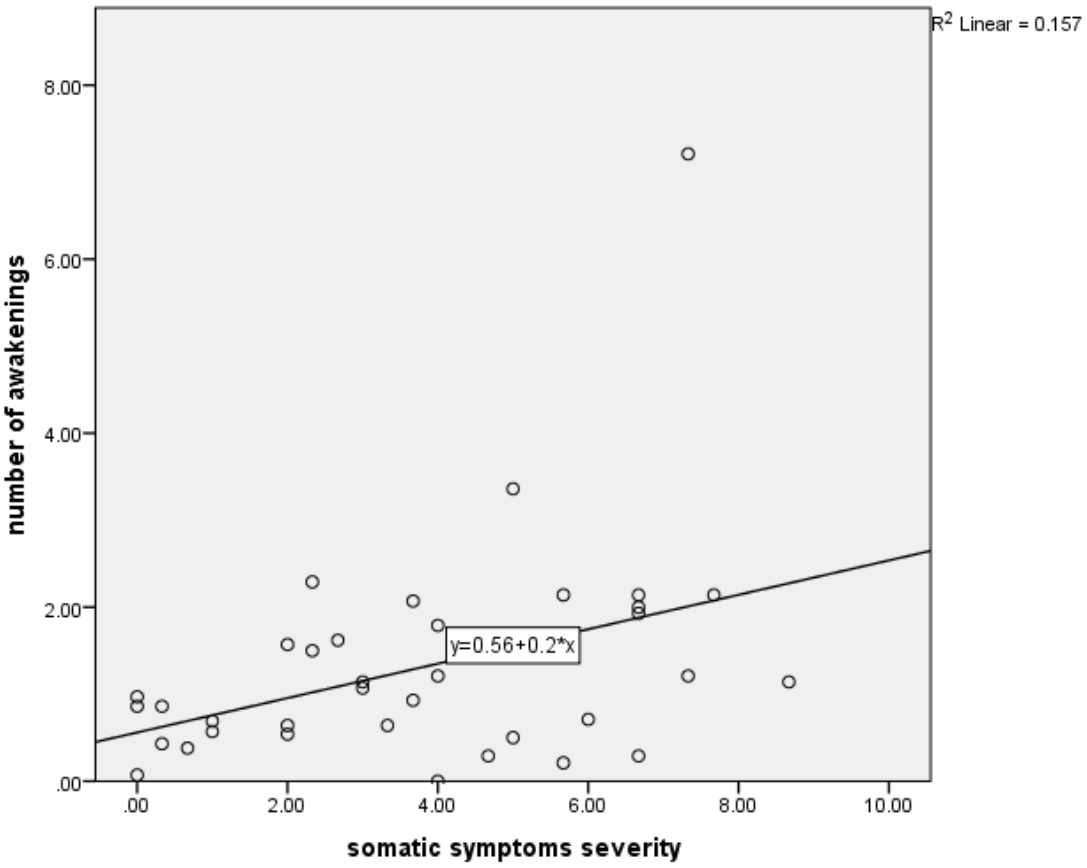


Figure 7 Somatic symptom severity plotted against number of awakenings.

There was a significant negative correlation between combined symptoms and total sleep time (r = -.360, N = 37, p < .05, two-tailed), 13 % of variance was explained (figure 8).

Figure 8.

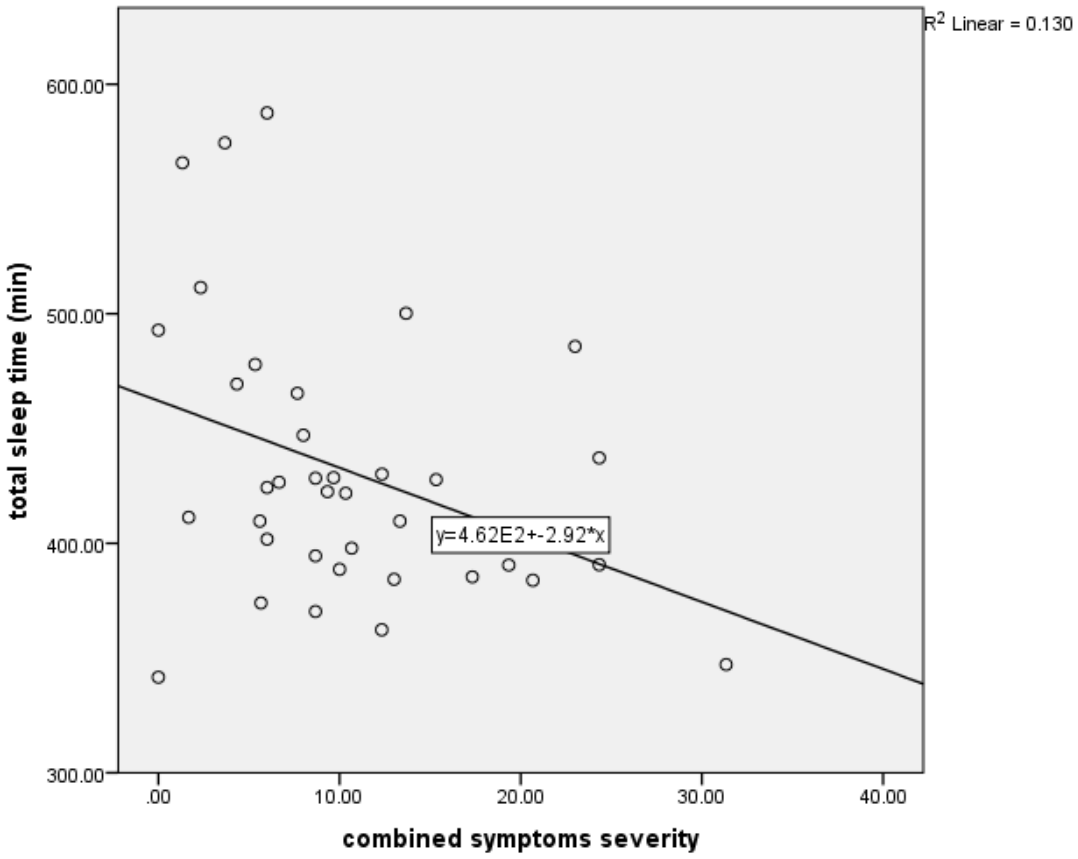


Figure 8 combined symptom severity plotted against total sleep time (min).

There was a significant positive correlation between combined symptoms and number of awakenings (r = -.406, N = 37, p < .05, two-tailed), 17 % of variance was explained (Figure 9).

Figure 9.

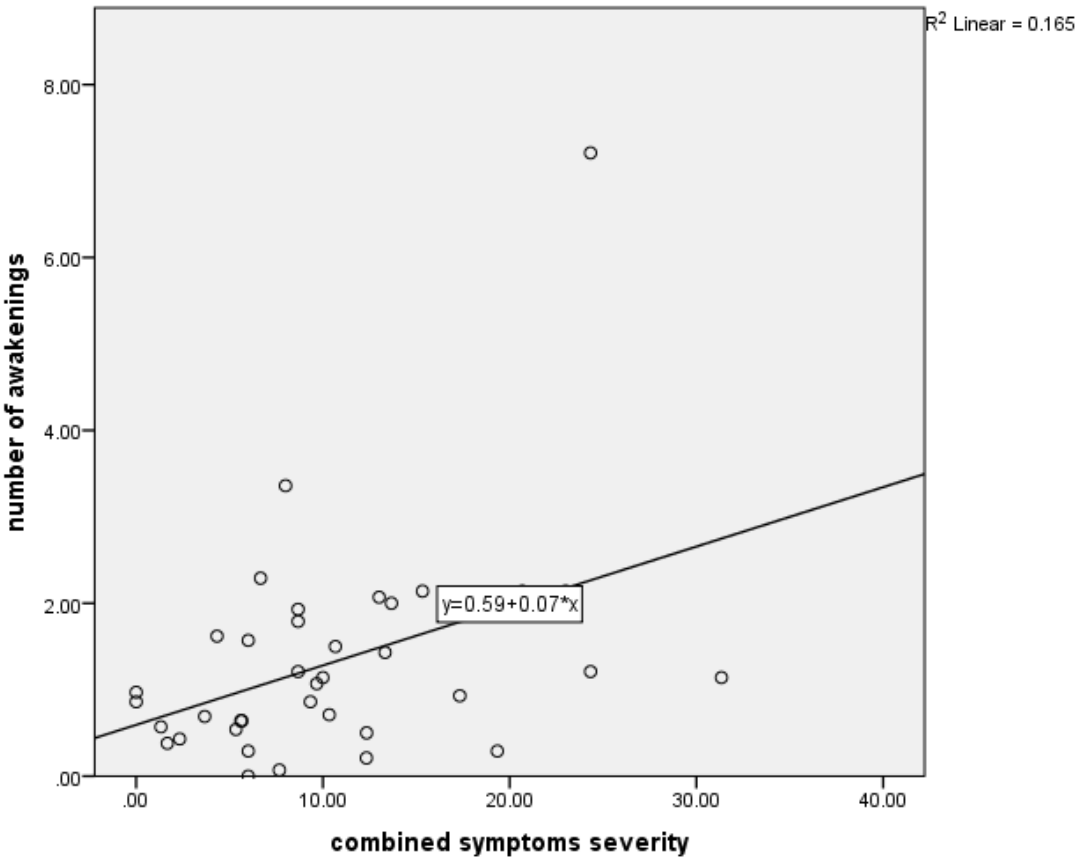


Figure 9 combined symptom severity plotted against number of awakenings.

4. Discussion

The results show that there is no significant difference between groups for various subjective and objective sleep measures. This supports my hypothesis that there is no difference in sleep quality between menopausal, age-matched premenopausal women and men in sleep. These results are in accordance with previous literature that used objective measures of sleep to compare gender differences, that men generally have

poorer sleep quality than women (Bixler et al., 2009; Goel et al., 2005; Voderholzer et al., 2003; Dijk et al., 1989), but the difference is diminished during menopause as menopausal women or women who exhibited menopausal symptoms reported a worsening of sleep quality (Freeman et al., 2015; Hung et al., 2014; Vousoura et al., 2015). As the premenopausal women are aged-matched with menopausal women and men, they are most likely experiencing menopausal related symptoms as well as a worsening of sleep. Contrary to the previous literature, this study is the first to have employed both subjective reports and objective measure (actigraphy) that compared sleep between age-matched menopausal, premenopausal women and men for two weeks, and yielded similar results.

However, there was a near significant difference between groups for L5 under actigraphy measures. Men exhibited higher activity levels during sleep than menopausal women but not premenopausal women. This means men had more restless sleep than menopausal women. Although no comparisons have been made between men and menopausal women previously, PSG studies have found that menopausal women spent more time in SWS and less in REM sleep than premenopausal women (Hachul et al., 2015; Young et al., 2003). This means, although menopausal women reported more sleep disruptions, they also experienced deeper and more restful sleep during the hours when they were asleep. This could be explained by Sleep homeostasis. Sleep pressure builds up as the duration of staying awake increases. As SWS is a standard marker for sleep homeostasis pressure, higher sleep pressure would result in longer SWS duration (Akerstedt et al., 1998; Dijk and Czeisler, 1995; Dijk et al., 1993; Feinberg, 1974). Also, sleep deprivation resulted in a bout of increases in the duration and intensity of SWS during subsequent recovery sleep (Jenni et al., 2005; Djik et al., 1993). SWS is known as the deepest sleep stage, characterised by large synchronisation of delta waves. Although there is no significant difference between groups for total sleep time, menopausal women had the least

amount of total sleep duration compared to the other two groups. Perhaps, it is our body's compensatory mechanism that attempts to induce deeper and more restful sleep when the total sleep duration is compromised due to sleep disruptions. Nevertheless, more research needs to be done to determine whether such mechanism is at work during menopause.

On the other hand, significant differences between weekdays and weekends for various sleep measures have been found. Duration of WASO was longer and there were more awakenings during the weekends than weekdays. The reason behind these results is unclear. It could be due to the consumption of alcohol or being disturbed by members of the family or noises on the street. Other studies have found the reverse result that sleep quality at the weekend was generally reported to be better than on weekdays (Groeger et al., 2004; 2002 Sleep in America Poll, National Sleep Foundation, 2003). More studies should look into possible reasons behind this disparity. There is a near significant difference for wake time. Weekend wake time is later than weekday. This could reflect "catching up" of sleep due to sleep deprivation as a result of sleep disruptions and the need to adhere to work schedules during the week (e.g. Valdes et al., 1996), or worse sleep quality during the weekend as reflected by longer WASO duration and greater number of awakenings. More interestingly, there was a significant interaction effect between group and day type for the amount of time spent in bed. Both premenopausal and menopausal women spent more time in bed during the weekends than weekdays, whereas men spent more time in bed during weekdays than weekends. Again, other studies have found contradicting results that women reported sleeping more during the weekdays than weekends (Groeger et al., 2004; 2002 Sleep in America Poll, National Sleep Foundation, 2003). Time in bed is different from total sleep time, it reflects time spent in inactivity or a lack of activity during sleep and wake. Perhaps, this is because women of this age group experience an increase in the feeling of fatigue due to sleep disruptions or other menopausal related problems

(Kong et al., 2008; Stein et al., 2000), hence they spend more time being less active when they have the opportunity to rest during the weekends, whereas men are not affected by menopause and hence spent less time resting in bed during the weekends.

Also, menopausal women reported more severe somatic, urogenital and combined menopausal symptoms than premenopausal women. Significant correlations have been found between the severity of menopausal symptoms and various sleep measures from the sleep diary reports and actigraphy. The level of severity for psychological symptoms including depressive mood, irritability, anxiety, and physical and mental exhaustion is positively correlated with the number of awakenings, and nearly negatively correlated with global sleep quality. This means the higher the severity of psychological symptoms, the more the number of awakenings and worse sleep quality. The level of severity for somatic symptoms including hot flushes, sweating, heart discomfort, and joint and muscular discomfort is negatively correlated with sleep efficiency and positively correlated with number of awakenings, as well as negatively related to L5 from the actigraphy data. This means the more severe the somatic symptoms the worse the sleep efficiency, the higher the number of awakenings, and less activity during the five consecutive hours with the least activity (sleep). The level of severity for combined symptoms including psychological, somatic and urogenital (sexual problems, bladder problems and dryness of vagina) symptoms is negatively correlated with total sleep time and positively correlated with the number of awakenings. This means the more severe the combined menopausal symptoms, the higher the number of awakenings and the less the time was spent sleeping. These results support our hypothesis that self-reported quality of sleep is significantly correlated with the severity of menopausal symptoms. They are consistent with previous literature that found higher psychological symptoms was associated with lower global sleep quality (Regestein, 2004) and higher sleep fragmentation (i.e. number of awakenings, Woods and Mitchell, 2010), higher somatic symptoms was

associated with higher sleep fragmentation (Vousoura et al., 2015; Woods and Mitchell, 2010; Ensrud et al., 2009) and worse sleep efficiency (Joffe et al., 2013). And combined menopausal symptoms was associated with a range of sleep related problems (Joffe et al., 2013). Sleep fragmentation is the number of awakenings during a night's sleep; sleep efficiency is the percentage of total sleep time in relation to total time spent in bed; and both measures affect sleep continuity. Subjective and objective studies have found that sleep continuity is one of the most important factors that determines good sleep quality (Słopień et al., 2015; Wilckens, 2014; Harvey et al., 2008; Åkerstedt et al., 1994; Zammit, 1988). Our results show that during menopause or the transition to menopause, a range of menopausal related symptoms, rather than menopausal status predicts worse sleep quality in women. Thus, intervention strategies to improve sleep quality for this population of women should be aimed at alleviating menopausal related symptoms which would indirectly improve sleep quality. As mentioned earlier, menopausal related symptoms are caused by the reduction of female hormones. Perhaps, more ways to help to restore ovarian hormone level should be investigated. On the other hand, higher somatic symptoms were related to lower L5, which means more restful sleep during the 5 hours of deepest sleep. Again, this could be our body's compensatory mechanism that tries to induce deeper sleep when sleep duration is compromised.

One thing to note is that although all subjects were age-matched, premenopausal women were significantly younger than menopausal women. But menopausal related problems could start years before the final cessation of menstruation (Young et al., 2003; Rannevic et al., 2008). This could explain why there is no significant difference in sleep quality between menopausal and premenopausal women, but correlations between sleep quality and menopausal symptoms were found. Perhaps, there is a need to raise more awareness of the sleeping problems that peri-menopausal women are facing, and the same approach to help alleviate sleep problems in menopausal

women can be used to help peri-menopausal women. No other baseline measures of sleep and mood difference was found between groups.

The main goal of this research was to obtain a baseline measure of sleep in middle aged and menopausal women since most research has been done on men (Ohayon et al., 2004), adolescents (Giannotti et al., 2002) and older people (Lewis, 2013). We cannot simply assume what applies to other demographic populations also applies to middle aged and menopausal women. For example, Boggio and colleagues (2010) explored the effects of tDCS on decision-making in older adults (over 60 years) and found that the positive effects of tDCS on decision-making is reversed in older people, although it is implicitly assumed in many papers that propose tDCS as a therapeutic intervention based on studies with younger subjects. Also, Scullin (2013) found that the positive association between SWS and memory consolidation found in younger people is not only absent but also reversed in older adults. Thus, the first step is to understand whether menopausal status or symptoms affect sleep quality and circadian rhythm of sleep. Other aspects of sleep in these women such as sleep architecture should then be explored. With the help of actigraphy, this study was able to obtain objective sleep quality measures and compare that with subjective self-report of sleep quality, and found that they exhibited similar results.

One problem with testing menopausal women is that there is a huge variation in individual differences of hormonal fluctuation, in both pre- and post-menopausal women (Chedraui and colleagues, 2010; Baker et al., 1997). If this study has to recruit women who do not have hormonal fluctuation associated with menopause to act as a control, much younger subjects have to be considered. However, age has a big influence on sleep, not only is the total sleep time reduced as we age, but also sleep architecture changes over time (Mander et al., 2017). The amount of SWS declines as we grow older and by the age of 74, there is almost no slow waves produced during sleep (Lewis, 2013; Mokhlesi et al., 2012; Van et al., 2000). Also, there is a phase delay

in adolescents and as people get older, their circadian phase shifts to the opposite direction (Giannotti et al., 2002; Laberg et al., 2001). Two measures have been taken to tackle this issue, one was to measure their menopausal symptoms and correlate them with various measures of sleep quality. Men were recruited as a hormonal control as they do not go through the profound hormonal changes associated with menopause. This is evident in studies that have found that androgen levels in men decline gradually with age (Harman et al., 2013; Feldman et al., 2013), unlike the erratic and sudden hormonal change in menopausal women.

In conclusion, this study aims to close two gaps in the literature. For one, longitudinal investigation on sleep quality of women experiencing menopause or the transition to menopause were employed by asking the subjects to wear the actiwatches for two weeks and compare it with subjective reports of sleep quality, and men were recruited as part of the control group. Secondly, we have found that menopausal related symptoms affect sleep, independent of age. Thus, this functional, descriptive study provide a critical first step in understanding sleep in middle aged and menopausal women.

Chapter 4: The effect of menopause on objective nap parameters and declarative memory performance

Abstract

Objective – There is an increase of both sleep and memory complaints during menopause. Few studies have investigated the nocturnal sleep architecture of women during menopause and no study has investigated the sleep architecture of menopausal women during a nap. In this experiment, I addressed the question of whether there is a difference in sleep architecture between premenopausal and menopausal women during a nap and whether the nap helps to improve declarative memory performance.

Methods - 16 premenopausal and 13 menopausal women between 42-59 years old participated in both nap and no nap sessions. The experiment assessed recall of the second word in 40 semantically related word pairs after napping or waking activity.

Results – Despite having near significantly longer duration of N2 sleep, menopausal women performed worse in the word recall than premenopausal women in both nap and no nap conditions.

Conclusion – These results demonstrate that the decline in memory performance during menopause is likely associated with poor memory encoding, rather than sleep-dependent memory consolidation. We suggest that decline in executive functions such as attention and working memory as a result of the reduction in ovarian hormone may affect memory encoding and retrieval in menopausal women.

1. Introduction

My previous chapter on menopause and sleep discussed the marked increase in sleep complaints amongst menopausal women compared to premenopausal women (Freeman et al., 2015; Hung et al., 2014; Cheng et al., 2008), and these sleep problems are associated with menopausal related symptoms (Freeman et al., 2015; Monterrosa-Gastro et al., 2013; Arakane et al., 2011). However, objective studies of sleep in menopause have gathered mixed findings. A large epidemiology study (Young et al., 2003), a cross sectional study (Hachul et al., 2015), and a prospective six-year follow-up study (Lampio et al., 2017) have found, contrary to subjective sleep complaints, that menopausal women had more slow wave sleep (SWS) than premenopausal women. As SWS is a marker for the deepest sleep stage, menopausal women seem to have better objective sleep quality than premenopausal women. On the other hand, some studies found no difference in other measures of sleep quality between menopausal and premenopausal women (Kalleinen et al., 2008; Freedman and Roehrs, 2004), while others found lower sleep efficiency (SE) in menopausal than premenopausal women (Xu et al., 2011) and in women experiencing menopausal vasomotor symptoms (Shaver et al., 1991, 1988). SE is a measure of sleep continuity. Lower SE means more awakenings during the middle of night and longer duration of these awakenings known as wake after sleep onset (WASO) or longer time to initiate sleep known as sleep onset latency (SOL). It seems that menopausal related symptoms lead to more awakenings, longer WASO and SOL, thus lower SE and more sleep complaints, whereas longer SWS could be a compensatory mechanism at work that tries to compensate for the lack of sleep continuity. Besides a night sleep, no study has investigated day time sleep in these groups of women. Napping often happens when a night sleep is disturbed. Although it is normal for babies to nap throughout the day, many people continue to take naps across the lifespan. A ‘Sleep in America’ survey found that 46% of respondents took naps at least twice in the last month, averaging 60 minutes for each

nap (National Sleep Foundation, 2008). The older we get, the more we nap (Picarsic et al., 2008; Ohayon and Zulley, 1999). Many studies found that napping is especially beneficial for a range of cognitive functions in people who are sleep-deprived (O'Connor et al., 2004; Song et al., 2002; Bonnet, 1991) and for shift workers (Purnell et al., 2002; Takahashi and Arito, 2000; Sallinen et al., 1998). However, to date, no study has investigated the sleep architecture of menopausal women during a nap. This gap in our knowledge has significant implications as napping could be adopted as an additional compensatory strategy for disrupted nocturnal sleep continuity.

Also, sleep plays an important and active role in memory consolidation (Ellenbogan et al., 2006; Smith, 2001; Plihal & Born, 1997), and a short nap has been found to be as effective as a full night's sleep to promote memory consolidation and learning (Seehagen et al., 2015; Lo et al., 2014; Lahl et al., 2008; Tucker et al., 2006; Mednick et al., 2003). For example, Lo and colleagues (2014) compared the effect of a daytime nap and nocturnal sleep on declarative memory consolidation and found that both a nap and nocturnal sleep improved unrelated word-pairs recall more than the wake condition for a similar time. Lahl and colleagues (2008) investigated memory performance of free recall of words between two groups of subjects, one group took a 60-minute nap and the other stayed awake for the same duration and found that memory performance was significantly better in the nap group. In order to test the effect of total sleep duration (TST) on memory consolidation, in their second experiment, they adopted repeated measures with three conditions (nap for 60 minutes, nap for 5 minutes and wake) and found that performance for both nap conditions were comparable and significantly better than the wake condition. In an earlier study, Mednick and colleagues (2003) found that an afternoon nap (60 minutes and 90 minutes) containing both SWS and rapid eye movement (REM) sleep led to sleep-dependent improvement in performance for a texture discrimination task, and the improvement was similar to that obtained after 8-hours nocturnal sleep. Furthermore,

different sleep stages have been found to selectively consolidate different types of memory. Tucker and colleagues (2006) investigated the effect of non-REM (NREM) sleep (predominantly SWS) during a nap by waking subjects at the onset of REM sleep and found that NREM sleep improved declarative but not procedural memory. Mednick and colleagues (2003) found nap containing both NREM and REM sleep rather than just NREM sleep helped to improve the texture discrimination task performance. Thus, REM sleep is especially important for procedural memory consolidation. Kurdziel and colleagues (2013) found 10 % more improvement in the spatial memory task after a nap compared to a wake condition, and this improvement is associated with sleep spindle density during N2 sleep. These results suggest that a nap could serve an equally important role in memory consolidation as nocturnal sleep.

On the other hand, menopause and the related decline in ovarian hormones also exert an influence on memory performance. There is a marked increase in memory related complaints during the menopausal transition period (perimenopause) and postmenopausal stage. In a large cross-sectional study of 16065 women between 40 to 55 years old, Women's Health Across the Nation (SWAN), 44% of perimenopausal and 41% of menopausal women reported memory complaints compared to 31% of premenopausal women (Gold et al., 2000). In the Seattle Midlife Women's Health Study, 62% of women reported memory decline during the transition to menopause, and they attributed memory changes to mostly old age, stress and health issues (Mitchell and Woods, 2001). In contrast, studies of objective memory performance have gathered mixed findings. A cross sectional study of 326 women found that there was no significant difference in episodic verbal memory using a supraspan word list recall task between different menopausal stages (early and late menopausal transitions, early and late post menopause) (Henderson et al., 2003). However, they did not compare memory performance with premenopausal women directly. A 4-year follow up study of 2362 women in SWAN found verbal memory as measured by the

East Boston Memory Test, declined from the premenopausal to the perimenopausal stage but there was a rebound from the perimenopausal to the postmenopausal stage (Greendale et al., 2009). More recently, a 14-year longitudinal study investigated 403 women in the Penn Ovarian Aging Cohort from premenopausal to postmenopausal stages, and found that immediate and delayed verbal recall measured by the Buschke Selection Reminding Test declined from premenopausal to postmenopausal stages (Epperson et al., 2013). Independent of the effect of aging, a significant decline for delayed verbal recall was evident during the early stages and a significant decline in immediate recall was evident during late transition. It seems that the decline in early stages of menopausal transition is due to decreased memory retention and the decline in late stages (e.g. post menopause) is affected by decreased memory encoding. Studies of women who had their ovaries removed surgically (oophorectomy), help to elucidate the effect of the absence of ovarian hormones on memory performance. One study compared memory performance before and two months after surgery and found that patients who received placebo HRT performed significantly worse on both immediate and delayed recall of word-pair associative task after surgery than before, whereas no difference was found for HRT group. (Phillips and Sherwin, 1992). Another study of the effect of oophorectomy found that the oophorectomy group performed significantly worse than the control group in both immediate and delayed recall of paragraphs. Even years after surgery was a significant negative predictor on word recall and verbal fluency after controlling for age (Au et al., 2016). Oophorectomy has also been found to be associated with an increased risk in dementia and other cognitive decline in older age (Kurita et al., 2016; Henderson, 2008; Hao et al., 2007; Rocca et al., 2007). Collectively, there are more memory complaints during menopause and they are validated by objective measures of memory performance, especially in women who have their ovarian steroid completely removed in the case of surgical menopause.

Another way of testing whether the decline in ovarian hormones during menopause leads to the decline in memory functions is to study the effect of HRT (commonly in the form of estrogen and progestin). Studies have found that HRT administered in a “critical period” helps to improve memory function. The Women’s Health Initiative Memory Study (WHIMS) is the largest clinical study to have investigated the effect of HRT on dementia and other cognitive impairment in 4532 women, and they found that HRT not only did not improve cognitive impairment but also increased risk for dementia in postmenopausal women (Shumaker et al., 2003). However, the average age of the participants in this study was 72 years old at the time of HRT, about 15 years postmenopausal. In contrast, results from animal models (Voytko et al., 2009; Hao et al., 2007; Rapp et al., 2003) and other human clinical trials have found that HRT administered during perimenopause and in the early years of postmenopause led to significant improvement in memory and other cognitive functions (Hara et al., 2015; Maki, 2013; Zhang et al., 2011; Verghese et al., 2000; Sherwin, 2009; Gibbs et al., 2003; Jacobs et al., 1998). Thus, HRT is effective in improving memory function in menopausal women when it is administered in the “critical period” of early menopausal transition, and this further demonstrates that the decline in ovarian hormones during menopause affects memory functions independent of age.

In addition, other studies investigated the predictors of memory decline during menopause. Menopausal related psychological symptoms such as depression have been consistently found to be associated with self-reported forgetfulness (Unkenstein et al., 2016; Drogos et al., 2013; Weber et al.,2012; Mitchell and Wood, 2011; Weber and Mapstone, 2009; Hunter et al., 2008; Ford et el., 2004). Other studies reported mixed findings of the associations between menopausal related vasomotor symptoms and subjective memory complaints (Drogos et al., 2013; Schaafsma et al., 2010; Hunter et al., 1986) as well as objective memory performance (Weber et al., 2013; Berent-Spillson et al., 2012; Mitchell and Wood, 2011), For example, hot flushes have

been found to be a significant predictor of subjective reports of forgetfulness (Mitchell and Wood, 2011). The frequency of vasomotor symptoms was associated with increased reports of inconvenience in daily life caused by memory problems (Schaafsma et al., 2010), and the severity of vasomotor symptoms was associated with the duration of memory and attentional problems. However, no association was found between vasomotor symptoms and objective memory performance (Greendale et al., 2010). On the other hand, the memory problems faced by menopausal women could be affected by the decline in other cognitive functions. Woods and colleagues (2008) found that forgetfulness was associated with difficulty in concentration and frequency of hot flushes. Other studies have also suggested a link between forgetfulness during menopause and decline in prefrontal cortex-dependent executive functions such as working memory or attentional control (Drogos et al., 2013; Weber et al., 2012; Schaafsma et al., 2010; Weber and Mapstone 2009; Kok et al., 2006). Furthermore, estrogen treatment has been found to improve executive functions instead of hippocampal dependent memory retention (Shanmugan and Epperson, 2014; Epperson et al., 2012; Krug et al., 2006). The decline in Estrogen level may have far reaching consequences in women's executive functions which can indirectly affect memory encoding and retrieval. Nevertheless, factors that lead to memory decline during menopause are multivariate. It could be indirectly affected by menopausal vasomotor and psychological symptoms as they have been found to affect sleep and sleep is important for memory consolidation. On the other hand, it is also possible that problems with concentration and attention are the result of poor sleep quality which leads to poor memory encoding in the first place.

As memory involves several processes such as encoding, consolidation and retrieval, the effect of sleep on memory consolidation has been until recently, overlooked in studies of memory decline during menopause. The aim of this study is to investigate the sleep architecture of menopausal women during a nap, and whether a nap helps

to improve memory performance using a word paired-associate task. We hypothesize that task performance will be better after a nap than staying awake for the same period of time. In view of the memory decline generally experienced by menopausal women, we also hypothesize that the declarative memory performance will be better in premenopausal women than menopausal women regardless of nap or no nap condition. The effect of menopausal vasomotor symptoms and psychological symptoms on nap and performance will also be looked into.

2. Method

2.1. Ethics and Participants

The research protocol was approved by University College London (UCL) Institute of Cognitive Neuroscience (ICN) ethics committee. Written informed consent was obtained from each participant. A total of 29 female participants between the ages of 42 to 59 were recruited. This includes 16 pre-menopausal women (mean age ± SD: 46.44 ± 4.02) who were still experiencing menstruation, 13 menopausal women (mean age ± SD: 53.46 ± 4.01) whose menstruation had ceased for at least one year and no longer than 5 years. The age range of women during menopause has been established by prior studies (e.g. Moline et al., 2003; Owen and Matthews, 1998). A t-test revealed that there is no significant difference in age between groups $t(27) = -4.69$, $p = .53$.

An initial telephone screen was carried out to determine the eligibility of the participants. The BMI cut-off point was 30. Women who had their last menstruation more than five years ago were excluded. Women having Hormone Replacement Therapy (HRT) were excluded. Participants who were taking prescribed anti-depressant medication, or had a recent history of diagnosed depression or anxiety, or suffering from any clinical sleep disorder, or taking any medication that has an effect on sleep (e.g. melatonin) were excluded from the study. There were 9 participants who were excluded due to the above reasons, and one dropped out during the nap session due to a back problem.

Participants refrained from alcohol or caffeinated drinks at least one day before and during the entire study.

2.2. Stimuli and apparatus

The word paired-associate task was adapted from Tucker and colleagues (2006). Forty-eight semantically related word pairs were selected from a larger pool of word pairs from Gais and Born (2004), and they were translated from German to English. The four words at the beginning and four words from the end were not included in the following response phase to avoid primacy and recency effect. The task was presented using Testable (Rezlescu, 2015) on a 17-inch monitor with a 75 Hz refresh rate and a 1280 × 1024 pixels resolution, at a viewing distance of approximately 55 cm. Responses were entered using a standard computer keyboard. Each word pair was presented for 5s with 100ms interstimulus interval (ISI). Immediately after the presentation of the forty-eight word pairs, an instruction was shown on the screen and participants proceeded to the response phase by pressing a key. The first word of each word pair was presented randomly and the participants were to type in the second word in the pair and press enter to proceed. These responses formed baseline performance. Regardless of the answer, the correct word was shown for 2s after each response, this was to reinforce the memory of the word pair. At retest after the nap or wake period, each first word in a pair was shown in a different random order and participants were to type in the second word to complete the pair, but this time no correct answer was shown. The performance was based on the improvement in the number of words correctly entered and the improvement in the percentage of the correct responses at retest from baseline.

Before the nap, polysomnography (PSG) recording was set up. PSG recordings were collected using 9 mm diameter gold-plated disc electrodes, a Comet XL Lab-based electroencephalogram (EEG) amplifier, and Twin EEG software (Grass-Telefactor,

West Warwick, RI, USA). Seven EEG channels were placed over the O1, O2, C3, C4, Fz, F3 and F4 based on 10-20 International EEG electrode placement system. Three electrooculography (EOG) channels were placed to the left of the left eye (LOG) and the right of the right eye (ROG) to record horizontal eye movements, and under the left eye (VOG) to record vertical eye movements. Two electromyography (EMG) channels were placed on the left and right sides of the chin. A reference electrode was placed at the left mastoid. The ground electrode was placed just on top of the nose in between the eye brows. The location of the electrodes was cleaned with alcohol wipes and NuPrep abrasive gel before applying electrodes so as to reduce impedance. A conductive, adhesive, water-soluble gel (Ten20 Conductive Paste by Weaver and Company) was then used to attach each electrode to the participant's scalp and face, and secured using 3M medical tape. Impedance checks were conducted to ensure that impedance values did not exceed 5 kΩ. The data acquisition rate was 200 Hz, with a notch filter of 50 Hz.

2.3. Design and procedure

The design of the study was mixed with a between-subject independent variable (IV), group (premenopausal vs menopausal), and a within-subject IV, condition (nap vs wake).

All participants participated in both sessions of nap and wake conditions on two separate days at the Institute of Cognitive Neuroscience sleep laboratory, University College London, either at 1pm or 5pm, with one day in between the two sessions. The order of the two conditions was randomised. Before the start of the study, each participant was informed which day was the nap condition and which day was the wake condition. If the first session was the nap condition, participants were instructed to come half an hour before the start of the experiment to familiarize themselves with the sleep laboratory environment. Informed consent was obtained and participants

answered some questions about their last night's sleep and then proceed to learn the word paired-associate list. At the beginning, participants were specifically instructed to concentrate and not let their thoughts wander while learning the word pairs. After learning the word pairs and response phase for the nap condition, participants were placed with electrodes for EEG recordings and proceeded to take a nap for approximately one and a half hour by themselves with light off. After the nap period, the lights were turned on, electrodes were removed, and participants were given 20 minutes to freshen up (use the washroom, drink water or just relax). This was to account for sleep inertia. After 20 minutes, the retest for the word pairs was carried out. For the wake condition, instead of napping, participants were to spend the same duration of time as the nap condition staying awake. They were allowed to watch a preselected movie or read preselected magazines. The movie and magazines were selected to minimise acquisition of new declarative memory of words. They also filled in the menopausal Rating Scale (MRS, Schneider et al., 2000) during this period. A full debrief was given at the end of the two sessions.

2.4. Data analysis

2.4.1. Task performance

T-tests and 2*2 mixed ANOVA were employed to analyse task performance using SPSS IBM SPSS Statistics (Version 22.0).

2.4.2. Sleep data analysis

Sleep data was analysed in MATLAB using SPM8 (Wellcome Trust, London, UK) and the SleepSMG toolbox (Walker laboratory; sleepsmg.sourceforge.net) running in MATLAB. Pre-processing of sleep data included importing to SPM, and bandpass filtering of the EEG (0.3–35 Hz), EOG (0.1–35 Hz) and EMG (40–100 Hz) data. The data were then scored manually by two researchers independently in 20s epochs according to the sleep scoring standards by American Academy of Sleep Medicine

(Berry et al., 2012). The researchers then re-examined all epochs that were rated inconsistently and agreed on a consistent rating for each epoch. Epochs with peak absolute activity larger than two standard deviation in any of the channels were excluded from the analysis. Epochs were then expressed as sleep stages (wake, N1, N2, N3, and REM). Duration (s) of each sleep stage was calculated, and expressed as a percentage of total sleep time (TST). TST is derived from total time spent (s) in all sleep stages (N1, N2, N3, and REM). Sleep onset latency (SOL) was calculated as the amount of time (s) from lights off to the experience of the first three epochs of N1 sleep, or from light off to the experience of the first epoch of other sleep stages. WASO was calculated as the amount of time (s) from wake epochs in between sleep stages. Sleep efficiency (SE) was calculated as TST/ total time in bed x 100%.

2.4.3. Correlation and multiple regression analyses

Pearson Correlations were carried out to determine the correlations between task improvements and sleep parameters, and between sleep parameters and menopausal symptoms.

Multiple regression analyses were carried out to investigate predictors of improvement and percentage of improvement in the number of words recalled, and the severity of somatic, psychological, urogenital, and combined symptoms as independent factors were entered in each model. Collinearity between the independent variables were also checked.

These analyses were done using SPSS IBM SPSS Statistics (Version 22.0).

3. Results

3.1. Paired-associate task performance

To measure the efficacy of training, we compared performance between immediately after training (baseline) and after both the sleep and wake period. For the nap condition,

there was a significant improvement in the number of words recalled after the nap (mean ± SD: 26.28 ± 9.30) than baseline (mean ± SD: 21.72 ± 10.19), $t(28) = -5.00$, $p < .001$. For the wake condition, there was significant improvement in the number of words recalled after wake (mean ± SD: 24.62 ± 9.56) than baseline (mean ± SD: 21.59 ± 9.24), $t(28) = -3.70$, $p = .001$. Number of words correctly recalled at baseline did not differ significantly between nap (mean ± SD: 21.72 ± 10.19) and wake condition (mean ± SD: 21.59 ± 9.24), $t(28) = .10$, $p > .05$.

An independent *t*-test was conducted to compare memory performance (averaged between nap and wake condition) at baseline immediately after learning the 40 word pairs between groups. No significant difference was found between premenopausal (mean ± SD: 19.91 ± 8.92) and menopausal groups (mean ± SD: 23.81 ± 8.90), $t(27) = -1.17$, $p > .05$.

A 2*2 mixed ANOVA with condition (nap vs wake) as a within-subject variable and group (premenopausal vs menopausal) as a between-subject variable was conducted for the improvement in the number of words recalled (see table 1 for descriptive statistics). The main effect of condition was not significant: $F(1,27) = 1.65$, $p = .210$, partial $\eta^2 = .06$. Although the improvement after nap (mean ± SE: 4.40 ± 0.89) was better than after the wake period (mean ± SE: 2.95 ± 0.82), there was no significant difference in the improvement after nap and wake periods. The condition by group interaction was not significant: $F(1,27) = 0.29$, $p = .595$, partial $\eta^2 = .01$. The main effect of group was not significant: $F(1,27) = 3.34$, $p = .079$, partial $\eta^2 = .11$. Although the improvement for the premenopausal group (mean ± SE: 4.84 ± 0.86) was better than the menopausal group (mean ± SE: 2.50 ± 0.95), there was no significant difference in the improvement after either the nap or wake periods.

Table 1.

	premenopausal	menopausal
improvement after nap	5.88 ± 4.27	2.92 ± 5.30
improvement after wake	3.81 ± 4.20	2.08 ± 4.65

Table 1 shows descriptive statistics for mixed ANOVA results for the improvement in the number of words recalled.

A 2*2 mixed ANOVA with condition (nap vs wake) as a within-subject variable and group (premenopausal vs menopausal) as a between-subject variable was conducted for the percentage of improvement in the words recalled (see table 2 for descriptive statistics). The main effect of condition was not significant: $F(1,27) = 2.08$, $p = .160$, partial $\eta^2 = .07$. Although the percentage improvement after nap (mean ± SE: 33.75 ± 8.98) was better than after the wake period (mean ± SD: 17.84 ± 5.58), there was no significant difference in the improvement after both nap period and wake period. The condition by group interaction was not significant: $F(1,27) = 0.67$, $p = .419$, partial $\eta^2 = .02$. However, the main effect of group was significant: $F(1,27) = 6.50$, $p = .017$, partial $\eta^2 = .19$. Premenopausal women (mean ± SD: 38.68 ± 6.77) improved significantly more (%) than menopausal women (mean ± SD: 12.91 ± 7.51) in the percentage of improvement (see figure 1).

Table 2.

	premenopausal	menopausal
improvement after nap (%)	51.15 ± 58.09	16.34 ± 31.42
improvement after wake (%)	26.20 ± 31.49	9.48 ± 27.81

Table 2 shows descriptive statistics for mixed ANOVA results for the percentage of improvement in the number of words recalled.

Figure 1.

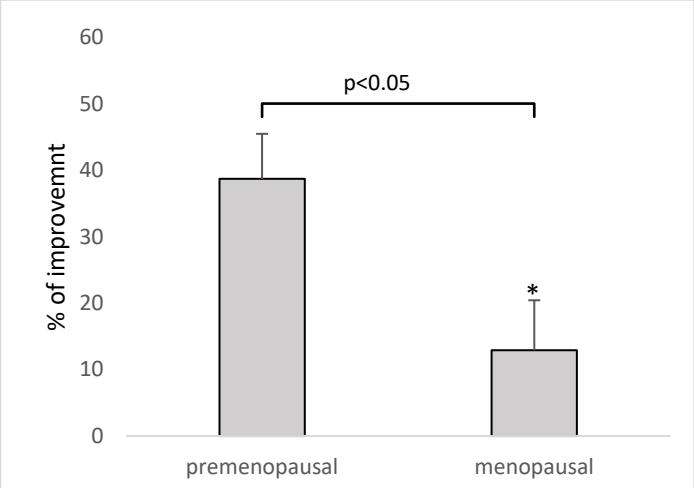


Figure 1 shows that the percentage improvement between baseline and test (after nap or wake) is higher for the premenopausal group than the menopausal group, $p < .05$.

3.2. Menopausal symptoms

Independent t-tests revealed that there is no significant difference in somatic score, $t(27) = -1.02$, $p > .05$, between premenopausal (mean ± SD: 3.13 ± 2.99) and menopausal group (mean ± SD: 4.38 ± 3.66), in psychological score, $t(27) = .77$, $p > .05$, between premenopausal (mean ± SD: 4.88 ± 3.44) and menopausal group (mean ± SD: 3.92 ± 3.12), in urogenital score, $t(27) = -1.29$, $p > .05$, between the premenopausal (mean ± SD: 1.94 ± 1.91) and the menopausal (mean ± SD: 3.00 ± 2.51) group, in combined score, $t(27) = -.51$, $p > .05$, between premenopausal (mean ± SD: 9.94 ± 7.03) and menopausal (mean ± SD: 11.31 ± 7.55) group.

3.3. Sleep parameters

A summary of the sleep stages obtained during the nap for both premenopausal and menopausal groups can be found in table 3. The mean total sleep time (TST) for premenopausal subjects was approximately 48.39 min, 14% of the TST was N1 sleep, 22% was N2 sleep, 37% was N3 sleep, and 27% was REM sleep. The mean sleep onset latency (SOL) and wake after sleep onset (WASO) for premenopausal subjects

was approximately 16.91 min and 14.97 min respectively. The mean TST for menopausal subject was approximately 49.36 min, 15% of the TST was N1 sleep, 40% was N2 sleep, 30% was N3 sleep, and 15% was REM sleep.

Table 3.

Sleep parameters

	Premenopausal Min ± SD	% of TST ± SD	Menopausal Min ± SD	% of TST ± SD
SOL	16.91± 21.51		17.77 ± 12.42	
WASO	14.97 ± 20.70		12.54 ± 14.43	
TST	48.39 ± 33.61		49.36 ± 35.43	
SE (%)	43.59 ± 30.33		44.70 ± 32.45	
N1	6.79 ±7.42	6.05 ± 6.51	7.49 ± 8.18	6.62 ± 7.00
N2	10.69 ± 9.22	9.51 ± 7.86	19.95 ± 15.20	18.06 ± 14.09
N3	17.98 ± 19.41	16.01±16.98	14.67 ± 17.20	13.33 ± 15.84
REM	12.94±15.37	12.02±14.73	7.26 ± 8.89	6.69 ± 8.21

Table 3 shows the duration (min) and percentage of different sleep stages, and the duration of sleep onset latency (SOL), wake after sleep onset (WASO) and total sleep time (TST) between premenopausal and menopausal groups.

To compare whether there was a difference in the sleep parameters between menopausal and premenopausal groups, independent t-tests were conducted. There was a near significant difference for N2 duration (mins), $t(27) = -2.03$, $p = .053$; the menopausal group spent more mins in N2 sleep stage (mean ± SD: 19.95 ± 15.20) than the premenopausal group (mean ± SD: 10.69 ± 9.22) (see figure 2). However, there was no significant difference for N1 duration, $t(27) = -.24$, $p > .05$, N2 duration, $t(27) = -2.03$, $p > .05$, N3 duration, $t(27) = .48$, $p > .05$, REM duration, $t(27) = 1.18$, $p > .05$, the percentage of N1 duration, $t(27) = -1.52$, $p > .05$, the percentage of N2 sleep stage, $t(27) = .-1.29$, $p > .05$, the percentage of N3 sleep duration , $t(27) = 1.04$, $p > .05$, the percentage of REM sleep duration, $t(27) = 1.52$, $p > .05$, SOL, $t(27) = -.13$, $p > .05$, WASO, $t(27) = .36$, $p > .05$, TST, $t(27) = -.08$, $p > .05$, and SE (%), $t(27) = -.10$, $p > .05$.

Figure 2.

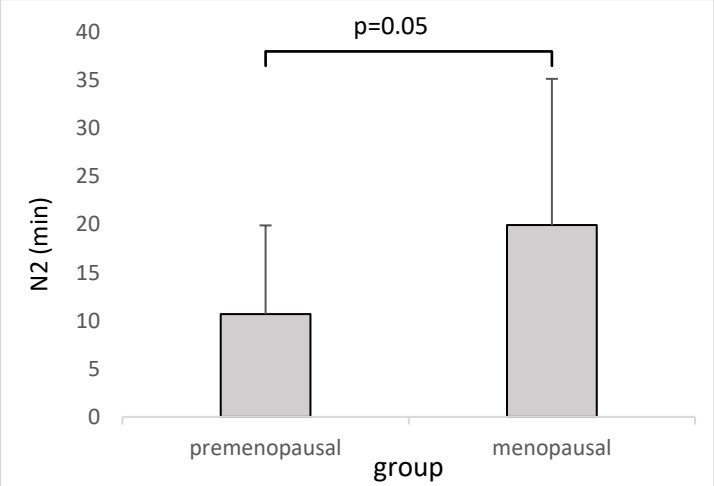


Figure 2 shows that N2 sleep duration (min) is almost significantly longer for the menopausal group than the premenopausal group.

A summary of pre-study self-reported sleep parameters is shown in table 4. Independent t-tests revealed no significant difference between premenopausal and menopausal groups in mins prior to study with nap, $t(27) = .44$, $p > .05$, mins prior to study without nap, $t(27) = .582$, $p > .05$, TST night before study with nap, $t(27) = 1.39$, $p > .05$, TST night before study without nap, $t(27) = 1.47$, $p > .05$, sleep quality (SQ) night before study with nap, $t(27) = .44$, $p > .05$, and SQ night before study without nap, $t(27) = .59$, $p > .05$.

Table 4.

	Premenopausal Nap	Wake	Menopausal Nap	Wake
Mins prior to study	460.94 ± 163.54	510.00 ± 160.90	435.38 ± 141.99	474.62 ± 165.37
TST night before study	499.69 ± 57.46	431.25 ± 118.30	443.46 ± 149.81	380.38 ± 43.28
SQ night before study	6.38 ± 1.93	6.25 ± 1.95	6.08 ± 1.71	5.85 ± 1.68

Table 4 shows summary of the pre-study sleep parameters between groups in terms of mins prior to study, total sleep time in mins (TST) night before study and sleep quality (SQ) night before study. The higher the SQ the better the sleep quality.

3.4. Correlations between task improvement and sleep parameters

Pearson's correlation analyses were carried out to determine whether there was any correlation between the improvements in the number of words recalled with various sleep parameters, and between percentages of improvement with various sleep parameters (see table 5). A near significant positive correlation was found between the improvement in the number of words recalled and SOL ($r = .37$, $N = 29$, $p = .05$, two tailed), 13 % of variance was explained. The scatter plot (figure 3) shows that the data points are moderately distributed along the regression line, in a linear manner. A positive correlation was found between percentage of task improvement and SOL ($r = .41$, $N = 29$, $p < .05$, two-tailed), and 16 % of variance was explained. The scatter plot (figure 4) shows that the data points are moderately distributed along the regression line, in a linear manner. No other significant correlation was found.

Table 5.

	Sleep parameters	n	*r* value	*p* value
Task improvement after a nap	N1 mins	29	-.05	.80
	% N1	29	-.02	.92
	N2 mins	29	-.26	.17
	% N2	29	-.25	.19
	N3 mins	29	.18	.35
	% N3	29	.17	.37
	REM mins	29	.05	.79
	% REM	29	.06	.78
	SOL	29	.37	.05
	WASO	29	.13	.51
	TST	29	.00	.98
	SE (%)	29	.01	.95
% task improvement after a nap	N1 mins	29	-.10	.61
	% N1	29	-.09	.66
	N2 mins	29	-.24	.21
	% N2	29	-.24	.22
	N3 mins	29	.12	.54
	%N3	29	.10	.61
	REM mins	29	-.03	.89

%REM	29	-.02	.91
SOL	29	.41	.03*
WASO	29	.13	.51
TST	29	-.06	.76
SE (%)	29	-.07	.74

Table 5 shows correlations between improvements in the number of words recalled with sleep parameters and between the percentages of improvement with sleep stage parameters.

Figure 3.

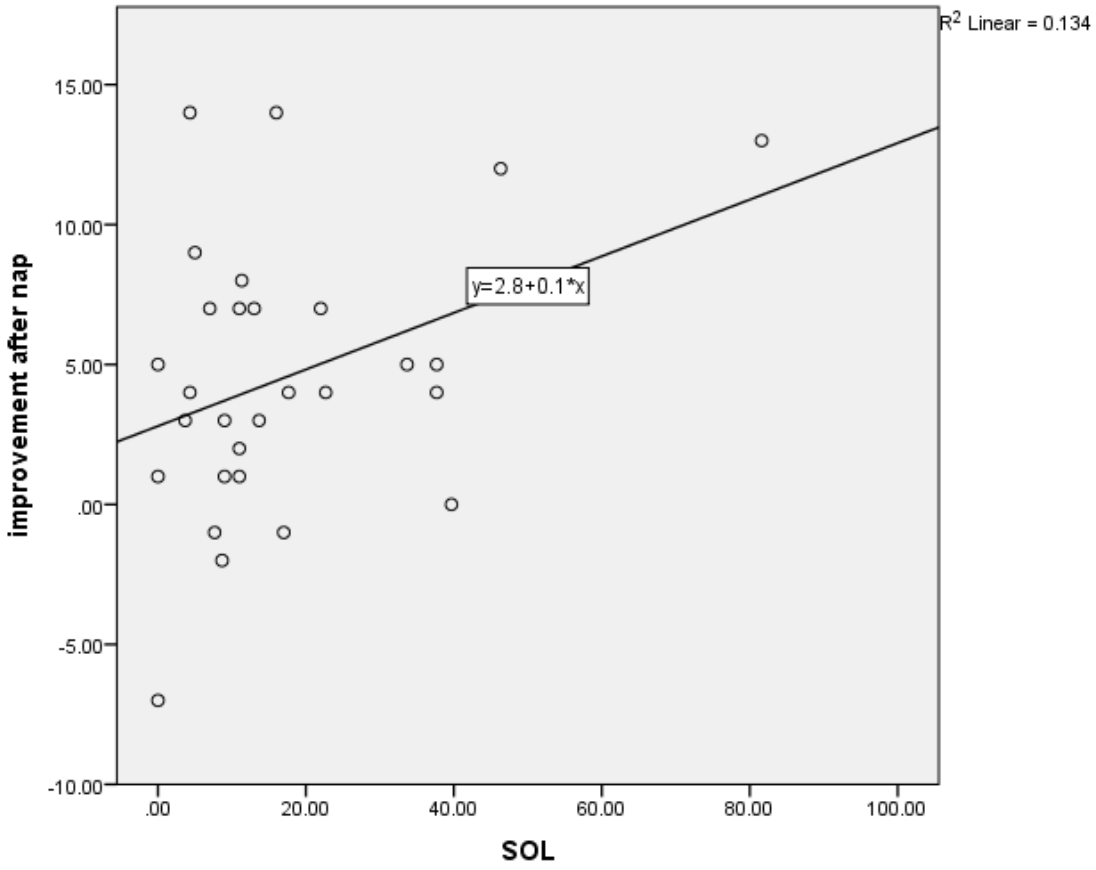


Figure 3 shows Improvement in the number of words recalled after nap plotted against SOL.

Figure 4.

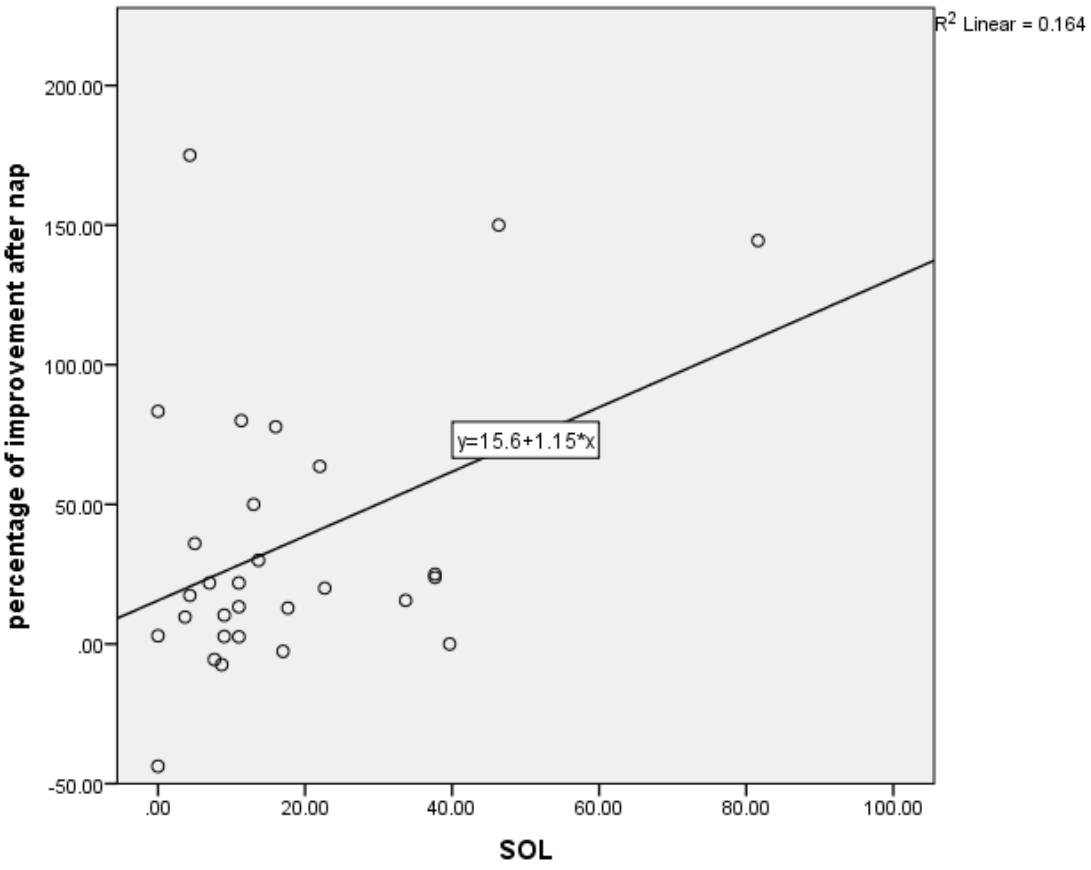


Figure 4 shows percentage of improvement in the number of words recalled after nap plotted against SOL.

3.5. Correlations between sleep parameters and the severity of menopausal symptoms

Pearson's correlation analyses were carried out to determine whether there was any correlation between sleep parameters and the severity of various menopausal symptoms (see table 6). The results revealed a significant negative correlation between SOL (min) and the severity of psychological symptoms ($r = -.45$, $N = 29$, $p < .05$), a 21 % of variance was explained. The scatter plot (figure 5) shows that the data points are moderately distributed along the regression line, in a linear manner. No other significant correlation was found.

Table 6.

	Menopausal symptoms	n	*r* value	*p* value
N1 mins	Somatic	29	.13	.49
	Psychological	29	.19	.32
	Urogenital	29	.09	.65
	Combined	29	.18	.36
% N1	Somatic	29	-.19	.33
	Psychological	29	-.27	.16
	Urogenital	29	-.16	.42
	Combined	29	-.26	.18
N2 mins	Somatic	29	.07	.71
	Psychological	29	.17	.39
	Urogenital	29	.16	.41
	Combined	29	.16	.41
% N2	Somatic	29	-.03	.86
	Psychological	29	.04	.85
	Urogenital	29	.14	.47
	Combined	29	.04	.82
N3 mins	Somatic	29	.02	.93
	Psychological	29	-.04	.83
	Urogenital	29	-.15	.43
	Combined	29	-.06	.77
% N3	Somatic	29	-.01	.95
	Psychological	29	-.18	.35
	Urogenital	29	-.24	.22
	Combined	29	-.16	.40
REM mins	Somatic	29	.07	.73
	Psychological	29	.35	.06
	Urogenital	29	.20	.29
	Combined	29	.25	.18
% REM	Somatic	29	.11	.59
	Psychological	29	.32	.10
	Urogenital	29	.21	.27
	Combined	29	.26	.18
SOL	Somatic	29	-.24	.22

	Psychological	29	-.45	.01*
	Urogenital	29	-.04	.85
	Combined	29	-.33	.08
WASO	Somatic	29	.32	.09
	Psychological	29	.35	.07
	Urogenital	29	-.17	.38
	Combined	29	.26	.18
TST	Somatic	29	.09	.64
	Psychological	29	.22	.25
	Urogenital	29	.08	.69
	Combined	29	.17	.39
SE (%)	Somatic	29	.07	.73
	Psychological	29	.22	.25
	Urogenital	29	.09	.63
	Combined	29	.16	.40

Table 6 shows the correlations between sleep parameters and the severity of menopausal symptoms.

Figure 5.

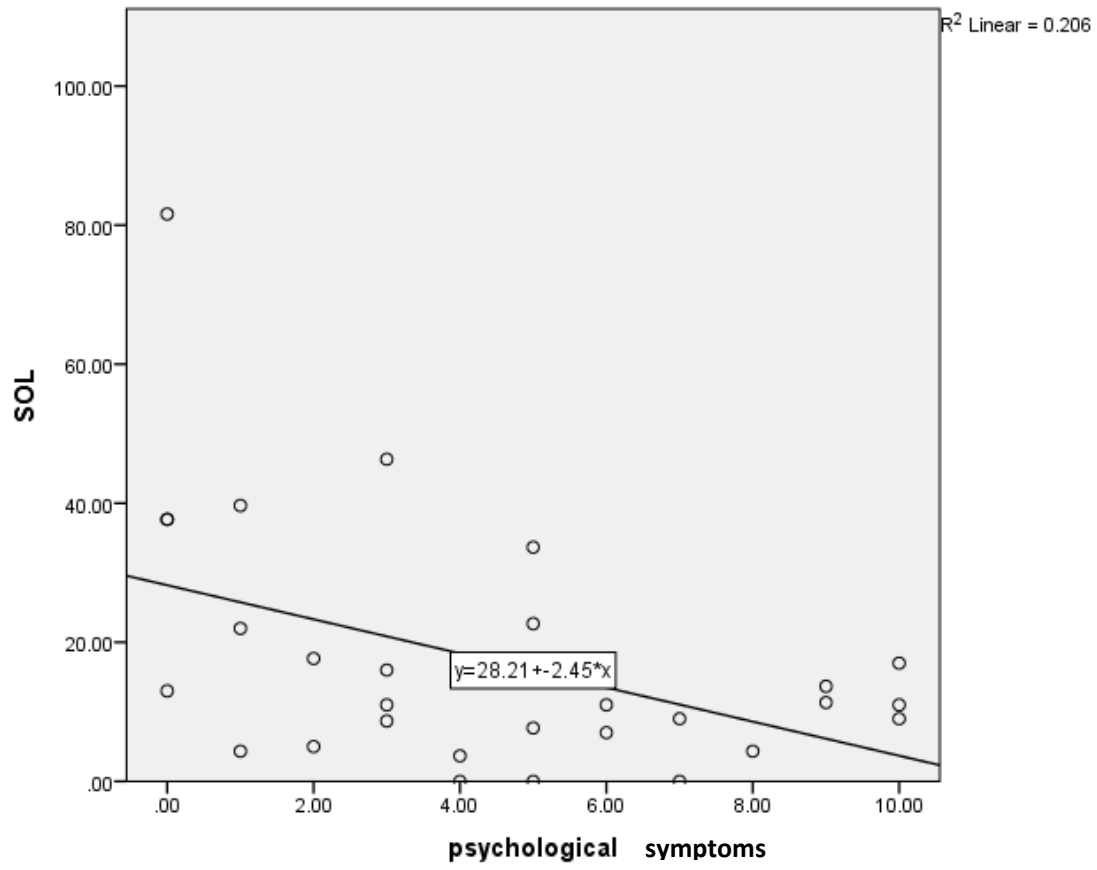


Figure 5 shows SOL (min) plotted against the severity of psychological symptoms of the MRS. The higher the psychological symptoms the shorter the SOL (min).
Note: multiple regression analysis was not chosen because it requires a large number of observations. Our study does not have enough participants to perform this analysis.

Multiple regression analysis: menopausal symptoms as predictors of task improvement

Using the enter method in SPSS, no significant model emerged for the improvement in the number of words recalled after nap: F (3, 25) = .435, p = .73. Table 7 gives the information for the predictor variables entered into the model. No significant predictor was found. No collinearity was found.

Table 7.

Variable	B	SE B	β
Psychological score	.11	.60	.07
Urogenital score	.28	.65	.13
Combined	-.25	.34	-.36

Table 7 shows the unstandardized and standardised regression coefficients for the variables entered into the model for the predictor of improvement in the number of words recalled after nap

Using the enter method, no significant model emerged for the percentage of improvement in the number of words recalled after nap: F (3, 25) = .044, p = .99. Table 8 gives the information for the predictor variables entered into the model. No significant predictor was found. No collinearity was found.

Table 8.

Variable	B	SE B	β
Psychological score	-1.29	6.36	-.08
Urogenital score	-1.22	6.88	-.05
Combined	.42	3.56	.06

Table 8 shows the unstandardized and standardised regression coefficients for the variables entered into the model for the predictor of the percentage of improvement in the number of words recalled after nap

Using the enter method, no significant model emerged for the improvement in the number of words recalled after the wake period: F (3, 25) = 1.59, p = .22. Table 9 gives the information for the predictor variables entered into the model. No significant predictor was found. No collinearity was found.

Table 9.

Variable	B	SE B	β
Psychological score	.41	.51	.30
Urogenital score	-.50	.55	-.25
Combined	-.24	.29	-.38

Table 9 shows the unstandardized and standardised regression coefficients for the variables entered into the model for the predictor of the improvement in the number of words recalled after wake period.

Using the enter method, no significant model emerged for the percentage of improvement in the number of words recalled after the wake period: F (3, 25) = 1.62, p = .21. Table 10 gives the information for the predictor variables entered into the model. No significant predictor was found. No collinearity was found.

Table 10.

Variable	B	SE B	β
Psychological score	3.98	3.54	.43
Urogenital score	-5.07	3.83	-.37
Combined	-1.18	1.98	-.28

Table 10 shows the unstandardized and standardised regression coefficients for the variables entered into the model for the predictor of percentage of the improvement in the number of words recalled after wake period.

4. Discussion

Our results show that task performance was better after a nap than wake period, although this result is not significant. On the other hand, the premenopausal group performed significantly better than the menopausal group in terms of the percentage of the task improvement after both nap and wake period, even though menopausal women had near significantly longer N2 sleep. This supports our hypothesis that the declarative memory performance is better in premenopausal than menopausal women regardless of nap or no nap condition.

Most previous studies of the effect of a nap on memory consolidation have found that a nap is as good as a full night's sleep in promoting memory consolidation (Seehagen et al., 2015; Lo et al., 2014; Lahl et al., 2008; Tucker et al., 2006; Mednick et al., 2003). Upon closer inspection of our subjects, 5 out of 29 subjects (3 from premenopausal and 2 from menopausal group) had less than 10 minutes of sleep during the entire nap period. Removal of these data led the data closer to significance. Furthermore, another two subjects (1 from premenopausal and 1 from menopausal group) had less than 15 minutes of sleep. In view of the high prevalence of sleep complaints in women of this

age range (Freeman et al., 2015; Hung et al., 2014; Cheng et al., 2008), it seems both nocturnal sleep and nap are affected, possibly by the reduction in ovarian hormones (Al-Azzawi & Palacios, 2009). Thus, the lack of significant difference in task performance between nap and no nap condition in this instance is likely the result of high proportion of participants experiencing difficulty initiating or maintaining sleep during an afternoon nap.

In accordance with previous subjective reports that there are more memory complaints in menopausal than premenopausal women (Mitchell and Woods, 2001; Gold et al., 2000), studies that used objective measures showed memory performance declined from premenopausal to menopausal stage (Epperson et al., 2013). Studies of memory decline in groups of women who went through oophorectomy in the case of artificial menopause (Au et al., 2016; Phillips and Sherwin, 1992). Premenopausal women performed significantly better in our paired-associate task than menopausal women in both conditions, even though menopausal women had near significantly longer N2 sleep during the nap condition. On the other hand, Greendale and colleagues (2009) posit that the effect of memory decline is transient as there is a rebound of memory performance from perimenopause to menopause. The rebound may be explained by the fact that some participants in their study were already postmenopausal at entry and as the years went by, the reduction in ovarian hormones exert a smaller influence on cognition or other related processes. N2 sleep has been found to promote declarative memory consolidation during sleep (Kurdziel et al., 2013; Genzel et al., 2013; Lahl et al., 2008; Schabus et al., 2004), and the longer duration of N2 in menopausal women during the nap had likely helped to promote memory consolidation but it was not reflected in memory performance. This could be due to problems with memory encoding in the first place, as other studies have suggested a link between forgetfulness during menopause and decline in working memory or attentional control (Drogos et al., 2013; Weber et al., 2012; Schaafsma et al., 2010; Weber and Mapstone

2009; Kok et al., 2006). For example, Woods and colleagues (2008) found that forgetfulness was associated with difficulty in concentration. Weber and Mapstone (2009) found that menopausal women with greater memory complaints performed significantly worse on tasks that require executive functions compared to other groups. Sleep deprivation on the night before study could lead to reduced cognitive performance such as attention and working memory, but our previous study suggests that there is no subjective or objective difference in nocturnal sleep quality and no difference was found for nocturnal TST and global sleep quality the night before the current study between groups. It thus seems that the decline in memory function during menopause is not related to sleep. On the other hand, there is a growing interest in the effect of estrogen on executive functions, and clinical studies are beginning to shed a light on the beneficial effect of estrogen on dorsolateral prefrontal cortex (DLPFC), an area responsible for executive functions such as working memory and attention (Shanmugan and Epperson, 2014; Epperson et al., 2011; Krug et al., 2006). Estrogen HRT administered during perimenopause and early years of menopause has been proven to improve memory and other executive functions (Hara et al., 2015; Maki, 2013; Zhang et al., 2011; Verghese et al., 2000; Sherwin, 2009; Gibbs et al., 2003; Jacobs et al., 1998). Thus, it is likely that the decline in estrogen led to impairment in PFC dependent executive functions which affected memory encoding and later retrieval. Furthermore, there is no significant difference in the severity of various reported menopausal symptoms between groups, and no menopausal symptoms were found to be a predictor of task performance. Thus, menopausal status as a result of reduction in ovarian hormones, instead of sleep or menopausal symptoms, seems to predict declarative memory performance.

Interestingly, our study found significant correlations between SOL and task improvement and between SOL and the severity of psychological symptoms. The higher the SOL the higher the task improvement, and the higher the SOL, the lower

the severity of psychological symptoms. SOL measures the duration of sleep initiation from lights off, longer SOL is normally associated with poorer sleep quality but in this case, it is associated with better performance. This could be related to memory rehearsal in short term working memory. The current model suggests that memory rehearsal is part of the central working memory that helps to keep information in mind (Baddeley, 2000), and studies have found that this process helps with memory encoding and later retrieval (Macrae et al., 2004; Davachi et al., 2001). Knowing that there is a test after the nap, some participants may have tried to rehearse the word pairs before trying to fall asleep, longer duration of SOL may reflect longer time spent in mental rehearsal. This again suggests that memory performance in our study was largely affected by memory encoding before the nap instead of memory consolidation during the nap. Furthermore, we found that longer SOL is associated with less severe psychological symptoms. This means the longer it takes to fall asleep, the shorter the sleep duration and the less severe the psychological symptoms such as depression. This supports evidence that identified longer REM sleep duration as a risk factor for depression (Palagini et al., 2012; Pillai et al., 2011; Tsuno et al., 2005), and sleep deprivation has been proven to be an effective treatment for depression (Dallaspezia and Benedetti, 2014; Hemmeter et al., 2010; Giedke and Schwarzler, 2002). Thus, women who have less severe psychological symptoms may have shorter TST, and shorter REM sleep in general due to factors such as longer SOL. Also, although we have not found evidence that menopausal psychological symptoms predict memory performance, previous studies have consistently shown that menopausal psychological symptoms are related to forgetfulness (Unkenstein et al., 2016; Drogos et al., 2013; Weber et al.,2012; Mitchell and Wood, 2011; Weber and Mapstone, 2009; Hunter et al., 2008; Ford et el., 2004). It is possible that psychological symptoms affect memory performance indirectly through affecting aspects of sleep such as SOL.

One thing to note is that performance after immediate learning at baseline was comparable between groups. It is only after the second exposure to the correct words in pairs and after a delay of around two hours with or without a nap that the difference between groups became apparent. Thus, although it appears that memory performance was affected by memory encoding, it could also be affected by memory retention and retrieval. Future studies should investigate the effect of menopause on different aspects of memory, such as encoding, consolidation, retention, and retrieval separately. This would help to illuminate the source of memory complaints and decline in menopausal women. Appropriate intervention strategies can then be developed to maximize the benefit of the intervention to improve targeted cognitive functions. Future studies should also consider the possibility of memory function rebound as the effect of hormone reduction becomes stabilised during later stage of menopause as this can also provide insights for intervention strategy targeting women during early years of menopausal transition who are affected the most. Perhaps male subjects can be included as a control group as men do not experience a sharp decline in their hormone levels. Lastly, although the current study did not find any association between nap and memory performance in menopausal women, the beneficial effect of nocturnal sleep or afternoon nap on memory consolidation is well documented. As there is an increase in both sleep and memory complaints during menopause, a more comprehensive view can be formed when sleep and memory functions are studied together.

Similar to my previous study (chapter 3), the difficulty in testing women of this age range is that there are huge individual differences in hormonal fluctuation especially in the premenopausal group as they are in the transition to menopause. Much younger subjects would have to be recruited if we were to compare subjects with or without ovarian hormone reduction. Age has a huge influence on sleep and a range of cognitive functions including memory (Gilsoul et al., 2017; Wang et al., 2017). We were able to demonstrate the effect of menopausal status on a nap and memory performance

independent of age as there is no significant difference in age between age-matched groups. We also measured menopausal symptoms and correlated them to sleep parameters and use them as regressors to predict task performance to account for the physiology of symptoms as a result of menopausal hormonal fluctuation. Also, a high proportion of participants experienced difficulty in initiating or maintaining sleep during the nap despite having acclimatised in the environment prior to the nap. A larger pool of subjects is recommended in comparison to studies of nap in younger subjects. It is also possible to instruct participants to nap every day for a certain time period to become a customised to napping in the afternoon before the commencement of the study.

In conclusion, this study aimed to investigate the sleep architecture of menopausal women during a nap, and assess whether a nap helps to improve memory performance using a word paired-associate task. Menopausal women did not perform as well as the premenopausal women despite having had longer duration of N2 sleep. We posit that the reduction in ovarian hormone has direct influence on executive functions dependent on the prefrontal cortex such as attention and working memory which indirectly affect memory encoding and retrieval. Thus, our results suggest that memory decline during menopause is mainly the result of problems with memory encoding, instead of sleep dependent memory consolidation.

Chapter 5: The time course of skill training involving executive functions

Abstract

Objective – Growing Evidence suggests that sleep plays an important role in various types of skill training. However, fewer studies have investigated the facilitating effect of sleep on cognitive training that involves higher order executive functions or fluid intelligence, and time course for cognitive training remains unknown. This study sets out to investigate whether sleep exerts an independent effect on various cognitive training tasks (task-switching, arithmetic, working memory, and visual search) by using a commercial cognitive training app called “Peak”.

Methods - Two groups of participants were recruited, 20 in each group. One group started the training in the morning, and then was tested 12 hours later in the evening following the wake period and then retested 12 hours later in the morning following a night of sleep, and the second group started the training in the evening, and then was tested the following morning after a night of sleep and then retested 12 hours later in the evening following the wake period**.** They also filled in a Karolinska sleep diary (KSD) to report their sleep quality following the night of sleep. Within-group t-statistics were used to compare task performance (accuracy and RT) between the three sessions for each group. Correlation analysis was used to find correlations between various measures of sleep quality and task improvement following the night of sleep.

Results – Our results show that sleep facilitated task-switching task improvement.

Conclusion – Thus, we postulate that the facilitating effect of sleep on various skill training can be extended to higher-function cognitive training.

1. Introduction

Growing evidence suggests sleep plays an important role in various types of skill training (Walker et al., 2003; 2002; Peigneux et al., 2001). Several factors are known to be involved in skill training. Repetition or practice is a critical factor for skill acquisition on both the behavioural level (Savion-Lemieux and Penhune, 2005; Ofen-Noy et al., 2003) and functional and structural brain changes (Wang et al., 2016; Kleim et al., 2002; Plautz et al., 2000; Karni et al., 1998). It is believed that after initial skill acquisition, the learnt skills undergo further processes of organisation and reorganisation known as consolidation. Studies have investigated the temporal contribution of consolidation of motor skills, and found that this consolidation happens exclusively during sleep (Doyon et al., 2009; Walker et al., 2003; 2002; Fischer et al., 2002). For example, Walker and colleagues (2003; 2002) trained participants on a finger tapping task at either 10 a.m. in the morning or 10 p.m. in the evening and then tested them on the task 12 hours later and 24 hours later. They found that a night of sleep resulted in practice-independent improvement in task performance, and additional nights of sleep resulted in further practice-independent task improvement, whereas the equivalent amount of a wake period had no influence on skill learning. Also, a significant correlation was found between task improvement and stage 2 NREM sleep. On the other hand, motor skill training has been found to increase sleep spindles and fast frequencies during post training sleep (Morin et al., 2008; Gais et al., 2002) as well as REM duration and density (Smith and Lapp, 1991). Thus, there is a two-way interaction between skill training and sleep. It seems reasonable to suggest that post training consolidation of motor skills happens exclusively during sleep rather than the mere passage of time, and the best time for motor skill training is in the evening before a night of sleep.

On the other hand, cognitive training that involves higher order executive functions have gained more attention in recent years as evidenced by rapid growth of “brain training” mobile applications and computer programs that are informed by

neuroplasticity research (Boot and Kramer, 2014). The aim of these programs is to improve cognitive functions or reverse the ageing-related cognitive decline in fluid intelligence such as task-switching, arithmetic, working memory, and attention based ability such as visual search, abilities that are crucial for academic and work-related achievements (Borella et al., 2017; Polderman et al., 2010; Gary and Thompson, 2004). Computerised training programs have also been used in developmental psychology in a bid to improve cognitive abilities in children (Loosli et al., 2012; Jaeggi et al., 2011; Thorell et al., 2009), children with learning disabilities (Kirk et al., 2015; Dunning et al., 2013; Holmes et al., 2009) and children from disadvantaged backgrounds (Mackey et al., 2011). The concept of cognitive training is based on the rationale that repeated practice in any task leads to higher proficiency in doing that task, and the improvements can also be transferred to other tasks involving the same or a broader range of cognitive abilities (Baniqued et al., 2015; Karbach and Kray, 2009; Kloo and Perner, 2003).

Improvements in various tasks after training have been found in the studies of task-switching (Kray et al., 2011; Karbach and Kray, 2009; Kray et al., 2008; Minea and Shah, 2008; Cepeda et al., 2001), arithmetic (Fendrich et al., 2014), working memory (Au et al., 2015; Rudebeck et al., 2012; Holmes et al., 2009; Jaeggi et al., 2008; Banigued et al., 2015) and visual search (Clark et al., 2015; Keller and Lefin-Rank, 2010; Pambakian et al., 2004; Ellison and Walsh, 1998; Walsh et al., 1998). Task-switching is known as an executive function that tests cognitive flexibility in shifting attention between tasks. An analogue task-switching task involves two tasks, A and B. They can be presented as single blocks of A or B, or mixed between A and B. Two types of task-switching costs can be calculated. Mixing costs are calculated as the differences between mean performance of mixed blocks and single blocks. Switching costs are calculated as the differences between mean performance of switch and non-switch trials. For example, Cepeda and colleagues (2001) found a reduction in mixing

costs especially in older adults and children after two sessions of task-switching training, whereas Kray and Lindenberger (2000) found a reduction in both mixing and switching costs after six sessions of training. Furthermore, Karbach and Kray (2009) found near transfer of these improvements to different task-switching tasks. Arithmetic is a type of mathematics skill that involves adding, subtracting, multiplying, and dividing number. Fendrich and colleagues (2014) found four sessions of simple one digit multiplication training (e.g. 2 X 9) in undergraduate students significantly decreased their reaction time (RT) and error rate. Working memory, is a term to describe our ability to temporarily store information (Miyake and Shah, 1999). An analogue working memory n-back task asks the participants to determine whether the location of current stimuli matches the one from n steps earlier. Using a dual n-back task. Jaeggi and colleagues (2008) not only found improvements on the task after training, but also this improvement was transferred to a different task that was a missing pattern was to be recognised. Also, Baniqued and colleagues (2015) employed “Mind Frontier”, a mobile game training program and found transfer effects on working memory n-back task after training. Visual search is a type of perceptual-attention skill that involves paying attention to scan an area and pick out an item. An analogue visual search task requires finding an odd item or items amongst a myriad of items. For example, Clark and colleagues (2015) trained participants on a visual search task for five days, one hour a day and found improved RT after training. Some might argue that these improvements after training are task-specific, which means they cannot be transferred to other tasks, or improve the executive functions in general, but many have found evidence of transfer of improvements (e.g. Banigued et al., 2015; Jaeggi et al., 2008). Nevertheless, the focus of this study is on task-specific improvement after training.

However, few studies have investigated the independent effects of sleep on this kind of cognitive training. Most studies have found that sleep deprivation (SD) impairs performance (Couyoumdjian et al., 2010; Bratzke et al., 2009; Nilson et al., 2005;

Steenari et al., 2003), and reduces task-related activation in the cortices (Chee et al., 2006; Thomas et al., 2000; Harrison et al., 2000). For example, Couyoumdjian and colleagues (2014) trained two groups of participants on a task-switching task four times on four consecutive mornings, SD group performed worse (accuracy and RT) than the sleep group after one night of sleep deprivation, and the effect of SD was eliminated after a recovery night. Also, studies have found that a nap or naps during the day after partial or complete sleep deprivation helps to improve task-switching performance (Kaida et al., 2013; Tempesta et al., 2013). On the other hand, Slama and colleagues (2015) studied the effect of a short afternoon nap (30 minutes) in the context of natural temporal drop of performance in mid-afternoon, they found that the nap group improved their task-switching performance after the nap whereas the control group's performance worsened after staying awake for the same duration of time as the nap. Furthermore, a correlation study has found that better sleep quality in terms of shorter Wake after Sleep Onset (WASO) and longer sleep duration is associated with better task-switching performance (Wilckens et al., 2014). However, none of the studies investigated whether sleep helps with post-training consolidation of task-switching skills. Other studies have found that SD also impairs arithmetic performance, and reduces prefrontal cortex (PFC) activity, an area critical for performing executive functions (Kim et al., 2001; Drummond et al., 1999). But no study to our knowledge has investigated the relationship between other aspects of sleep and arithmetic training. Studies of sleep and working memory gathered similar findings that SD affects working memory performance (Hagewoud et al., 2010; Turner et al., 2007; Mu et al., 2005). Also, Kuriyama and colleagues (2008) trained two groups of participants on a n-back working memory task and they found that subjects trained in the morning and then tested 10 hours later in the evening demonstrated no significant improvement but when they were retested again 10 hours later in the morning after a night of nocturnal sleep, there was significant improvement in the task performance but not RT. Similarly, another group of participants who were first trained in the evening demonstrated

significant improvement in task performance but not RT 10 hours later in the morning after a night of nocturnal sleep, but no significant improvement after another 10 hours of wake period when retested in the evening. This study demonstrated that post training consolidation of working memory training happens exclusively during sleep, which is similar to the time course of motor skill training (Walker et al., 2003; 2002). A more recent study (Scullin et al., 2012) also found that backward digit span performance, a type of working memory, improved after nocturnal sleep in patients being treated for Parkinson's disease. Furthermore, Nielsen and colleagues (2015) found a correlation between working memory performance (Corsi Block) and percentage of REM sleep. Thus, it is possible that other types of cognitive training could also benefit from post training consolidation during sleep. Studies on the effects of sleep on visual search training mainly focus on the memory aspects of perceptual learning. Performance was better after a nocturnal sleep or a nap when trials were repeated without the participants' awareness when implicit memory was involved (Geyer et al., 2013; Mednick et al., 2009). On the other hand, Karni and Sagi (1993) provided evidence of post training consolidation of textual segmentation after at least 8 hours, and this consolidation was facilitated when REM sleep was present during the consolidation stage (Karni et al., 1994). But, when it comes to visual search that involves top down attentional control, Sireteanu and Rettenbach (2000) did not find evidence of post training consolidation, and they argued all improvements happen during training. However, their study did not employ separate training time such as morning, evening and then morning to determine whether there is a difference between the efficacies of the mere passage of time or sleep. Thus, it is unknown whether sleep helps with post training consolidation of visual search training.

The question of whether sleep helps with post training consolidation of tasks requiring executive functions and fluid intelligence remain largely unanswered, and it remains unknown whether the temporal contribution of the consolidation of these skills and

different practice regimes would benefit the acquisition of these skills differently. We employed a mobile training platform called “Peak”, which contains a myriad of tasks that aim to train for various executive functions and fluid intelligence. In particular, we selected four tasks that train for task-switching, arithmetic, working memory and visual search. All tasks are adaptive in the level of difficulty with the amount of practice, and a scoring system is in place to gauge for improvement. We also employed Walker and colleagues’ (2003; 2002) training protocol that has two groups of participants, one group start the training in the morning, then are tested in the evening and then retested in the following morning, whereas the other group start the training in the evening, are then tested the following morning, and retested again in the evening. The aim of our study is to investigate the effects of sleep on the four types of higher order cognitive task training and to postulate the best time course for these task training. We hypothesize that there will be improvement in task performance after training, and the improvement is facilitated by a nocturnal sleep.

2. Method

2.1. Ethics and Participants

The research protocol was approved by University College London (UCL) Institute of Cognitive Neuroscience (ICN) ethics committee. Participants were screened for any history or ongoing neurological disease, mental health problems and sleep disorders. They were also instructed to refrain from any caffeinated or alcoholic beverages, as well as drugs at least a day prior to the experiment. Written informed consent was obtained from each participant. A total of 40 UCL students between the ages of 18 to 32 from were recruited. This includes 27 females (mean age ± SD: 21.73 ± 3.76) and 13 male participants (mean age ± SD: 23.92 ± 4.31). They were randomly allocated to Group A or Group B, 20 participants in each group. 23 participants were paid a remuneration fee of £20, and 17 were allocated course credits.

2.2. Design

It is a within-subject design as each participant participated in both testing sessions. Participants in Group A would start the game at 9 a.m. in the morning, then 9 p.m. in the evening, and 9 a.m. the next day morning, 12 hours apart from each session. Participants in Group B would start the game at 9 p.m., then next day 9 a.m. in the morning, and 9 p.m. in the evening, 12 hours apart from each session. The dependent variable is the test score of the four different tasks. The scoring system was designed in terms of level of difficulty, accuracy and reaction time adjusted for test scores of pilot subjects. The independent variable is the testing session (either tested after the wake period or after the sleep period). Dependent variables for correlation analyses are test scores and sleep variables.

2.3. Apparatus and measures

Participants' own touch screen smart mobile devices (iPhone or android devices) were used as a platform to assess the mobile APP "Peak – Brain Training" (Rainbow Limited, 2017), which contains four preselected tasks, "Refocus", "Size Count", "Tunnel Trance" and "Unique". These games became increasingly more difficult when they were repeatedly played. At the beginning of the first session for each of the four games, animated instructions were shown and they were repeated until the participants fully understood the task requirement and proceed to playing the games. The games become more difficult with repeated sessions. The scoring system was designed in terms of level of difficulty, accuracy and reaction time based on game designer experience and adjusted for test scores of their pilot subjects. The level of difficulty within a session was maintained. A new stimulus appeared immediately after answering the previous question in a session. Each game has a set time and the faster someone answers the questions the more questions can be answered and more points can be gained. A description of the scoring system for each game is described below.

For the scoring system, Refocus, Size Count and Tunnel Trance all use Peak's streak scoring system and Unique uses a slightly different streak addition system. Streak: One base score per difficulty with a multiplier which goes up and down based on streaks. Streak Addition: Baseline score per correct answer determined by difficulty level. Delta is added to the baseline and becomes larger with consecutive correct answers.

2.3.1. Task-switching - Refocus

This is a task-switching game. It tests the ability to shift attention between tasks. The analogue version is shown in Figure 1 below. Initially, there are two boxes aligned vertically. The question on top of the first box is always "Is the number even?" and the question below the second box is always "Is the letter a vowel?" for the first few sessions. The stimuli consist of a letter and a number such as "7M" that appears randomly either in the box on top or in the box below. Participants need to tap on either "Yes" or "No" to answer the question where the stimuli appear, and in this case, the correct answer should be "NO". As the game progresses with repeated sessions, there is an added level of difficulty with an additional box that asks, "Is the number odd?". There is a time limit of 1 minute per session. The more correct answers, the higher the mark granted per session. The faster the reaction time, the more questions can be answered. A multiplier is added to the scores if more answers are answered correctly in a row.

Figure 1.

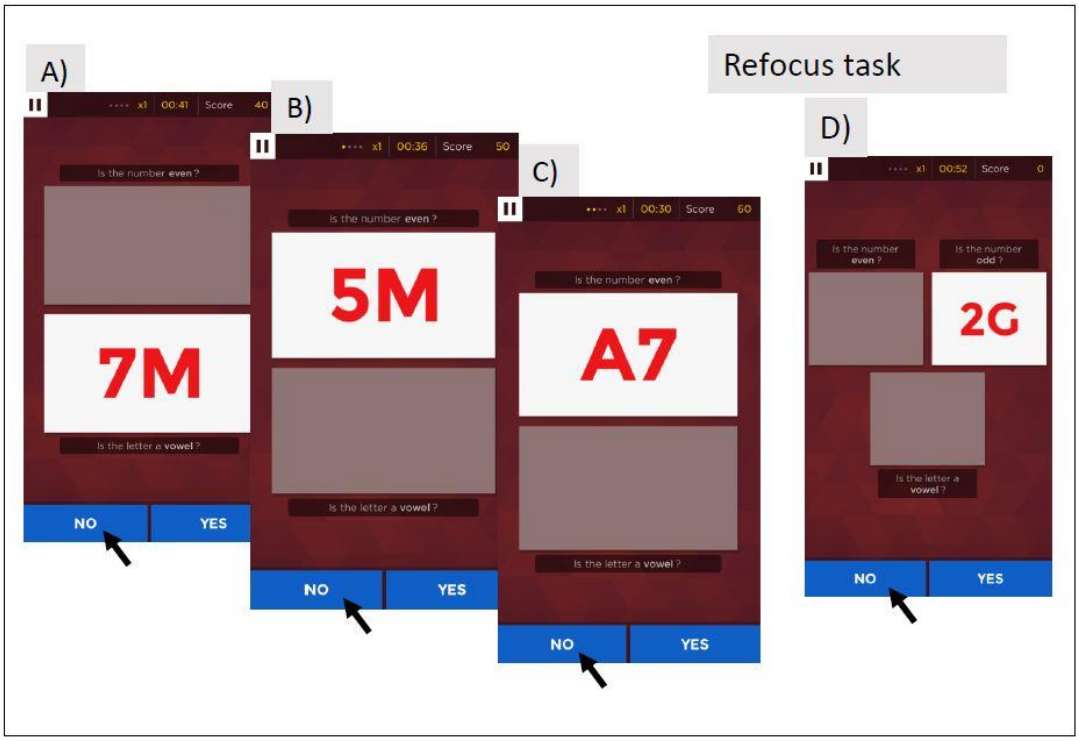


Figure 1 shows the Refocus analogue task-switching task user interface. A), B), and C) show changing stimuli within a session. The arrows point at the correct answers the participants were supposed to tap. D) shows a stimulus in a session with added difficulty as an additional question that asked “Is the number odd?” was added.

2.3.2. Arithmetic - Size Count

This is a game to test arithmetic ability (Figure 2). It starts with simple numbers and then adding equations to compare which number is larger, or asking whether both numbers are equal. With repeated sessions, it becomes more difficult as more equations and less single number comparisons appeared. The initial time given for each session is 50 seconds. Each correct answer would get a score depending on the level of difficulty for that session, and each wrong answer would receive a deduction of 3 seconds. There could be multiplier marks if more questions were answered correctly in a row.

Figure 2.

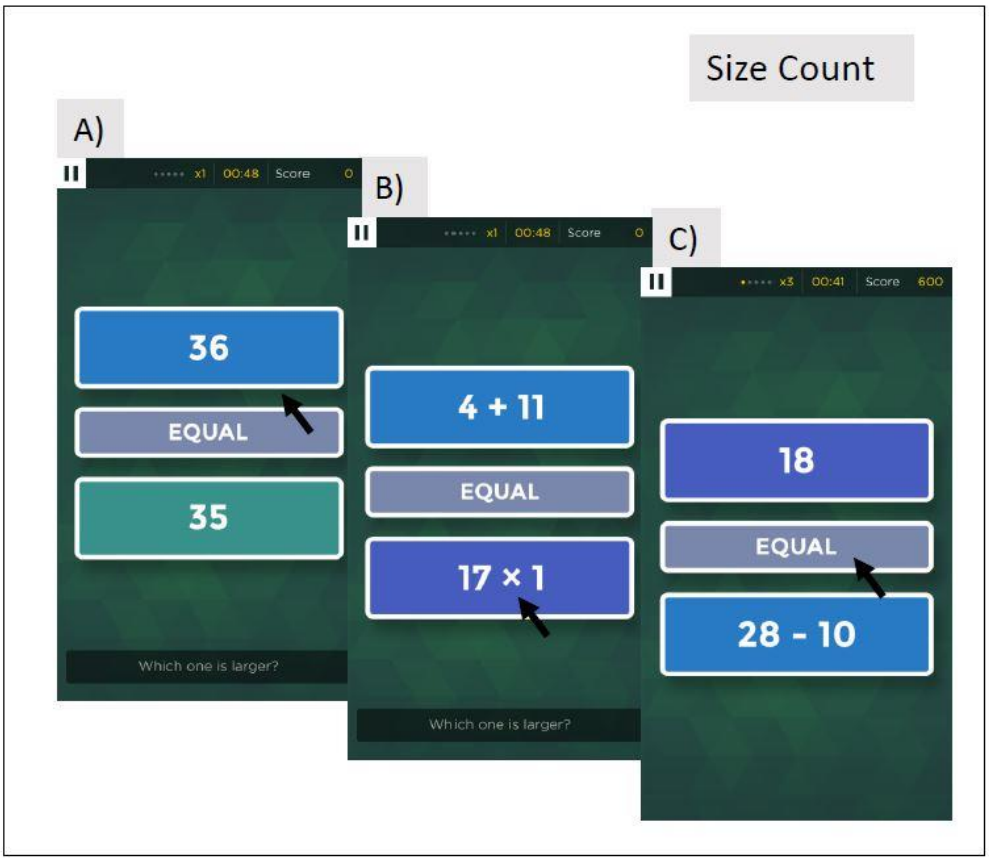


Figure 2 shows a Size Count analogue arithmetic task. The figure shows different stages and user interface within a session. A), B), and C) are three different stimuli within a session. The arrows show where the correct answers were to be tapped.

2.3.3. Working memory - Tunnel Trance

This is a classic n-back task that tests working memory (see figure 3). Each session lasts 45 seconds, each correct answer gains a point depending on the level of difficulty, more points are allocated if there are a few correct answers in a row. At the beginning of each session, it shows whether the session contains 2-back or 3-back tasks. The level of difficulty starts with the two-back task, participants needs to determine whether the position of the shape matches the one from two steps earlier. With repeated sessions, the level of difficulty increases, the two-back task becomes a three-back task, and participants need to determine whether the position of the shape matches the one from three steps earlier. Also, the colour of the shape may change and participants

need to determine not only the position but also whether the colour matches from two steps or three steps earlier.

Figure 3.

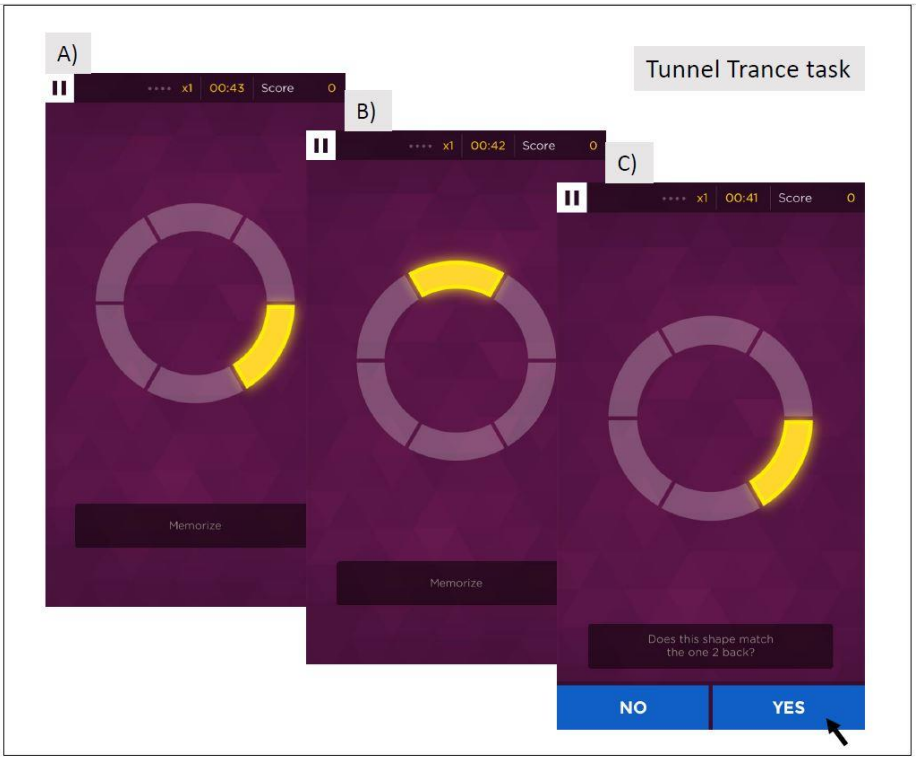


Figure 3 shows the Tunnel Trance analogue n-back task. The figure shows different stages and user interface of the task within a session. A) Participants were to memorize the location of the yellow shape. B) Participants were to memorize the location of the yellow shape. C) Participants were to answer whether the location of the yellow shape matches the one from two steps earlier, and in this case the answer is yes, they need to tap on “YES” on the screen as pointed out by the arrow.

2.3.4. Visual search - Unique

This is an analogue visual searching task. Each session lasts for 1 minutes and 10 seconds (see Figure 4). Participants were to visually search the odd shape out and tap on it. With repeated sessions, the level of difficulty rises in terms of number of shapes and characteristics of the shapes (colour, rotation). Each session lasts for 1 minute and 10 seconds. This task tests more specifically visual attention and visual recognition as the participant needs to pay attention while scanning the objects and recognise and

pick out the odd object in each trial. The locations of the odd objects are randomised so there is no memory component for this task.

Figure 4.

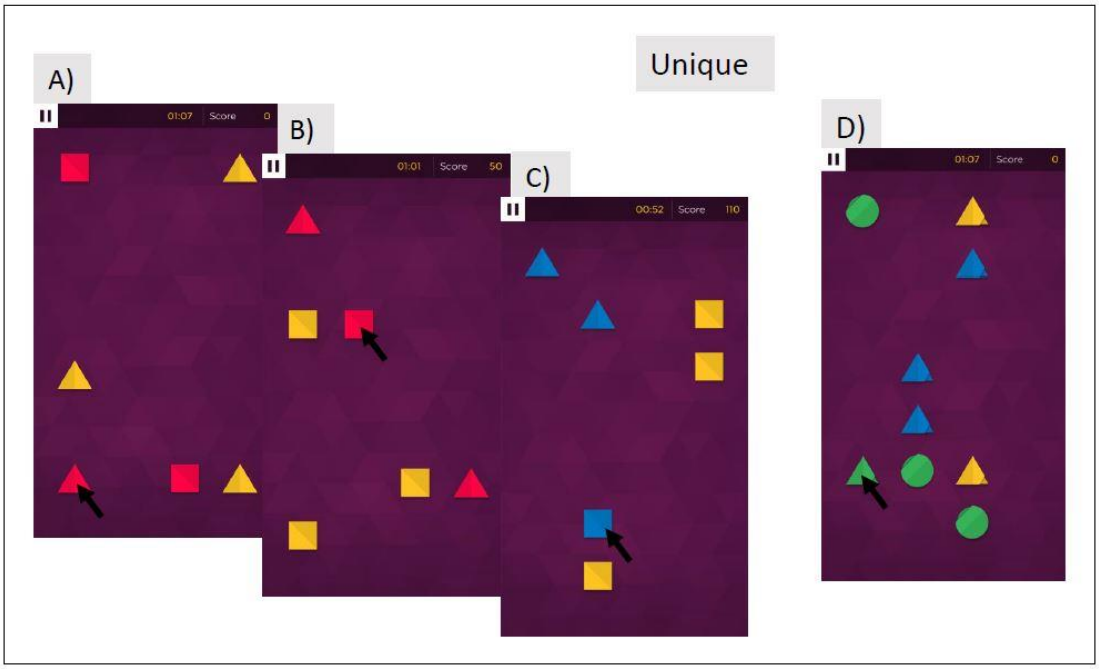


Figure 4 shows the Unique analogue visual search task. The figure shows different stages and user interface of the task within a session as well as increased difficulty in another session. A), B) and C) show different stages of the game within a session. D) shows another session with increased difficulty level. The arrows are pointing at the correct answers that should be tapped.

2.3.5. Sleep Measures

The Karolinska Sleep Diary (KSD, Akerstedt et al., 1994) was used to record subjective measures of sleep quality and duration.

2.4. Procedures

Subjects in Group A came to UCL ICN 9 a.m. in the morning to play the games, then 12 hours later at 9 p.m., and lastly 12 hours later at 9 a.m. the next day morning. Subjects in Group B came to UCL ICN 9p.m. in the evening to play the games, then 12 hours later 9 a.m. the next day morning, and lastly 12 hours later at 9 p.m. They were given an instruction sheet that provided all the information to download and log in with their individually assigned accounts. They were instructed to play each game five times

consecutively, after finishing playing one game, and move on to the next game. They were also told to note down the number of times they played the games to ensure they did not over play or under play the games. The order of the games was randomised for each subject. At the beginning of each game, they were shown animated instructions, and they were told to repeat the instructions as many times as they need and not to proceed to play the games until they fully understand the rules and requirements. On the second day morning, they were asked to fill in the KSD about their last night's sleep. At the end of the three sessions, a formal debrief was given to each participant.

2.5. Statistical Analysis

At the beginning, Peak created more than 40 accounts for this study. Each participant has his or her unique sign-in information. While playing the games, the data in terms of composite scores based on the number of correct answers and reaction time were automatically uploaded through the app after each session. Subjects were able to see their test scores for each session from the app. I then logged in to the research platform https://library.peak.net with my admin login information, and retrieved the composite scores and reaction time data from each subject for data analysis.

Between-subject t-tests with Bonferroni corrections were used to compare initial task performance and RT during training between Group A and Group B. Within-subject t-tests with Bonferroni corrections were used to compare task performance between sessions for both scores and RT in each group. Correlation analysis was used to correlate task performance or RT and various measures of sleep quality derived from KSD. All analyses were conducted using IBM SPSS Statistics (Version 22.0).

3. Results

3.1. Initial Training phase (Baseline score and reaction time)

All subjects were trained on the four games over 5 trials per game either at 9 a.m. or 9p.m. They had to finish training with one game before moving on to the next game. The order of the games was randomised. Independent *t*-tests were conducted, Bonferroni p-value was set at .0125. There were no significant differences in performance scores between subjects trained at 9 a.m. or 9 p.m. for all tasks (table 1).

However, there was a significant difference for Size Count RT (ms), t (193) = 2.9, p <. 05, Reaction time was significantly faster for Group B (Mean ± SD: 2557.24 ± 620.20) than Group A (Mean ± SD: 2809.44 ± 594.25) (table 2).

Table 1.

Variable	Initial Training 9 a.m.	Initial Training 9 p.m.	*t*	*df*	*p*
Refocus	3128.90 ± 1097.33	3158.97 ± 1404.52	-.17	195	.870
Size Count	6953.50 ± 6374.47	8376.53 ± 7618.91	-1.42	183.52	.160
Tunnel Trance	2006.61 ± 1173.19	2616.45 ± 4502.57	-1.30	193	.190
Unique	10989.00 ± 5720.30	11171.35 ± 6666.84	-.21	194	.840

Table 1 summarises the initial training scores statistics and t-tests between group A (9 a.m.) and group B (9 p.m.), which revealed that there was no significant difference between training at 9 a.m. or 9 p.m. for all tasks.

Table 2.

Variable	Initial Training 9 a.m.	Initial Training 9 p.m.	*t*	*df*	*p*
Refocus	1367.18 ± 476.92	1320.70 ± 397.82	.74	195	.460
Size Count	2809.44 ± 594.25	2557.24 ± 620.20	2.90	193	.004**
Tunnel Trance	1596.39 ± 747.19	1523.02 ± 515.20	.79	192	.430
Unique	3493.46 ± 958.79	3347.01 ± 833.20	-.21	194	.260

Table 2 summarises the initial training RT (ms) statistics and t-tests between group A (9 a.m.) and group B (9 p.m.), which revealed that there was no significant difference between training at 9 a.m. or 9 p.m. for Refocus, Tunnel Trance and Unique. However, there is a significant difference for Size Count, t (193) = 2.9, p <. 0125, Reaction time was significantly faster for Group B (Mean ± SD: 2557.24 ± 620.20) than Group A (Mean ± SD: 2809.44 ± 594.25).

3.2. Group A: Cognitive performance following Wake then Sleep

20 subjects were trained first at 9 a.m. in the morning, then tested on 9 p.m. the same day, and then retested at 9 a.m. the next day morning to determine whether a night of

sleep could help to improve the performance of various tasks (see table 3-8, figure 5-6). A series of 12 *t*-test were conducted, significant p-value was set at 0.004 with Bonferroni correction. For Refocus, subjects demonstrated a significant 35% improvement in performance following the wake period [*t* (96) = -6.02, *p* < .0001], a further significant 128% improvement after the sleep period [*t* (94) = -14.45, *p* < .0001], and an overall 210% significant improvement from initial training to final retest [*t* (94) = -14.45, *p* < .0001]. For Unique, subjects demonstrated a significant 49% improvement in performance following the wake period [t (99) = -8.57, *p* < .0001], a further significant 18% improvement after the sleep period [*t* (99) = -4.95, *p* < .0001], and an overall 76% significant improvement from initial training to final retest [*t* (99) = -13.10, *p* < .0001]. For Tunnel Trance, subjects demonstrated a significant 37% improvement in performance following the wake period [*t* (98) = -6.83, *p* < .0001], however, there is a significant 18% drop after the sleep period [*t* (94) = 3.12, *p* = .002], and there is no significant difference from initial training to final retest [*t* (94) = -1.20, *p* > .05]. For Size count, subjects demonstrated no significant improvement in performance following the wake period [*t* (97) = -2.05, *p* > .004], no significant further improvement following the sleep period [*t* (97) = 1.55, *p* > .05], and no overall significant difference from initial training to final retest [*t* (99) = - .27, *p* > .05].

For Refocus RT, subjects demonstrated a significant 20% decrease in RT following the wake period [*t* (96) = 9.04, *p* < .0001], following with no significant difference after the sleep period [*t* (92) = -1.39, *p* > .05], and an overall 18% significant decrease in RT from initial training to final retest [*t* (94) = 5.84, *p* < .0001]. For Size Count RT, subjects demonstrated no significant difference in RT following the wake period [*t* (97) = 3.56, *p* > .004], following with a significant 12% increase in RT after the sleep period [*t* (97) = -5.20, *p* < .0001], but no significant difference in RT from initial training to final retest [*t* (99) = -.50, *p* > .05]. For Tunnel Trance RT, subjects demonstrated a significant 23% decrease in RT following the wake period [*t* (97) = 3.56, *p* < .0001], following with no

significant difference after the sleep period [*t* (94) = - .33, *p* > .05], and an overall 21% significant decrease in RT from initial training to final retest [*t* (94) = 6.17, *p* < .0001]. For Unique RT, subjects demonstrated no significant difference in RT following the wake period [*t* (99) = .74, *p* > .05], following with no significant difference after the sleep period [*t* (99) = -.64, *p* > .05], and no significant difference in RT from initial training to final retest [*t* (99) = .24, *p* > .05].

Table 3.

Variable	Initial Training 9 a.m.	9 p.m.	*t*	*df*	*p*
Refocus	3128.90 ± 1097.33	4234.34 ± 1808.50	-6.02	96	.000***
Size Count	6953.50 ± 6374.47	8391.80 ± 8095.12	-2.05	97	.043
Tunnel Trance	2006.61 ± 1173.19	2755.71 ± 1330.53	-6.83	98	.000***
Unique	10989.00 ± 5720.30	16394.30 ± 4637.78	-8.57	99	.000***

Table 3 summarises the results of *t*-tests (scores) between initial training and first test after 12 hours of waking at 9 p.m. There was a significant difference for Refocus**,** *t* (96) = -6.02, *p* < .0001, performance was significantly improved after 12 hours of wake (Mean ± SD: 4234.34 ± 1808.50) than initial training (Mean ± SD: 3128.90 ± 1097.33); for Size count, *t* (97) = -2.05, *p* > .004, there was no significant improvement in performance after 12 hours of wake (Mean ± SD: 8391.80 ± 8095.12) than initial training (Mean ± SD: 6953.50 ± 6374.47); for Tunnel Trance, *t* (98) = -6.83, *p* < .0001, performance was significantly improved after 12 hours of wake (Mean ± SD: 2755.71 ± 1330.53) than initial training (Mean ± SD: 2006.61 ± 1173.19); for Unique, *t* (99) = -8.57, *p* < .0001, performance was significantly improved after 12 hours of wake (Mean ± SD: 16394.30 ± 4637.78) than initial training (Mean ± SD: 10989.00 ± 5720.30).

Table 4.

Variable	Initial Training 9 a.m.	9 p.m.	*t*	*df*	*p*
Refocus	1367.18 ± 476.92	1090.61 ± 282.23	9.04	96	.000***
Size Count	2809.44 ± 594.25	2549.27 ± 605.16	3.56	97	.001**
Tunnel Trance	1596.39 ± 747.19	1236.04 ± 761.19	6.41	98	.000***
Unique	3493.46 ± 958.79	3390.23 ± 1152.34	.74	99	.460

Table 4 summarises the results of RT (ms) *t*-tests between initial training RT and first test after 12 hours of wake at 9 p.m. There was a significant difference for Refocus**,** *t* (96) = -9.04, *p* < .0001, RT was significantly faster after 12 hours of wake (Mean ± SD: 1090.61 ± 282.23) than initial training (Mean ± SD: 1367.18 ± 476.92); for Size count, *t* (97) = 3.56, *p* < .05, RT was significantly faster after 12 hours of wake (Mean ± SD: 2549.27 ± 605.16) than initial training (Mean ± SD: 2809.44 ± 594.25); for Tunnel Trance, *t* (98) = 6.41, *p* < .0001, RT was significantly faster after 12 hours of wake (Mean ± SD: 1236.04 ± 761.19) than initial training (Mean ± SD: 1596.39 ± 747.19). There was no significant difference in RT for Unique, *t* (99) = .74, *p* > .05.

Table 5.

Variable	9 p.m.	9 a.m.	*t*	*df*	*p*
Refocus	4243.16 ± 1827.09	9695.47 ± 5041.16	-10.90	92	.000***
Size Count	8391.80 ± 8095.12	7142.30 ± 5845.10	1.55	97	1.25
Tunnel Trance	2755.71 ± 1330.53	2258.74 ± 1389.49	3.12	94	.002**
Unique	16394.30 ± 4637.78	19362.40 ± 6073.85	-4.95	99	.000***

Table 5 summarises the results of *t*-tests (scores) between first test at 9 p.m. and retest after 12 hours including a night of sleep at 9 a.m. There was a significant difference for Refocus**,** *t* (92) = -10.90, *p* < .0001, performance was significantly improved after sleep (Mean ± SD: 9695.47 ± 5041.16) than first test at 9 p.m. (Mean ± SD: 4232.16 ± 1827.09); for Tunnel Trance, *t* (94) = 3.12, *p* = .002, performance was significantly dropped after sleep (Mean ± SD: 2258.74 ± 1389.49) than first test at 9 p.m. (Mean ± SD: 2755.71 ± 1330.53); for Unique, **,** *t* (99) = -4.95, *p* < .0001, performance was significantly improved after sleep (Mean ± SD: 19362.40 ± 6073.85) than first test at 9 p.m. (Mean ± SD: 16394.30 ± 4637.78). There was no significant difference for Size Count, *t* (97) = 1.55, *p* = 1.25.

Table 6.

Variable	9 p.m.	9 a.m.	*t*	*df*	*p*
Refocus	1090.61 ± 282.23	1125.22 ± 249.26	-1.39	92	.170
Size Count	2549.27 ± 605.16	2844.82 ± 631.34	-5.20	97	.000***
Tunnel Trance	1236.04 ± 761.19	1262.17 ± 618.65	- .33	94	.740
Unique	3390.23 ± 1152.34	3471.09 ± 783.25	-.64	99	.522

Table 6 summarises the results of RT (ms) *t*-tests between first test at 9 p.m RT. and retest after 12 hours including a night of sleep at 9 a.m. There was a significant difference for Size Count**,** *t* (97) = -5.20, *p* < .0001, RT was significantly slower after sleep (Mean ± SD: 2844.82 ± 631.34) than first test at 9 p.m. (Mean ± SD: 2549.27 ± 605.16). However, there was no significant difference for Refocus, *t* (92) = -1.39, *p* > .05, Tunnel Trance, *t* (94) = - .33, *p* > .05, and Unique, *t* (99) = - .64, *p* > .05.

Table 7.

Variable	Initial Training 9 a.m.	9 a.m. (24 hour later)	*t*	*df*	*p*
Refocus	3128.90 ± 1097.33	9695.47 ± 5041.16	-14.45	94	.000***
Size Count	6953.50 ± 6374.47	7142.30 ± 5845.10	-.27	99	.790
Tunnel Trance	2006.61 ± 1173.19	2258.74 ± 1389.49	-1.20	94	.240
Unique	10989.00 ± 5720.30	19362.40 ± 6073.85	-13.10	99	.000***

Table 7 summarises the results of *t*-tests (scores) between initial training and last retest after 24 hours including a night of Sleep at 9 a.m. There was a significant difference for Refocus**,** *t* (94) = -14.45, $p < .0001$, performance was significantly improved after 24 hours (Mean ± SD: 9695.47 ± 5041.16) than initial training (Mean ± SD: 3128.90 ± 1097.33); for Unique, *t* (99) = -13.10, $p < .0001$, performance was significantly improved after 24 hours (Mean ± SD: 19362.40 ± 6073.85) than initial training (Mean ± SD: 10989.00 ± 5720.30). There was no significant differences for Size Count, *t* (99) = - .27, $p = .79$ and Tunnel Trance *t* (94) = -1.20, $p = .24$.

Table 8.

Variable	Initial Training 9 a.m.	9 a.m. (24 hour later)	*t*	*df*	*p*
Refocus	1367.18 ± 476.92	1125.22 ± 249.26	5.84	94	.000**
Size Count	2809.44 ± 594.25	2844.82 ± 631.34	- .50	99	.620
Tunnel Trance	1596.39 ± 747.19	1262.17 ± 618.65	6.17	94	.000***
Unique	3493.46 ± 958.79	3471.09 ± 783.25	.24	99	.810

Table 8 summarises the results of RT (ms) *t*-tests between initial training and last retest after 24 hours including a night of Sleep at 9 a.m. There was a significant difference for Refocus**,** *t* (94) = 5.84, $p < .0001$, RT was significantly faster after 24 hours (Mean ± SD: 1125.22.47 ± 249.26) than initial training (Mean ± SD: 1367.18 ± 476.92), and for Tunnel Trance, *t* (94) = 6.17, $p < .0001$, RT was significantly faster after 24 hours (Mean ± SD: 1262.17 ± 618.65) than initial training (Mean ± SD: 1596.39 ± 747.19). There were no significant differences for Size Count, *t* (99) = - .50, $p > .05$ and Unique *t* (99) = .24, $p > .05$.

Figure 5.

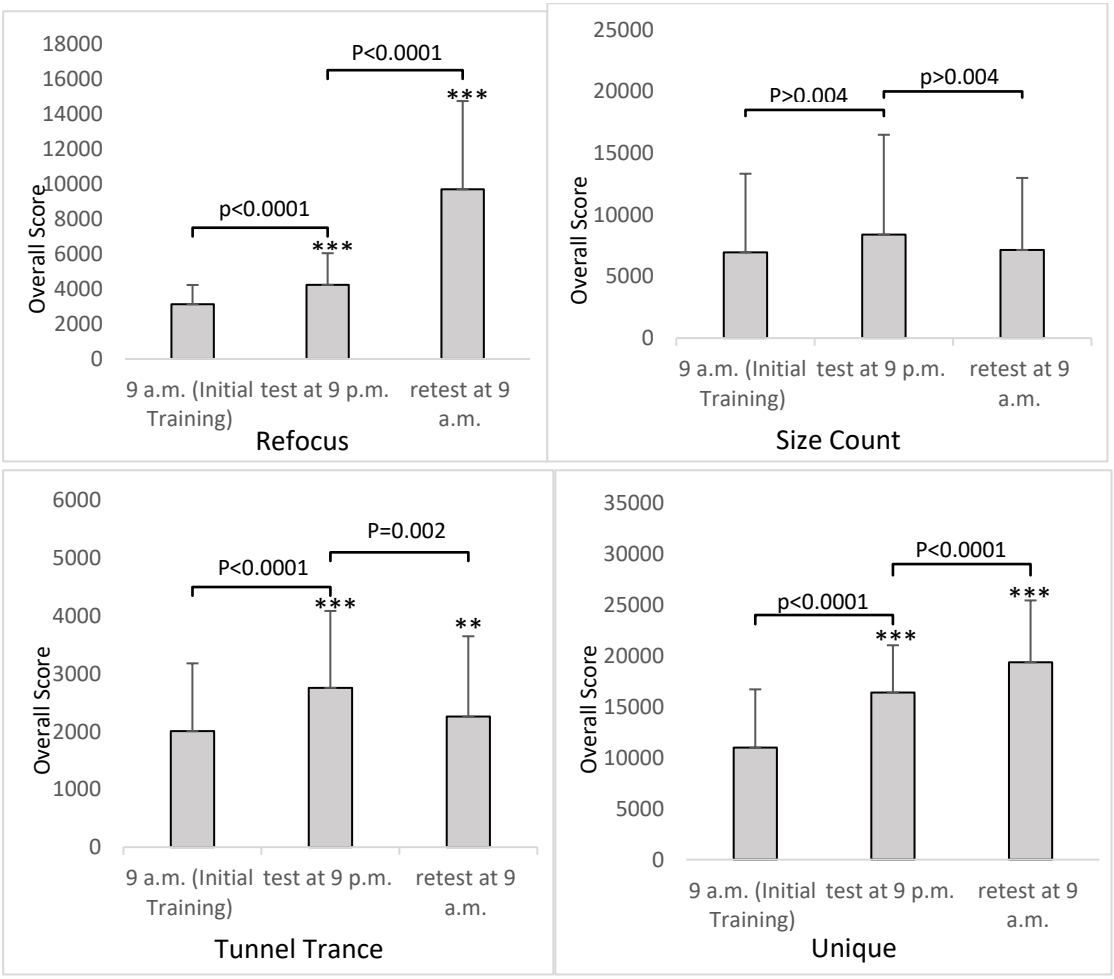


Figure 5 shows differential effects of wake and sleep on the four tasks performed by group A. For both Refocus and Unique, significant improvement were shown after both wake period (tested at 9 p.m.) and after sleep period (tested at 9 a.m.). Performance for Size count only had a significant improvement after wake period at 9 p.m. Performance for Tunnel Trance was significanlty improved after wake period but significantly dropped after sleep.

Figure 6.

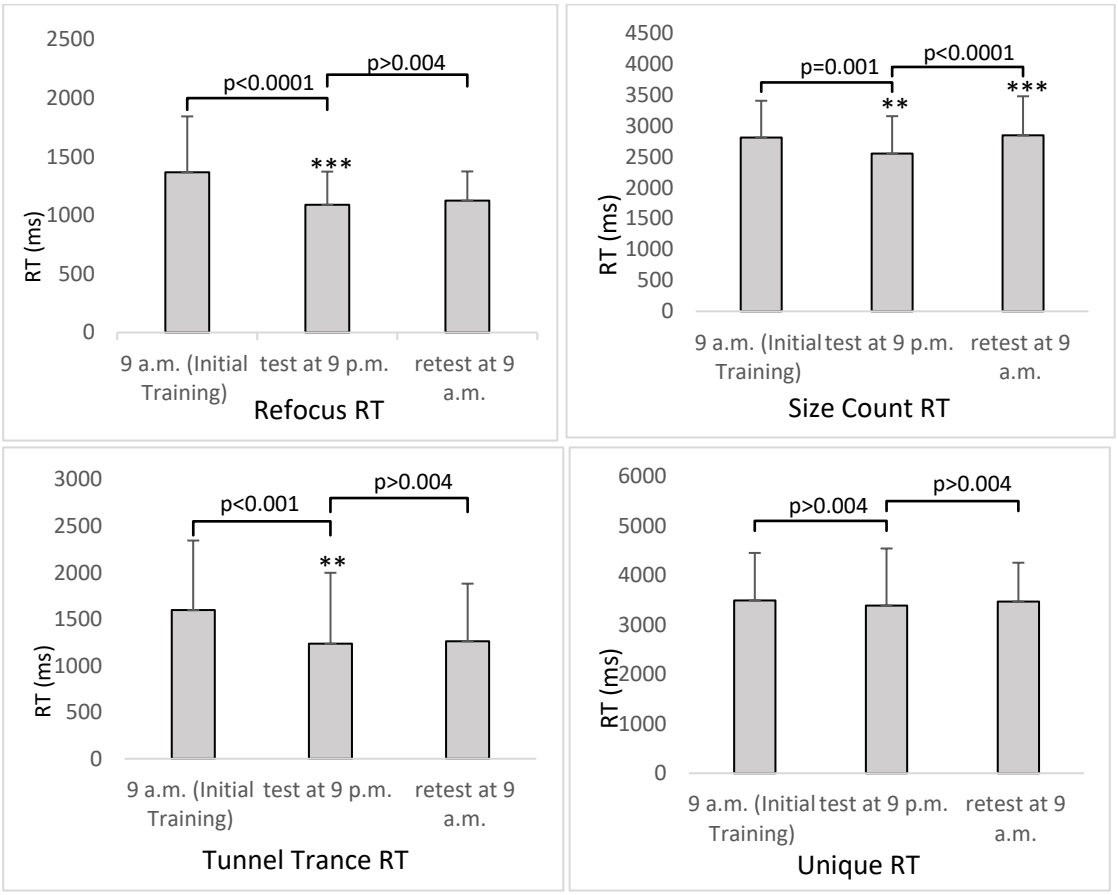


Figure 6 shows differential effects of wake and sleep on the RT pf the four tasks performed by group A. For Refocus, significant decrease were shown after wake period (tested at 9 p.m.) but no significant difference after sleep period (tested at 9 a.m.). For Size count, significant decrease in RT was found after wake period at 9 p.m, and significant increase in RT was found after sleep period at 9 a.m. For Tunnel Trance, significant decrease was found after wake period, and no significant difference was found after sleep period. There is no significant difference in RT between all sessions for Unique.

3.3. Group B: Cognitive Performance following Sleep then Wake

20 subjects were trained first 9 p.m. in the evening, then tested on 9 a.m. the next day morning, and then retested on 9 p.m. on the same day to determine whether a night of sleep could help to improve the performance of various tasks (see table 9-14, figure 7-8). A series of 12 *t*-tests were conducted with the significant p-value set at .004 after Bonferroni correction. For Refocus, subjects demonstrated a significant 181% improvement in performance following the sleep period [t (94) = -11.53, p < .0001], a

further significant 33% improvement after the wake period [*t* (89) = -4.87, *p* < .0001], and an overall 274% significant improvement from initial training to final retest [*t* (89) = -11.76, *p* < .0001]. For Unique, subjects demonstrated a significant 48% improvement in performance following the sleep period [t (92) = -7.98*, p* < .0001], a further significant 49% improvement after the wake period [*t* (89) = -2.42*, p* > .004], and an overall 120% significant improvement from initial training to final retest [*t* (89) = -4.03*, p* < .0001]. For Tunnel Trance, subjects showed no significant improvement in performance following the sleep period [*t* (93) = -1.21*, p* > .05], however, there is a significant 19% improvement after the wake period [*t* (88) = -2.46*, p* > .004], and there is an overall 35% significant improvement from initial training to final retest [*t* (89) = -3.56*, p* = .001]. For Size count, subjects demonstrated no significant difference in performance following the sleep period [*t* (92) = .70*, p* > .05], and following the wake period [*t* (88) = .59, *p* > .05], and no overall significant difference from initial training to final retest [*t* (88) = .59, *p* > .05].

For Refocus RT, subjects demonstrated a significant 17% decrease in RT following the sleep period [*t* (94) = 5.60, *p* < .0001], a further significant 6% decreased after the wake period [*t* (89) = 3.32, *p* < .05], and an overall 21% significant decrease in RT from initial training to final retest [*t* (89) = 6.80, *p* < .0001]. For Size Count RT, subjects demonstrated a significant 10% increase in RT following the sleep period [*t* (92) = -4.47, *p* < .0001], followed by no significant difference after the wake period [*t* (89) = .66, *p* > .05], and no overall significant difference in RT from initial training to final retest [*t* (88) = -2.76, *p* > .004]. For Tunnel Trance RT, subjects demonstrated a significant 15% decrease in RT following the sleep period [*t* (92) = -5.11, *p* < .0001], a further significant 10% decreased after the wake period [*t* (88) = 3.54, *p* > .004], and an overall 23% significant decrease in RT from initial training to final retest [*t* (88) = 7.66, *p* < .0001]. For Unique RT, subjects demonstrated a significant 14% increase in RT following the sleep period [*t* (92) = -3.99, *p* < .0001], followed by no significant difference after the

wake period [*t* (89) = 3.22, *p* > .0504], and no significant difference in RT from initial training to final retest [*t* (89) = -.84, *p* > .05].

Table 9.

Variable	Initial Training 9 p.m.	9 a.m.	*t*	*df*	*p*
Refocus	3136.00 ± 1437.38	8813.23 ± 5147.60	-11.53	94	.000***
Size Count	8376.53 ± 7618.91	7830.32 ± 6409.82	.704	92	.483
Tunnel Trance	2616.45 ± 4502.57	2980.09 ± 3766.41	-1.21	93	.228
Unique	11171.35 ± 6666.84	16480.74 ± 6729.04	-7.98	92	.000***

Table 9 summarises the results of *t*-tests (scores) between initial training and first test after 12 hours of sleep period at 9 a.m. There was a significant difference for Refocus**,** *t* (94) = -11.53, *p* < .0001, performance was significantly improved after 12 hours of sleep (Mean ± SD: 8813.23 ± 5147.60) than initial training (Mean ± SD: 3136.00 ± 1437.38); for Unique, *t* (92) = -7.98, *p* < .0001, performance was significantly improved after 12 hours of sleep (Mean ± SD: 16480.74 ± 6729.04) than initial training (Mean ± SD: 11171.35 ± 6666.84). There is no significant difference for Size Count, *t* (92) = - .704, *p* = .483, and Tunnel Trance, *t* (93) = -1.21, *p* = .228.

Table 10.

Variable	Initial Training 9 p.m.	9 a.m.	*t*	*df*	*p*
Refocus	1320.70 ± 397.82	1102.07 ± 139.34	5.60	94	.000***
Size Count	2557.24 ± 620.20	2820.51 ± 553.73	-4.47	92	.000***
Tunnel Trance	1523.02 ± 515.20	1298.67 ± 455.64	-5.11	92	.000***
Unique	3347.01 ± 833.20	3814.07 ± 910.77	-3.99	92	.000***

Table 10 summarises the results of RT (ms) *t*-tests between initial training RT and first test after 12 hours of sleep period at 9 a.m. There was a significant difference for Refocus**,** *t* (94) = 5.60, *p* < .0001, RT was significantly decreased after 12 hours of sleep (Mean ± SD: 1102.07 ± 139.34) than initial training (Mean ± SD: 1320.70 ± 397.82); for Size Count, *t* (92) = -4.47, *p* < .0001, RT was significantly increased after 12 hours of sleep (Mean ± SD: 2820.51 ± 553.73) than initial training (Mean ± SD: 2557.24 ± 620.20); for Tunnel Trance, *t* (92) = -5.11, *p* < .0001, RT was significantly decreased after 12 hours of sleep (Mean ± SD: 1298.67 ± 455.64) than initial training (Mean ± SD: 1523.02 ± 515.20); for Unique, *t* (92) = -3.99, *p* < .0001, RT was significantly increased after 12 hours of sleep (Mean ± SD: 3814.07 ± 910.77) than initial training (Mean ± SD: 3347.01 ± 833.20).

Table 11.

Variable	9 a.m.	9 p.m.	*t*	*df*	*p*
Refocus	8813.23 ± 5147.60	11714.56 ± 7270.59	-4.87	89	.000***
Size Count	7830.32 ± 6409.82	7840.11 ± 7143.12	-.516	89	.607
Tunnel Trance	2980.09 ± 3766.41	3544.22 ± 4703.36	-2.46	88	.016
Unique	16480.74 ± 6729.04	24603.78 ± 31940.79	-2.42	89	.018

Table 11 summarises the results of *t*-tests (scores) between first test at 9 a.m. and retest after 12 hours of wake period at 9 p.m. There was a significant difference for Refocus**,** *t* (89) = -4.87, $p < .0001$, performance was significantly improved after wake (Mean ± SD: 11714.56 ± 7270.59) than first test at 9 a.m. (Mean ± SD: 8813.23 ± 5147.60); for Tunnel Trance, *t* (88) = -2.46, $p < .05$, performance was significantly dropped after wake (Mean ± SD: 3544.22 ± 4703.36) than first test at 9 a.m. (Mean ± SD: 2980.09 ± 3766.41); for Unique, **,** *t* (89) = -2.42, $p < .05$, performance was significantly improved after wake (Mean ± SD: 24603.78 ± 31940.79) than first test at 9 a.m. (Mean ± SD: 16480.74 ± 6729.04). There was no significant difference for Size Count, *t* (89) = -.516, $p > .05$.

Table 12.

Variable	9 a.m.	9 p.m.	*t*	*df*	*p*
Refocus	1102.07 ± 139.34	1038.71 ± 174.32	3.32	89	.001**
Size Count	2820.51 ± 553.73	2805.18 ± 681.03	.66	89	.510
Tunnel Trance	1298.67 ± 455.64	1173.13 ± 492.17	3.54	88	.001**
Unique	3814.07 ± 910.77	3441.36 ± 744.03	3.22	89	.002**

Table 12 summarises the results of RT (ms) *t*-tests between first test at 9 a.m RT. and retest after 12 hours of wake period at 9 pm. There was a significant difference for Refocus**,** *t* (89) = 3.32, $p < .05$, RT was significantly decreased after wake (Mean ± SD: 1038.71 ± 174.32) than first test at 9 a.m. (Mean ± SD: 1102.07 ± 139.34); for Tunnel Trance, *t* (88) = 3.54, $p < .05$, RT was significantly decreased after wake (Mean ± SD: 1173.13 ± 492.17) than first test at 9 a.m. (Mean ± SD: 1298.67 ± 455.64); for Unique, **,** *t* (89) = 3.22, $p < .05$, RT was significantly decreased after wake (Mean ± SD: 3441.36 ± 744.03) than first test at 9 a.m. (Mean ± SD: 3814.07 ± 910.77). There was no significant difference for Size Count, *t* (89) = .66, $p > .05$.

Table 13.

Variable	Initial Training 9 a.m.	9 p.m. (24 hour later)	*t*	*df*	*p*
Refocus	3136.00 ± 1437.38	11714.56 ± 7270.59	-11.76	89	.000***
Size Count	8376.53 ± 7618.91	7840.11 ± 7143.12	.59	88	.559
Tunnel Trance	2616.45 ± 4502.57	3544.22 ± 4703.36	-3.56	89	.001**
Unique	11171.35 ± 6666.84	24603.78 ± 31940.79	-4.03	89	.000***

Table 13 summarises the results of *t*-tests (scores) between initial training and last retest after 24 hours including a night of Sleep at 9 p.m. There was a significant difference for Refocus**,** *t* (89) = -11.76, $p < .0001$, performance was significantly improved after 24 hours (Mean ± SD: 11714.56 ± 7270.59) than initial training (Mean ± SD: 3136.00 ± 1437.38); for Tunnel Trance, *t* (89) = -3.56, $p = .001$, performance was significantly improved after 24 hours (Mean ± SD: 3544.22 ± 4703.36) than initial training (Mean ± SD: 2616.45 ± 4502.57); for Unique, *t* (89) = -4.03, $p < .0001$, performance was significantly improved after 24 hours (Mean ± SD: 24603.78 ± 31940.79) than initial training (Mean ± SD: 11171.35 ± 6666.84). There was no significant differences for Size Count, *t* (88) = .59, $p = .56$.

Table 14.

Variable	Initial Training 9 a.m.	9 p.m. (24 hour later)	*t*	*df*	*p*
Refocus	1320.70 ± 397.82	1038.71 ± 174.32	6.80	89	.000***
Size Count	2557.24 ± 620.20	2805.18 ± 681.03	-2.76	88	.007
Tunnel Trance	1523.02 ± 515.20	1173.13 ± 492.17	7.66	88	.000***
Unique	3347.01 ± 833.20	3441.36 ± 744.03	-.84	89	.401

Table 14 summarises the results of RT (ms) *t*-tests between initial training RT and last retest after 24 hours including a night of Sleep at 9 p.m. There was a significant difference for Refocus**,** *t* (89) = 6.80, $p < .0001$, RT was significantly decreased after 24 hours (Mean ± SD: 1038.71 ± 174.32) than initial training (Mean ± SD: 1320.70 ± 397.82); for Size Count, *t* (88) = -2.76, $p < .05$, RT was significantly increased after 24 hours (Mean ± SD: 2805.18 ± 681.03) than initial training (Mean ± SD: 2557.24 ± 620.20); for Tunnel Trance, *t* (88) = 7.66, $p < .0001$, RT was significantly decreased after 24 hours (Mean ± SD: 1173.13 ± 492.17) than initial training (Mean ± SD: 1523.02 ± 515.20). There were no significant differences for Unique, *t* (89) = -.84, $p > .05$.

Figure 7.

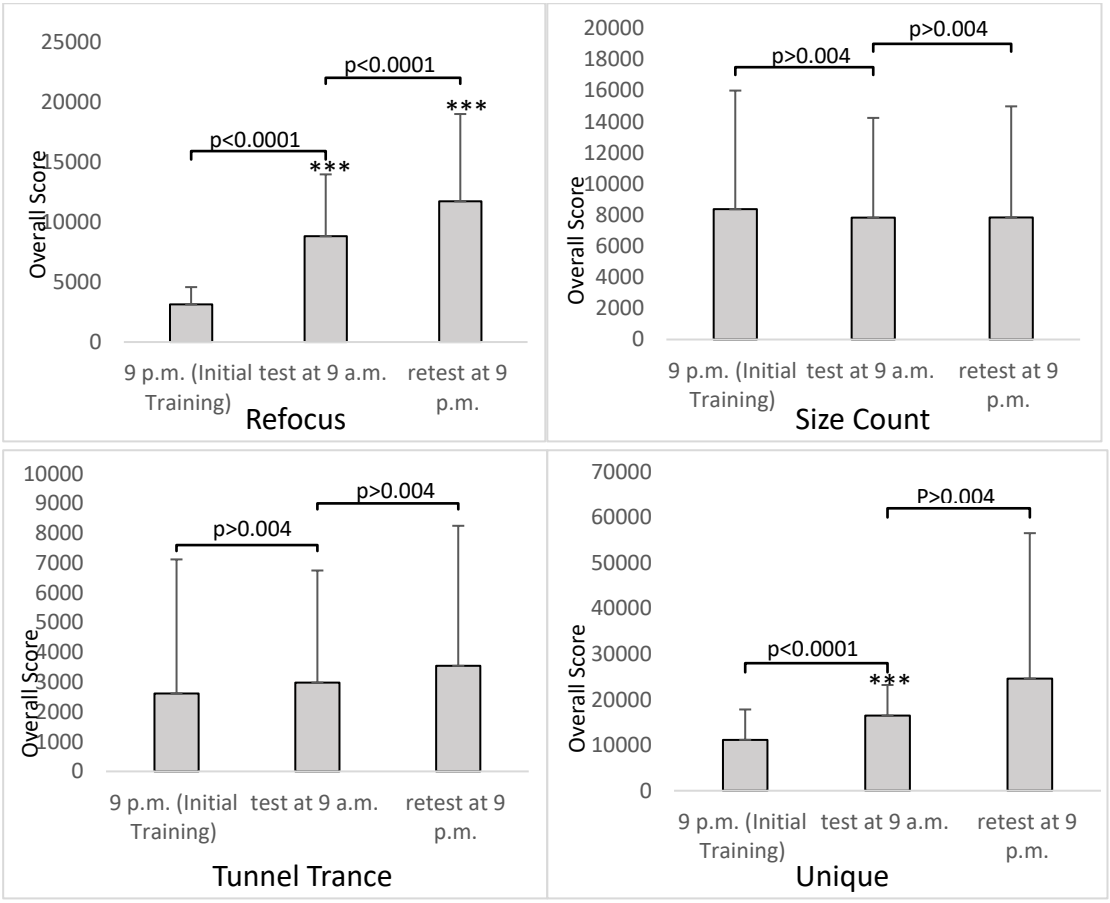


Figure 7 shows differential effects of sleep and swake on the four tasks performed by group B. For both Refocus and Unique, significant improvement were shown after both sleep period (tested at 9 a.m.) and after wake period (tested at 9 p.m.). There was no significant difference in the performance for between the initial training, test and retest sessions for Size Count. There was no significant difference between initial training and first test, but there is a significant improvement between test and retest for Tunnel Trance.

Figure 8.

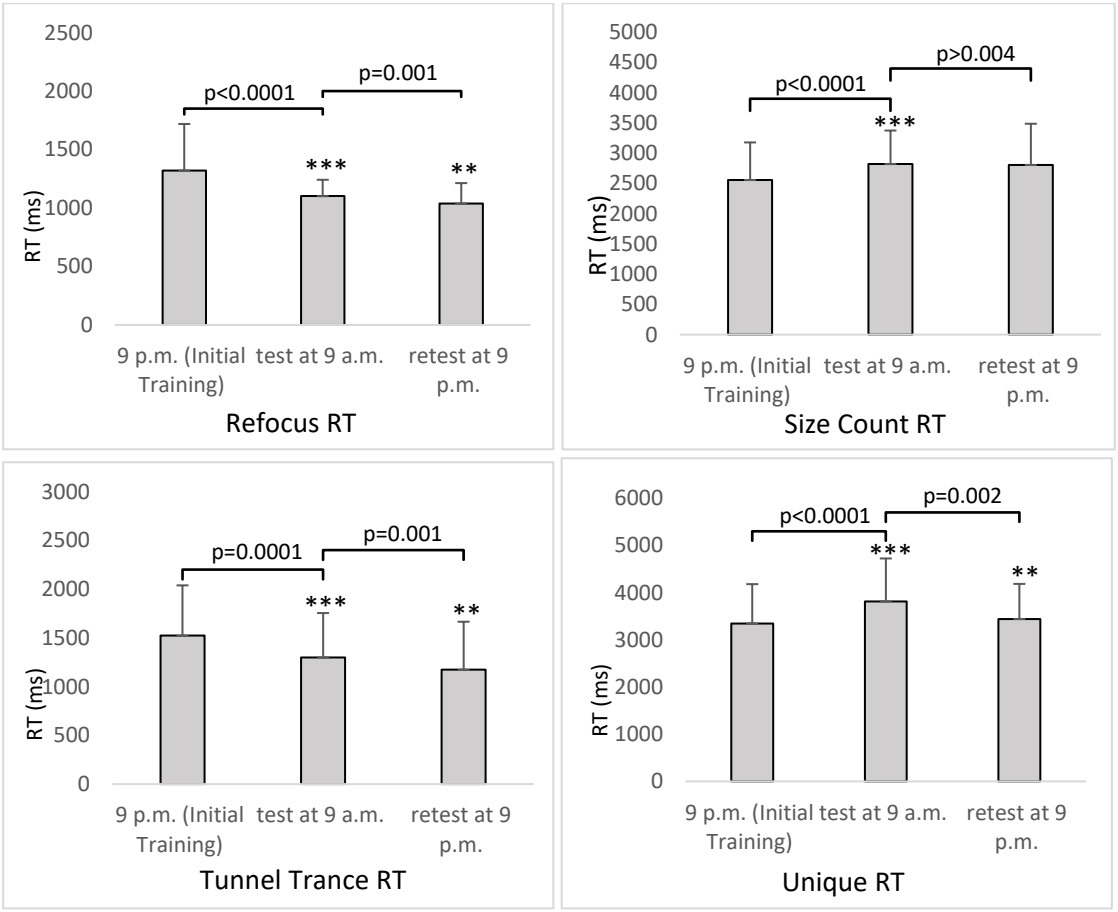


Figure 8 shows differential effects of sleep and swake on the RT of the four tasks performed by group B. For both Refocus and Tunnel Trance, significant decrease in RT were shown after both sleep period (tested at 9 a.m.) and after wake period (tested at 9 p.m.). For both Size Count and Unique, there were a significant increase in RT after sleep period (tested at 9 a.m.), followed by no significant difference after wake period for Size Count, and significant decrease in RT after wake period for Unique.

3.4. Correlations between overnight task improvement and sleep variables

Correlation analyses were carried out to determine whether there is any correlation between the percentage of overnight improvement (score and RT) from previous test and various self-reported sleep variables from KSS sleep diary. However, no significant correlation was found (see table 8-9).

Table 8.

% task improvement overnight	Sleep diary variables	n	*r* value	*p* value
Refocus	Bed time (minutes from midnight)	39	.11	.50
	Wake time (minutes from 0800)	39	.10	.54
	SOL	39	-.21	.20
	Sleep quality	39	-.16	.34
	Sleep efficiency (%)	39	.23	.16
	Time in bed (min)	39	.04	.83
	Total sleep duration (min)	39	.05	.78
	WASO (min)	39	.16	.34
	Number of awakenings	39	.16	.34
Size Count	Bed time (minutes from midnight)	39	-.07	.69
	Wake time (minutes from 0800)	39	-.03	.86
	SOL	39	-.01	.94
	Sleep quality	39	-.13	.42
	Sleep efficiency (%)	39	.20	.23
	Time in bed (min)	39	.05	.77
	Total sleep duration (min)	39	.08	.63
	WASO (min)	39	.01	.95
	Number of awakenings	39	.02	.93
Tunnel Trance	Bed time (minutes from midnight)	39	-.14	.39
	Wake time (minutes from 0800)	39	-.06	.73
	SOL	39	.01	.96
	Sleep quality	39	.04	.82
	Sleep efficiency (%)	39	.10	.56
	Time in bed (min)	39	.14	.38
	Total sleep duration (min)	39	.20	.23
	WASO (min)	39	-.09	.60
	Number of awakenings	39	-.05	.76
Unique	Bed time (minutes from midnight)	39	.02	.91
	Wake time (minutes from 0800)	39	-.11	.52
	SOL	39	.01	.95
	Sleep quality	39	.01	.95
	Sleep efficiency (%)	39	.25	.13
	Time in bed (min)	39	-.05	.75
	Total sleep duration (min)	39	.06	.74
	WASO (min)	39	-.13	.42
	Number of awakenings	39	-.22	.17

Table 8 summarises the correlations between percentage improvement of the four tasks performance and various sleep variables.

Table 9.

% task RT improvement overnight	Sleep diary variables	n	*r* value	*p* value
Refocus	Bed time (minutes from midnight)	39	.09	.59
	Wake time (minutes from 0800)	39	.03	.86
	SOL	39	.14	.40
	Sleep quality	39	.16	.33
	Sleep efficiency (%)	39	-.01	.97
	Time in bed (min)	39	-.08	.64
	Total sleep duration (min)	39	-.01	.97
	WASO (min)	39	-.19	.26
	Number of awakenings	39	.08	.62
Size Count	Bed time (minutes from midnight)	39	.03	.86
	Wake time (minutes from 0800)	39	-.23	.16
	SOL	39	.07	.67
	Sleep quality	39	.28	.09
	Sleep efficiency (%)	39	-.19	.24
	Time in bed (min)	39	-.26	.11
	Total sleep duration (min)	39	-.24	.14
	WASO (min)	39	-.19	.25
	Number of awakenings	39	.22	.19
Tunnel Trance	Bed time (minutes from midnight)	39	.21	.21
	Wake time (minutes from 0800)	39	.05	.77
	SOL	39	.09	.57
	Sleep quality	39	.17	.30
	Sleep efficiency (%)	39	-.09	.60
	Time in bed (min)	39	-.19	.25
	Total sleep duration (min)	39	-.14	.40
	WASO (min)	39	-.16	.32
	Number of awakenings	39	-.04	.81
Unique	Bed time (minutes from midnight)	39	.09	.59
	Wake time (minutes from 0800)	39	-.26	.11
	SOL	39	.20	.22
	Sleep quality	39	-.12	.46
	Sleep efficiency (%)	39	.00	.99
	Time in bed (min)	39	-.31	.06
	Total sleep duration (min)	39	-.21	.20
	WASO (min)	39	-.09	.58
	Number of awakenings	39	-.01	.94

Table 9 summarises the correlations between percentage improvement of the four task RT (min) and various sleep variables.

4. Discussion

4.1. Task-switching

Our results show that there was significant improvement in scores for task-switching task (Refocus) from training to first test after 12 hours, from first test to retest after 12 hours, and from training to retest after 24 hours, for both group A and B. There was also significant reduction in RT from training to first test for both groups, from first test to retest for group B but not A, and from training to retest for both groups. This demonstrates that training and practice helps to improve task-switching task performance both in terms of accuracy and RT. Also, the percentage of improvement in scores but not RT after a night of nocturnal sleep for both groups are significantly higher (e.g. 128% improvement for group A and 181% for group B) than after the same duration of the wake period (e.g. 35% for group A and 33% for group B). This illustrates that sleep exerts a practice-independent effect on the improvement of task performance. These results support our hypothesis that training leads to task-switching task performance, and a night of sleep following training facilitates this task improvement.

In accordance with previous studies (Kray et al., 2011; Karbach and Kray, 2009; Kray et al., 2008; Minea and Shah, 2008; Cepeda et al., 2001), our participants demonstrated significant improvement after each training session even though the level of difficulty is adaptive (e.g. increasing difficulty level with each new trial), and the scoring system is different from other studies as only accuracy and RT were taken into account instead of mixing or switching costs. Nevertheless, the differential rate of improvement following the wake period and nocturnal sleep is evident as participants achieved significantly higher improvement following sleep than the wake period for both groups. Similarly, Slama and colleagues (2015) found a short 30 minutes nap is enough to improve task-switching performance, although their study was conducted in

the context of natural temporal dip of performance in the afternoon, the effect of post-training consolidation during sleep cannot be ruled out. Also, correlation study (Wilckens et al., 2014) found better task-switching performance is associated with better sleep quality in terms of WASO and total sleep duration. Although we did not find any correlation between sleep quality and task performance, all participants reported sufficient sleep duration with a minimum of 260 minutes. Hence, our study presents the first evidence that a night of sleep facilitates the consolidation of task-switching skill, similar to the consolidation of motor skills during sleep (Walker et al., 2003; 2002).

4.2. Visual search

Visual search task (Unique) has also shown significant improvement in scores from training to first test after 12 hours, from first test to retest after 12 hours, and from training to retest after 24 hours, for group A. Group B only had significant improvement after a night of sleep. There was no significant difference in RT for group A between sessions, but the RT significantly increased after sleep and significantly decreased after the wake period for Group B. This shows that training and practice helps to improve general performance but not RT for the visual search task. However, the percentage of increase at first test for both groups are comparable (49% for group A and 48 % for group B), but there is no significant improvement after the wake period for Group B. Taken together, these results show that training leads to visual search task improvement and a night of sleep facilitate this improvement.

These results support previous literature that training leads to task-specific improvement in visual search task (Clark et al., 2015; Keller and Lefin-Rank, 2010; Pambakian et al., 2004; Ellison and Walsh, 1998; Walsh et al., 1998). Also, in contrary to Sireteanu and Rettenbach (2000), we found evidence that sleep helps to improve visual search performance. Unlike studies that have included an implicit memory

component in their task and found that sleep led to improved performance (Geyer et al., 2013; Mednick et al., 2009), our visual search task “Unique” does not contain a memory component as the locations of the odd objects are randomised. The only sub-skills involved are top-down visual attention and recognition. It seems that sleep facilitates improvement in visual search task training even when the memory component of the task is absent.

4.3. Working memory

Working memory task (Tunnel Trance) has shown significant improvement in scores from training to first test after 12 hours of waking for group A (37%), but not after 12 hours of sleep for group B, a significant decrease in scores for group A after sleep (-18%)The RT followed a more predicable trajectory, there was a significant reduction in RT from training to first test for both groups, a further significant reduction from test to retest for group B but not group A, and an overall reduction from training to final retest for both groups. These results show that sleep not only does not help to facilitate post-training improvement as improvements were only made after the wake period for both groups but also seem to hinder performance as Group A had a significant reduction in scores after sleep.

Similar to other studies (Au et al., 2015; Rudebeck et al., 2012; Holmes et al., 2009; Jaeggi et al., 2008; Banigued et al., 2015), training did lead to improvement in task performance albeit the effect seems to be reversed after a night of sleep. However, using a similar protocol to ours, Kuriyama and colleagues (2008) have found the opposite results, significant improvement in working memory task performance was only found after a night of sleep but not after the same period of waking. The differences in our results could be due to the fact that their n-back working memory task included 9 levels of difficulty whereas our “Tunnel Trance” task progressed from 2-back to 3-back task and then adding an additional colour component of the spatial location. Also,

our difficulty level adapts to individual's performance level in each trial, it could be that participants in group A did not do well during initial training but they did significantly better and scored higher during the second session as the level of difficulty only increased slightly, and by the time they went for the last session, the level of difficulty becomes significantly higher due to their previous good performance so their performance dropped from the previous session but not from initial training. On the other hand, participants in group B might have performed better during initial training, and they did not score higher during the second session as the level of difficulty becomes significantly higher, but they improved in the last session as the level of difficulty might have only increased slightly due to poor performance from the previous session. Also, other studies support the idea that sleep facilitates working memory training (Nielsen et al., 2015; Scullin et al., 2012). Our results might be due to the differential rate of increase in difficulty level. Thus, the effect of sleep on training-independent improvement is unclear.

4.4. Arithmetic

Arithmetic task (Size Count) has shown no significant difference in scores between sessions for both groups.There was significant decrease in RT following waking for group A and significant increase following sleep for group B from training to first test, no significant difference between test and retest for both groups, and an overall increase in RT from training to retest for group B but not group A. Task improvement (both improvement in overall score and decrease in RT) following training was only achieved in group A from initial training to first test after 12 hours of waking. Thus, it seems that training does not lead to reliable improvement in arithmetic task performance, and sleep has no facilitation effect for task improvement.

In contrary to Fendrich and colleagues (2014), our study did not find training related improvement in the arithmetic task. This could be due to differences in methodologies

used. They have only included multiplication task in their arithmetic training whereas our study included not only multiplication, but also division, addition and subtraction and simple comparisons between numbers at the beginning. Also, our task was adaptive in the level of difficulty including a multitude of equations. In comparison, it is more difficult for our task to detect a short-term effect of training with these constant changing multitude of equations. As the facilitating effect of sleep has only been found when something is already learnt or trained, perhaps “Size Count” is not efficient or effective in arithmetic training. Adjustment can be made so that the tasks only include only one mode of calculation such as multiplication, or division. On the other hand, our study only investigated the short-term effect of cognitive training, perhaps, improvement can be made with more training sessions over a longer period of time.

4.5. General discussion and conclusion

We used a commercial cognitive training app to study the effect of time and sleep on cognitive training. Although the efficacy of the arithmetic task “Size Count” training is not apparent for short term training, training leads to task-specific improvement on all other tasks. The training-independent effect of sleep on task-switching task and visual search task improvement has demonstrated that the consolidation effect of sleep for motor skills and other memories can be extended to higher-order executive function cognitive training. The next step would be studying the facilitating effect of sleep on higher-order cognitive training over a longer period of time. Also, polysomnography can be used to record different sleep stages during a nocturnal sleep or nap, and correlations can be drawn between the duration of specific sleep stages with different task improvement. Furthermore, the main objective of cognitive training is that improvement in one task can be transferred to other tasks involving the same cognitive function or different cognitive functions. As sleep has been found to help with integration of information (Durrant et al., 2012; Lewis and Durrant, 2011; Lau et al. 2011; Ellenbogen et al., 2006) as well as inspiring insights (Wagner et al., 2004) and

creativity (Cai et al., 2009), sleep might play an important role in skill transfer. Thus, more studies should investigate the effect of sleep on the transfer of cognitive training.

In conclusion, this study supports previous findings that task-specific improvement can be achieved through cognitive training, and provides the first evidence that shows sleep facilitates the improvement of task-switching cognitive training by using a commercial cognitive training app “Peak”. Hence, I postulate that the best time course of task-switching task training is in the evening before a night of sleep. The next step would be studying the effect of a nap on task improvement, and the transfer of improvement to other tasks, as well as the training-independent effect of sleep on these task transfer.

Chapter 6: The role of rapid eye movements during REM sleep

Abstract

Objective - Studies have shown that the direction of eye movements during Rapid Eye Movement (REM) sleep are not random, but rather imitate the scanning of dream scenes. It has also been found that newly learnt materials are replayed, possibly as dream images, during different sleep stages, which in turn enhances memory consolidation. There is a missing link between these two lines of evidence, and it remains unknown whether the direction of rapid eye movements (REMs) during REM sleep reflects memory replay of previously learnt materials and whether such memory replay in turn enhances memory consolidation. Thus, the aim of this chapter is to investigate whether direction, amplitude, and other quantitative characteristics of REMs during REM sleep are affected by previously learnt materials and whether they correlate with consolidation of declarative memory.

Methods - 28 participants were recruited and each participated in three conditions (Horizontal/Vertical/Mixed) in a repeated measures design. In the Horizontal condition, subjects learned images consisting of three common objects located horizontally leading to mostly horizontal eye movements (EMs) as measured by an Eyelink eye tracker. The subjects then napped for about 90 minutes while their PSG including horizontal and vertical EOG channels was recorded. They were subsequently tested on an old/new recognition task. In the Vertical condition, subjects followed the same protocol as in the Horizontal condition but the three objects in images were located vertically leading to mostly vertical eye movements. In the Mixed condition subjects learned both horizontally and vertically oriented images that elicited a roughly equal mix of horizontal and vertical eye movements and then stayed awake rather than napped for the same period of time as the nap before being tested on the recognition task. The order of the three conditions was randomised.

Results – Correlation analyses show that the amount of horizontal EMs in the Horizontal condition during encoding was significantly correlated with horizontal REMs

during the ensuing nap and the vertical EMs in the Vertical condition during encoding was significantly correlated with vertical REMs during the ensuing nap. The amount of Vertical REMs were significantly associated with improvement in memory performance in the Vertical condition, and horizontal REMs were significantly associated with improvement in memory performance in the Horizontal condition.

Conclusion - These results provide evidence that REMs are not random, they are affected by preciously learnt materials prior to sleep, and are related to memory consolidation.

1. Introduction

There is a long-standing debate on the directional properties of eye movements (EMs) during rapid eye movement (REM) sleep, concerning whether they are linked to shifts of gaze ("scanning hypothesis") related to dream imageries or they are random marker of PGO waves (Leclair-Visonneau et al., 2010; Peigneux et al., 2001; Herman et al., 1984; Jacobs et al., 1972; Mouret et al., 1963; Dement and Kleitman, 1957). Also, other studies have tried to demonstrate a "complementary" relationship between EMs prior to sleep and during REM sleep, for example, more EMs before sleep resulted in less rapid eye movements (REMs) during REM sleep, and more leftward saccade before sleep resulted in more rightward saccade during REM sleep (De Gennaro et al., 1995; Herman and Roffwarg, 1983; Berger, 1968). However, none of these studies investigated whether these REMs were influenced by learnt materials prior to sleep, other than pure physiological conditioning.

The question of whether REMs are random has been investigated by studying the associations between REMs and dreaming, as well as the influence of prior waking experience on REMs. The scanning hypothesis posits that REMs in REM sleep are not random, but reflects scanning of dream scenes. It has been challenged by both human (Gross et al., 1965) and animal studies (Arnulf et al., 1998; Zhou and King, 1997; Jouvet, 1962). Subjects who have been blind since birth have REMs during REM sleep even though they never experienced visual images in dreams (Gross et al., 1965). Cats that have had their visual cortex (Jouvet et al., 1962) and pontine preparations (Arnulf et al., 1998) lesioned continue to experience REMs during REM sleep. The directions of left and right eyes are not conjugated (lacking a focus point) in some REMs, thus unlikely to be tracking dream images (Zhou and King, 1997). REMs and PGO waves occur in parallel instead of in series, thus REMs seem to be a by-product of brain-stem activity (Vanni-Mercier and Debilly, 1998). Visual dreams can appear in non-REM sleep without overt EMs (Fosse et al., 2001). Other researchers dismissed the 'scanning

hypothesis' and postulated that the function of the REMs during REM sleep is to lubricate the ocular surface and to inform conjunctiva-associated lymphoid tissue system (Murube, 2008), is a measure of sleep need (Lucidi et al., 1996), maintain temperature in central nervous system (CNS) (Wehr, 1992), or that they stimulate and help to develop higher brain functions (Roffwarf et al., 1966).

Despite the opposing views, the possibility that REMs during REM sleep are related to scanning of dream images cannot be ruled out. A more recent study suggests that congenitally blind people may have visual contents in their dreams as their EEG alpha attenuation (related to visual activity) and dream report of visual contents are comparable to normal subjects (Bertolo et al., 2003). On the other hand, moles that do not have a visual system, have no experience of REMs during PS (Allison and Van Twyver, 1970). These studies also raised the question that whether congenitally blind people are devoid of all visual perception, and whether a lack of visual perception would result in an absence of visual mentation. Also, although the cats that had their visual cortex and pontine preparations lesioned continue to have REMs during REM sleep, the amount of REMs is reduced by about 66 percent and the complexity of the REMS is altered (Jeannerod et al., 1965), indicating a lack of visual processing has a strong influence on REMs. Visual dreams can be present in different sleep stages, but the dreams are reported to be more vivid and active during bursts of REMs (Mutz and Javadi, accepted; Berger and Oswald, 1962). Furthermore, studies have shown that it is possible to supress PGO waves via lesions of several brain regions without supressing REMs (Datta and Hobson, 1995; Sakai et al., 1976; Hobson, 1965), and conversely, it is possible to supress REMs with drug without supressing PGO waves (Jouvet, 1972). These studies imply that PGO waves are not the sole determinant of REMs during REM sleep. By using a more direct approach, awakening the subjects during or just after they have experienced REMs during REM sleep, assessing reports of their dream content, some studies found a 70-80% correlation between gaze

directions in dreams with actual PSG recorded EMs (Herman et al., 1984; Roffwarg et al., 1962; Dement and Wolpert, 1958) whereas others found correlations between 9-32% (Jacobs et al., 1972; Moskowitz and Berger, 1969). For example, one subject who exhibited vertical EMs during REM sleep reported dreaming of climbing a ladder while looking up and down (Dement and Kleitman, 1957). On the other hand, another subject who exhibited only horizontal EMs but reported looking at columns of buttons vertically (Moskowitz and Berger, 1969). These mixed findings can be the results of the methodology limitations and challenges shared by these early studies. Retrospective reports of dreams are highly subjective and are prone to forgetting. Also during wake states, eyes and head coordinate together to produce a gaze whereas only eyes can be moved during REM sleep due to atonia of the body muscles.

To overcome these limitations, a recent study that investigated EMs during REM sleep in people with REM sleep behaviour disorder (RBD) has shown that EMs during REM sleep indeed imitate the scanning of dream scenes (Leclair-Visonneau et al., 2010). RBD is a form of parasomnia involving dream enactment, patients act out parts of their dreams such as hand movements, searching and reaching motions, kicking or yelling, due to problems with muscle atonia during REM sleep (Schenck et al., 1986). Using video and sleep monitoring techniques, Leclair-Visonneau and colleagues (2010) found an 82% concordance rate between REMs accompanied by goal directed body movements and target locations, and the concordance rate increased to 90% with restriction to determinant REMs. However, REMs were missing in 41.7% of the goal directed body movements, and 78.3% of REMs were not associated with these body movements. The authors attribute these phenomena to incomplete body atonia, and the possibility that during part of REMs, patients were passively “watching” moving dream images. Nevertheless, the results of the study suggest directions of EMs during REM sleep are congruent with goal-directed behaviour during dreaming, and this can be applied to normal REM as no difference in REM characteristics was found between

RDB patients and control group. Another recent study (Valli et al., 2011) systematically assessed the relationship between dream content recalled after being awakened during REM sleep and video-recorded overt motor behaviours during REM sleep in RBD patients, seven blind judges were employed, and they found a link between dream content and motor behaviours above chance level. Although this study did not assess REMs, it suggests that motor behaviours in dream content are subserved by the same systems that generate overt motor behaviours. Furthermore, a more recent study investigated the neural substrate of REMs during REM sleep and found that brain oscillations associated with REMs in medial temporal lobe (MTL) are similar to visual processing during wakefulness (Andrillon et al., 2014). This suggests that visual processing similar to wakefulness is involved in REMs during REM sleep. Taken together, REMs do not seem to be random, but rather represent viewing of the dream scenes.

Other studies found that EMs prior to sleep affects REMs in a “complementary” way, which means systems that are more active during wakefulness will exhibit reduced activity for recovery purposes (De Gennaro et al., 1995; Herman and Roffwarg, 1983; Berger, 1968). An early animal study found that monkeys conditioned to have reduced EMs during wakefulness had increased EMs during the following REM sleep (Berger, 1968). Similarly, human subjects who experienced reduced amplitude and frequency of EMs by wearing goggles that curtailed vision had increased amplitude and frequency of EMs during subsequent REM sleep (Herman and Roffwarg, 1983). Also, an increased number of rightward saccades during wakefulness not only resulted in a decrease of rightward saccades but also an increase of leftward saccades (De Gennaro et al., 1995), and this complementary effect is only found in the saccade system as no significant difference was found after optokinetic stimulation of the eyes (De Gennaro and Ferrara, 2000). These studies however employed small sample sizes, and have not been replicated since. Nevertheless, they support the idea that REMs are

not random, and are influenced by prior wake experience, in a pure physiological sense. However, the functionality of REMs remains unknown.

On the other hand, the role of REM sleep in memory consolidation has been well documented. Many studies have confirmed that duration of REM sleep is correlated with consolidation of procedural memory (Wager et al., 2001; Plihal & Born, 1997), and others show that REM sleep can also improve declarative memory consolidation (Fogel et al., 2007; Rauchs et al., 2004; Walker et al., 2002; Stickgold et al., 1999; De Koninck et al., 1989). However, the question of how these memories are consolidated remain unclear. Imaging studies of neural substrates found that regions of the brain that were activated during learning when awake were reactivated again during sleep. For example, several brain regions (e.g. visual, motor and premotor cortices) activated while doing a serial reaction task (Maquet et al., 2000), or sequence learning task (Peigneux et al., 2000; 2003) during wakefulness shows similar patterns of activation during REM sleep, and the performance of the tasks were improved after sleep. Activation of these brain regions, known to be involved in visual (Haxby et al., 1991) and motor (Stephan et al., 1995; Matelli et al., 1993) processing, seem to show that participants were mentally rehearsing the tasks. Other studies found that previous waking experiences are replayed in dreams (Kusse et al., 2012; Fosse et al., 2003; Schwartz, 2003; Stickgold et al., 2000; Domhoff. 1996; Dement et al., 1965). For example, Dement and colleagues (1965) analysed reports of dreaming during REM sleep and found that 22% of the dream reports contain elements of the laboratory settings that they were being tested on, this includes 12% of the reports containing elaborate and non-isolated representations of the laboratory settings. More recently, a study of sleepwalkers provided a first direct evidence of memory replay in the form of dream enactment of previously learnt motor sequence, and this is linked to improved performance upon awakening (Oudiette et al., 2011). Furthermore, other studies suggested memory replay in the form of repeating sensory cues (playing the same

sounds or spraying the same scents during learning and during sleep) associated with previously learnt materials during sleep helps to improve memory performance (Oudiette et al., 2013; Rudoy et al., 2009; Rasch et al., 2007). Taken together, these results suggest that newly-formed memory prior to sleep is often replayed during different stages of sleep in the forms of dreaming, and this in turn enhances memory consolidation. However, in none of these studies were eye movements considered. The only parameter that had been considered was the duration of REM sleep, ignoring other aspects of eye movements such as direction of saccades. The question of whether REMs are involved in memory replay and memory consolidation is not explored.

We have discussed studies that suggest the directions of REMs during REM sleep are not be random, but rather imitate the scanning of dream scenes (e.g. Leclair-Visonneau et al., 2010), or are part of the “complementary” process (De Gennaro et al., 1995). But whether these REMs are influenced by previously learnt materials have not been explored. Also, REM sleep have been found to be involved in memory consolidation, newly learnt materials are replayed, possibly as dream images, during REM stages, which in turn enhances memory consolidation (e.g. Stickgold et al., 2000). But whether REMs during REM sleep are part of the memory consolidation process have not been investigated. Thus, the aim of our study is to investigate whether REMs during REM sleep are indeed random, or that they are influenced by previously learnt materials. Also, whether they are related to improved memory performance upon awakening, therefore are involved in memory consolidation. Using a nap paradigm, we hypothesize memory performance after a nap is better than after staying awake for the same period of time. There are more horizontal REMs in horizontal condition than vertical condition and there are more vertical REMs in vertical condition than horizontal condition during the nap. The directions of EMs during learning are correlated with directions of REMs

during REM sleep. EMs of the corresponding direction with the condition is correlated with improved memory performance upon awakening.

2. Method

2.1. Ethics and Participants

The research protocol was approved by University College London (UCL) Institute of Cognitive Neuroscience (ICN) ethics committee. Written informed consent was obtained from each participant. A total of 26 participants between the ages of 18 to 26 were recruited. (mean age ± SD: 23.34 ± 3.72). Participants were screened to exclude those that were taking prescribed anti-depressant medication, or have a recent history of diagnosed depression or anxiety, or suffering from any clinical sleep disorder, or taking any medication that has an effect on sleep (e.g. melatonin) were excluded from the study. Participants were refrained from alcohol or caffeinated drinks at least one day before and during the entire study. They had normal or corrected vision. They were naïve to the study.

2.2. Stimuli and apparatus

2.2.1. Piloting for the stimuli

The first set of stimuli we piloted consists of images that contain an implicit graphic orientation either horizontal or vertical (see figure 1-2). Figure 1 shows one image with horizontal orientation and Figure 2 shows one image with vertical orientation. We investigated whether the implicit information of the orientations of the images would trigger horizontal or vertical eye movements in accordance with the orientation of the images during learning. The analysis showed that eye movements were mostly random with no clear orientation while looking at the images. As such, we have to come out with new images that illicit clear horizontal or vertical eye movements during learning.

Figure 1. Image with horizontal orientation

Figure 2. Image with vertical orientation.

The second set of stimuli we piloted consists of images that contain three objects either aligned horizontally or vertically (see figure 3-4). Figure 3 shows one horizontal image and Figure 4 shows one vertical image. The objects we used for horizontal stimuli came from 40 categories and there were 6 items per category (e.g. six different apples in the Apple category). This gave us 240 objects. 80 horizontal stimuli were created consisting of 3 objects each. These objects were repeated to create another 80 vertical stimuli. The reason why we had multiple objects within one category was to prevent participants from memorizing the categories as a concept rather than the images themselves. We also prevented objects of the same category to appear in one stimuli image, as this may render the image easier to memorize than others. Participants showed clear horizontal eye movements while learning the horizontal images and vertical eye movements while learning the vertical images. However, the results from the recognition task showed that they performed at chance level. This means that these stimuli were too difficult to remember as there were competing images of the same category (e.g. six different perfume bottles with differences in colour, shape or orientation) in different stimuli. This became overly complicated and may involve unnecessary cognitive functions to differentiate the competing stimuli images.

Figure 3.

Figure 3 shows an image with horizontal alignment

Figure 4.

Figure 4. shows an image with vertical alignment.

Lastly, we decided to simplify the stimuli we used. We found 240 objects, each belongs to a different category (e.g. one apple, one banana, one iron). We used 120 of these objects to create 40 horizontal images for learning (see figure 3). The order of the three

objects in each image was changed randomly to create another horizontal image for testing, so we have 40 new images for testing. All 80 images were used during the pilot recognition test. Another 120 objects were used to create 80 vertical images (see figure 4). Participants first learnt 40 images of horizontal or vertical modality, took a two-hour break and then were tested on the recognition task of the same modality. The results show that participants performed at 67% accuracy. This run has proven to be successful so we have decided on using these stimuli for this study. We asked the pilot subjects to provide feedbacks on how they were trying to remember the stimuli. All subjects reported that they simply tried to remember the three objects in each image with the right order, and there was not enough time to mentally categorize the objects and then try to remember them by categories. Thus, we deem these images as suitable stimuli for our study.

2.2.2. Adopted stimuli and apparatus

Stimuli consisted of three objects placed either horizontally or vertically next to each other and they were designated as Horizontal and Vertical stimuli, respectively. 360 objects were first found. They were common, neutral objects, such as apple and phone and each belongs to a different category. 120 of these objects were used to create 40 horizontal stimuli (see figure 3) known as “Old” stimuli. The order of the three objects in each stimulus was changed randomly to create another 40 set of horizontal stimuli known as “New” stimuli. So, there are 80 horizontal stimuli in total, 40 Old stimuli were used for the encoding phase, 40 “Old” stimuli from the encoding phase and the rest of the 40 stimuli known as “New” stimuli were used to be tested on during the Old/New recognition phase. Another 120 objects were used to create 80 vertical stimuli for learning and testing similar to the horizontal stimuli (see figure 4). The last 120 objects were used to create 40 horizontal and 40 vertical stimuli for the mixed condition. 20 horizontal and 20 vertical objects (Old) were randomly selected for each participant to

be learnt during the encoding phase, and all 80 mixed stimuli (Old and New) were used during the recognition phase.

The experiments were programmed and run with the use of MATLAB (r2015b, The MathWorks Inc.) and Psychtoolbox v3 (Brainard, 1997, Pelli, 1997). Task was presented in colour on a 17-inch monitor with a 75 Hz refresh rate and a 1280 × 1024 pixels resolution, at a viewing distance of approximately 53 cm. Responses were entered using a standard computer keyboard. Participants were instructed to use the index and middle fingers on their right hand to respond.

Participants' EMs were tracked during the Encoding phase using a head-mounted Eyelink II eye tracker manufactured by SR Research Ltd. (Canada) with 200 samples per second during the learning phase.

Sleep electroencephalogram (EEG) recording was set up after the learning phase before sleep. EEG recordings were collected using 9 mm diameter gold-plated disc electrodes, a Comet XL Lab-based PSG amplifier, and Twin PSG software (Grass-Telefactor, West Warwick, RI, USA). Seven EEG channels were placed over the O1, O2, C3, C4, Fz, F3 and F4 based on 10-20 International EEG electrode placement system. Three electrooculography (EOG) channels were placed on the left of the left eye (LOC) and the right of the right eye (ROC) to record horizontal movement of the left and right eye, respectively, and under the right eye (VOC) to record vertical movement of the right eye. Two electromyography (EMG) channels were placed on the left and right-hand sides of the chin. Reference electrode was placed on the tip of the nose. Location of the electrodes was cleaned with alcohol wipes and NuPrep abrasive gel before applying electrodes so as to reduce impedance. A conductive, adhesive, water-soluble gel (Ten20 Conductive Paste by Weaver and Company) was then used to attach each electrode to the participant's head and secured using surgical tape. Impedance checks were conducted to ensure that impedance values did not exceed 5 kΩ. The data acquisition rate was 200 Hz, with a notch filter of 50 Hz.

2.3. Design and procedure

Each subject attended three experimental conditions (Horizontal, Vertical, and mixed) on three different days within a week. Figure 5 shows the progression of phases in each condition. In the Horizontal and Vertical conditions, only Horizontal and Vertical stimuli were presented, respectively. In the Mixed condition, half of the stimuli were Horizontal stimuli and the other half were Vertical stimuli.

Each session consisted of Encoding phase, retention interval and recognition phase. In the Encoding phase, Old stimuli were presented to participants and they were asked to memorise the order of objects in each set. Stimuli were presented for 5 s on a white background followed by a fixation cross screen presented for 1 s. During retention interval, they either took a nap or stayed awake and read books for two hours. During Recognition phase both Old and New stimuli were presented to participants and they were asked to judge whether the presented set was Old (same order as shown before) or New (altered order). Stimuli were presented one by one and participants were asked to response as accurately as possible. They were given 5 s to response for each stimulus. Following their response, a fixation cross screen was presented for 1 s and followed by the next stimulus.

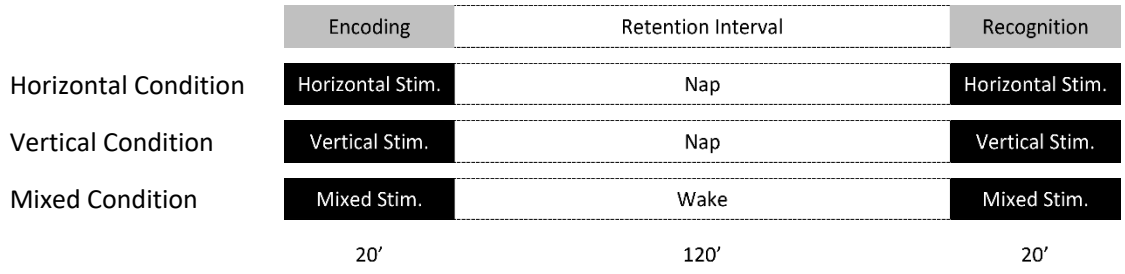


Figure 5. Procedure of the three conditions of the study. Eyes were tracked during the encoding phase. Sleep EEG including EOG was recorded during nap in Horizontal and Vertical conditions. Note: Stim. stands for Stimuli.

2.4. Data analysis

2.4.1. Sleep data analysis

Sleep data was analysed in MATLAB using SPM8 (Wellcome Trust, London, UK) and the SleepSMG toolbox (Walker laboratory; sleepsmg.sourceforge.net) running in MATLAB. Pre-processing of sleep data included importing to SPM, and bandpass filtering of the EEG (0.3–35 Hz), EOG (0.1–35 Hz) and EMG (40–100 Hz) data. The data were then scored manually by two researchers independently in 20 s epochs according to the sleep scoring standards by American Academy of Sleep Medicine (Berry et al., 2012) using the SleepSMG toolbox. Epochs with peak absolute activity larger than two standard deviation in any of the channels were excluded from the analysis (2.569 % of all epochs). The standard deviation of the horizontal and vertical EOG channels for rapid eye movement (REM) and non-rapid eye movement (NREM) phases were extracted for data analysis.

2.4.2. Eye tracker and Task data analysis

Memory performance in the Recognition phase, EMs during Encoding phase and during sleep was recorded for analysis. An one-way repeated measures of ANOVA was run to investigate the effect of sleep on memory performance with Condition (Horizontal/Vertical/Mixed) as within subject independent factor and memory performance as dependent variable. A three-way repeated measures ANOVA was run to investigate the pattern of EMs during sleep with Condition (Horizontal/Vertical), Phase (REM/NREM) and EOG channel (ROG/VOG) as within subject independent factors and EMs as dependent variable. Post hoc paired sample t-tests were conducted to compare performance in between the conditions. The p value threshold of 0.05 was considered as significant difference. Also, to investigate the relation between EMs during sleep and memory performance, measures of memory performance difference

for Horizontal and Vertical conditions (performance in the Vertical and Horizontal conditions minus performance in the Mixed condition) were calculated. Subsequently the correlations of these measures with activity of ROG and VOG channels were calculated separately for Horizontal and Vertical conditions. Similarly, the p value threshold of 0.05 was considered as significant difference.

To investigate the relation between EMs during Encoding phase with EMs during sleep, correlation analyses were conducted between EMs during Encoding, and ROG and VOG channels.

3. Result (Mean ± SD: 3136.00 ± 1437.38)

Four participants had to be excluded as their performance in at least one of sessions was less than chance level 55%. Therefore, the behavioural data is analysed using n = 22 participants. rANOVA on d' scores for the three sessions showed a main significance difference [$F(2, 42) = 4.172$, $p = 0.022$, $\eta_p^2 = 0.166$] (Horizontal (Mean ± SD: 0.857 ± 0.477), Vertical (Mean ± SD: 0.901 ± 0.538), Mixed (Mean ± SD: 0.687 ± 0.408). Similar results were found for performance accuracy (%) for both old and new stimuli $F(2, 42) = 3.521$, $p = 0.039$, $\eta_p^2 = 0.144$ (d' (SD) Horizontal (Mean ± SD: 74.090 ± 11.631), Vertical (Mean ± SD: 75.227 ± 13.890), Mixed (Mean ± SD: 70.227 ± 11.237). rANOVA on response times (ms) showed no significant main effect of [$F(2, 42) = 1.827$, $p = 0.173$, $\eta_p^2 = 0.080$] (Horizontal (Mean ± SD: 1.816 ± 0.329), Vertical (Mean ± SD: 1.957 ± 0.291), Mixed (Mean ± SD: 1.872 ± 0.329). The rest of the analysis is done on d' scores of the Horizontal and Vertical Conditions. Post-hoc paired-sample *t*-tests on d' showed a significant differences between Horizontal and mixed conditions [$t(21) = 2.945$, $p = 0.008$], between vertical and mixed conditions [$t(21) = 2.653$, $p = 0.015$], and no significant difference between the Horizontal and Vertical conditions [$t(21) = -0.477$, $p = 0.638$]. Post hoc *t*-tests on accuracy (%) performance showed similar results (Horizontal vs Mixed [$t(21) = 2.370$, $p = 0.027$], Vertical vs Mixed [$t(21)$

= 2.488, p = 0.021], Horizontal vs Vertical [t(21) = -0.508, p = 0.617]. The rest of the analysis is done on d' scores of the Horizontal and Vertical Conditions.

Five participants were further excluded as they had very short duration of REM sleep (lower than 2 minutes) in at least one of the two sessions. Therefore, the sleep data is analysed using n = 17 participants. A 2 x 2 rANOVA on duration (m) of sleep phase (REM/NREM) and Condition (Horizontal/Vertical) showed a significant main effect of phase [F(1, 16) = 176.278, p < 0.001, η_p^2 = 0.917] with duration (m) of NREM (Mean ± SD: 68.462 ± 27.507) more than REM (Mean ± SD: 9.848 ± 7.455, a significant main effect of Condition [F(1, 16) = 8.342, p = 0.011, η_p^2 = 0.343] with duration of sleep in Horizontal condition (Mean ± SD: 43.060 ± 18.162) more than Vertical condition (Mean ± SD: 35.250 ± 18.067), and a nonsignificant interaction effect [F(1, 16) = 0.003, p = 0.955, η_p^2 < 0.001] (Horizontal-REM (Mean ± SD: 17.510 ± 14.569), Horizontal-NREM (Mean ± SD: 82.746 ± 14.403), Vertical-REM (Mean ± SD: 7.803 ± 6.801), Vertical-NREM (Mean ± SD: 72.666 ± 22.910).

EMs recorded from the ROC and LOC channels showed a very high correlation (p < 0.001). Therefore, for the rest of the analysis we used only LOC. Because there was a great difference between duration of REM and NREM, we analysed amount of eye-movements (median of difference of EOG values recorded by ROC, LOC and VOC) during these two phases separately. Similar results were achieved using ROC. A 2 x 2 rANOVA on amount of eye-movement (LOC/VOC) during REM sleep and Condition (Horizontal/Vertical) showed a significant main effect of eye-movement [F(1, 16) = 22.862, p < 0.001, η_p^2 = 0.559], a significant main effect of Condition [F(1, 16) = 8.420, p = 0.010, η_p^2 = 0.319] and a significant interaction effect [F(1, 16) = 5.308, p = 0.033, η_p^2 = 0.228] (Horizontal-LOC (Mean ± SD: 81.980 ± 69.14), Horizontal-VOC (Mean ± SD: 69.913 ± 59.432), Vertical-LOC (Mean ± SD: 33.802 ± 43.221), Vertical-VOC (Mean ± SD: 28.117 ± 30.140). Post-hoc paired-sample t-tests between LOC during Horizontal and Vertical conditions showed a non-significant difference [t(18) = 0.657, p

= 0.519], between VOC during Horizontal and Vertical conditions showed a non-significant difference [$t(18) = -0.619, 0.544$] and a significant difference between LOC and VOC for the Horizontal condition [$t(18) = 6.137$, $p < 0.001$] and a significant difference between LOC and VOC for the Vertical condition [$t(18) = 5.572$, $p < 0.001$].

Similar rANOVA was run for the amount of EM during NREM that showed significant main effect of EM ($F(1, 16) = 71.715$, $p < 0.001$, $\eta_p^2 = 0.782$), with more LOC (Mean ± SD: 286.611 ± 62.226) than VOC (Mean ± SD: 240.245 ± 54.395), a non-significant main effect of Condition ($F(1, 16) = 3.014$, $p = 0.098$, $\eta_p^2 = 0.131$) and a non-significant interaction effect ($F(1, 16) = 0.604$, $p = 0.446$, $\eta_p^2 = 0.029$) [Horizontal-LOC (Mean ± SD: 304.091± 63.339), Horizontal-VOC (Mean ± SD: 255.018 ± 59.587), Vertical-LOC (Mean ± SD: 269.129 ± 90.600), Vertical-VOC (Mean ± SD: 225.471 ± 73.449)].

To investigate the relation between EM during sleep and behavioural performance, we ran a bootstrap analysis using non-parametric spearman's rho pair-wise correlation on d', Phase (REM/NREM), Duration of each Phase, EM (ROC/LOC/VOC) and multiplication of EM and Duration. 6 summarises this correlation analysis.

		d' Horizontal Condition		*d'* Vertical Condition	
		R	*p*	R	*P*
Horizontal Condition					
REM	Duration	-0.343	0.210		
	ROC	-0.434	0.106		
	LOC	-0.384	0.157		
	VOC	-0.434	0.106		
	ROC × Duration	0.588	0.021*		
	LOC × Duration	0.592	0.020*		
	VOC × Duration	0.469	0.078		
NREM	Duration	0.732	0.002*		
	ROC	-0.209	0.454		
	LOC	-0.184	0.511		

	VOC	-0.093	0.742		
	ROC × Duration	0.443	0.098		
	LOC × Duration	0.402	0.137		
	VOC × Duration	0.465	0.081		
Vertical Condition					
REM	Duration			-0.390	0.151
	ROC			-0.343	0.210
	LOC			-0.231	0.408
	VOC			-0.150	0.593
	ROC × Duration			-0.068	0.810
	LOC × Duration			0.130	0.643
	VOC × Duration			0.557	0.031*
NREM	Duration			0.649	0.009*
	ROC			-0.511	0.051
	LOC			-0.472	0.076
	VOC			-0.506	0.054
	ROC × Duration			0.660	0.007*
	LOC × Duration			0.685	0.005*
	VOC × Duration			0.713	0.003*

Table 6. Summary table of the correlations for different conditions with different parameters of duration, eye-movement and duration × eye-movement. ROC = horizontal right-EOG (electrooculography), LOC = horizontal left-EOG, VOC = vertical EOG. n = 17. Correlations reported using 20,000 bootstrap repetition of Spearman's rho paired-wise correlation. R correlation coefficient. * $p < 0.05$ are highlighted.

Finally, to investigate the correlation between EM during memorisation and EM during sleep, we ran correlation analysis between the two. Based on the results summarised in 6, we focused on EM during REM and the product of LOC and VOC by duration. Four pair-wise correlation analyses were run for the combination of horizontal and vertical EM as recorded by the eye-tracker during the learning phase, corresponding LOC- and VOC x duration, and session Condition (Horizontal/Vertical). See 7 for the summary of the analysis.

Table 7.

Condition	Parameters	R	p
Horizontal	Horizontal EM and LOC x Duration	0.589	0.021*
	Vertical EM and VOC x Duration	0.265	0.340
Vertical	Horizontal EM and LOC x Duration	0.414	0.125
	Vertical EM and VOC x Duration	0.532	0.041*

Table 7shows summary of the correlation analysis between eye-movement during the learning phase and eye-movement x duration during REM.

4. Discussion

Despite decades of research, the functional significance of REMs, an important marker of REM sleep remains unclarified. Our results show for the first time that REMs are not random, they are associated with previously learnt materials prior to sleep, as well as memory performance after sleep. The amount of horizontal EMs in the horizontal condition during encoding was significantly correlated with horizontal REMs during the ensuing nap and vertical EMs in the vertical condition during encoding was significantly correlated with vertical REMs during the ensuing nap. Furthermore, the nap helped to promote memory performance as performance in both the horizontal and vertical conditions were significantly better than after staying awake for the same period of time in the mixed condition. Amount of Vertical REMs were significantly associated with the improvement in memory performance from the no nap condition to the vertical nap condition, and horizontal REMs were significantly associated with the improvement in memory performance from the no nap to the nap horizontal condition.

The results of the study are consistent with previous findings indicating the direction of REMs during REM sleep are not random. Studies of REMs in RBD patients found evidence that REMs imitate the scanning of dream scenes (Leclair-Visonneau et al., 2010), and enacted motor behaviours during REM sleep were associated with dream content (Valli et al., 2011). These results suggest that motor behaviours including visual motor behaviours in dreams are subserved by the same system that generate

overt motor behaviours. Furthermore, neuroimaging study found brain oscillations associated with REMs in medial temporal lobe (MTL) are similar to visual processing during wakefulness (Andrillon et al., 2014). This suggests that visual processing similar to wakefulness is involved in REMs during REM sleep. Although we did not assess dream content, our results show that REMs imitate the direction of EMs during learning prior to sleep, which in turn helps with memory performance. This draws parallel to imaging studies that found regions of the brain such as visual, motor and premotor cortices activated while doing a serial reaction task (Maquet et al., 2000), or sequence learning task (Peigneux et al., 2000; 2003) prior to sleep were activated again during ensuing REM sleep, and the performances of the tasks were improved after sleep. Activation of these brain regions, known to be involved in visual (Haxby et al., 1991) and motor (Stephan et al., 1995; Matelli et al., 1993) processing, seem to show that participants were mentally rehearsing the tasks. Also, other studies found that previous waking experiences are replayed in dreams (Kusse et al., 2012; Oudiette et al., 2011; Fosse et al., 2003; Schwartz, 2003; Stickgold et al., 2000; Domhoff. 1996; Dement et al., 1965). For example, a study of sleepwalkers provided a first direct evidence of memory replay in the form of dream enactment of previously learnt motor sequence, and this is linked to improved performance upon awakening (Oudiette et al., 2011). Thus, our behavioural data suggests that REMs are involved in the mental rehearsal of the tasks prior to sleep, perhaps by viewing them as dream imageries.

Also, we found higher amplitude and amount of horizontal than vertical REMs across conditions. The reason behind this is unclear. This pattern of results could be due to the “saccadic bias” in the visual system which subsequently influences REMs. Studies have assessed the oculomotor tendency in our saccadic system and found that people tend to make more horizontal saccades and the amplitude for horizontal saccades are larger than vertical saccades (Van Renswoude et al., 2016; Tatler and Vincent 2009; 2008; Foulsham et al., 2008; Gilchrist & Harvey, 2006). Several factors have been

suggested for the “saccadic bias”. One possibility is that it is easier to make horizontal saccades as only two muscles (the lateral and medial rectus) are needed to control these movements (Viviani et al., 1977) whereas vertical saccades require the involvement of extraocular activity (Henn & Cohen, 1973). Also, the concentration of photoreceptors in the retina is higher in the horizontal than vertical direction (Curcio et al., 1990). Lastly, we might have learnt that most interesting or important objects in our environments are aligned in a horizontal manner (e.g. houses, people, and traffic) so the horizontal saccadic bias is developed to help us maximize our efficiency in information processing. Thus, the finding of higher amount of horizontal than vertical REMs across conditions may be influenced by the “saccadic bias” in our visual experience.

Although REMs are found to be associated with enhanced memory performance, REM sleep alone is not likely the sole contributor for this improvement. Memorizing the order of the pictures falls mainly in the category of declarative memory. Although REM sleep has been found to promote declarative memory consolidation (Fogel et al., 2007; Rauchs et al., 2004; Walker et al., 2002; Stickgold et al., 1999; De Koninck et al., 1989), it is normally associated with procedural learning or non-declarative memory consolidation (Mednick et al., 2003; Fischer et al., 2002; Plihal & Born, 1997, 1999) whereas slow wave sleep (SWS) is normally associated with declarative memory consolidation (Ngo et al., 2013; Marshall et al., 2006; Ellenbogan et al., 2006; Plihal & Born, 1997). Our results show that memory performance in both horizontal and vertical conditions are also associated with NREM sleep (duration). The dual-process theory posits that the two sleep stages (REM, SWS) contribute to two distinct types of memory consolidation (Maquet, 2001). On the other hand, the results of this study support the Sequential Theory (Giuditta et al., 1995) which contends that both SWS and REM sleep occurring in succession is the most conducive for both declarative and procedural memory consolidationThere may not be a strict functional distinction between the two

stages, but rather a more complementary one, or there could be a separate process that contribute to memory consolidation on top of the functional distinction between the two sleep stages. As memory replay of prior waking experience in the form of dreams has been found in different sleep stages (Kusse et al., 2012; Fosse et al., 2003; Schwartz, 2003; Stickgold et al., 2000; Domhoff. 1996; Dement et al., 1965), perhaps memory replay plays a separate, additional role in memory consolidation.

It is important to acknowledge some limitations of this study. First, reports of dreams were not collected and assessed in relation to the REMs. Nevertheless, many studies have found vivid recollection of dreams when awoken during or immediately after REM sleep (Nir and Tononi, 2010), and some found correlations between gaze direction of REMs and dream reports (Herman et al., 1984; Jacobs et al., 1972; Moskowitz and Berger, 1969; Roffwarg et al., 1962; Dement and Wolpert, 1958). Furthermore, such correlations were found by assessing EMs during REM sleep in RBD patients (Leclair-Visonneau et al., 2010). It is reasonable to assume that REMs during REM sleep assessed in this study is associated with dreaming of prior waking experience. Second, some might argue that REMs is affected purely by the mechanisms of horizontal and vertical eye movements during learning, instead of visualising the actual stimuli. However, previous animal or human studies that investigated the relationship between the mechanisms of EMs prior to sleep and during REM sleep found “complementary relationships” where properties of saccades prior to sleep and during REM sleep exhibited opposite directions, e.g. less EMs prior to sleep led to more REMs (De Gennaro et al., 1995; Herman and Roffwarg, 1983; Berger, 1968). On the other hand, our study does not demonstrate either complementary or continuous relationships. Thus, REMs assessed here is unlikely influenced purely by the mechanisms of EMs prior to sleep. Lastly, no baseline performance was obtained immediately after training so memory performance improvement cannot be assessed directly before and after sleep. From our piloting work, we found that recognition test performance was at

chance level when the objects in each stimulus changed positions more than once, and it becomes too easy if all objects are completely different for the construction of "new" stimuli. Thus, if we perform a test immediately after learning, memories of the "new" stimuli during the first test may interfere with memories of the "old" stimuli during the retest after sleep. Also, it is well established that a nap is as good as a full night's sleep in promoting memory consolidation (Seehagen et al., 2015; Lo et al., 2014; Lahl et al., 2008). It is reasonable to conclude that improvement from no nap condition to nap condition is brought by the beneficial effect of memory consolidation during the nap.

The functional significance of this study is that REMs serve an important function in memory consolidation, and it is not simply a by-product of brain stem activity. It is also important to not dismiss the fact that PGO waves are a prominent feature during REM sleep and they often coincide with REMs (Miyauchi et al., 2009; Lim et al., 2007; Vanni-Mercier and Debilly, 1998). However, little is known about how these processes influence each other. Using a simultaneous fMRI and PSG neuroimaging method, Miyauchi and colleagues (2009) showed that brain stem regions, primary visual cortex, putamen and limbic regions were activated in association with time-locked REMs activity, and a control experiment revealed no primary visual cortex activation when waking subjects made saccades in total darkness. As PGO waves are produced by brain stem activity, this suggests that both PGO waves and visual activity happen concurrently but may not be related to each other. Higher level of visual activity is also involved during REMs as the pure mechanisms of eye movements in total darkness do not engage the primary visual cortex. Also, parahippocampal gyrus and amygdala activation happened simultaneously with REMs. Together, these results show that brain areas involved in memory, emotion and vision, not just the brain stem activity and PGO waves are associated with REMs during REM sleep, which suggests REMs are likely to be associated with dreaming.

Some practical implications may derive from this study. As REM sleep has been found to play an important role in emotional memory consolidation (Groch et al., 2013; Nishida et al., 2008; Wagner et al., 2006), and regulation of emotions (Mauss et al., 2013; Minkel et al., 2012; Yoo et al., 2007), evidence show that people with depression tend to have more REM sleep and most antidepressant drugs have the effect of reducing REM sleep (see review, Palagini et al., 2013). The finding that REMs are affected by previously learnt materials opens new avenues of research on interventional strategies that alleviate depression. Perhaps it is possible to induce memory replay of positive information after viewing positive stimuli which may regulate mood and depressive symptoms upon awakening.

In conclusion, our study provides the first evidence that REMs during REM sleep are affected by previously learnt materials prior to sleep and these REMs are related to improved memory performance. These results draw parallel to the neural substrates during REMs which are similar to learning prior to sleep, and which led to improved memory performance (Maquet et al., 2000; Peigneux et al., 2000; 2003). It also shows that REMs are not random, they may be involved in viewing dream imageries during dreaming as study of RBD patients showed eye movements imitated scanning of dream scenes (Leclair-Visonneau et al., 2010). As REMs are related to memory performance improvements, and other studies have found that previous waking experiences are replayed in dreams (Kusse et al., 2012; Oudiette et al., 2011; Fosse et al., 2003), we posit that REMs during REM sleep are involved in memory replay in the form of imitating scanning of dream scenes of prior waking experience, which then lead to improved memory performance upon awakening. Future studies may look into the functions of REMs by incorporating fMRI as well as dream reports to form a more conclusive view about how REMs are affected by prior waking experience. Also, since REMs can be influenced by prior waking experience, the next step is to look at whether REMs can be affected by direct stimuli during REM sleep. A recent study that used

repeated exposure of acoustic noise during different stages of sleep and found that REM sleep is especially conducive in the formation of new acoustic memories whereas SWS supresses the formation of new memories during sleep (Andrillon et al., 2017). This suggests new memories can be formed during sleep and REM sleep is receptive to external stimuli. It would be interesting to find out whether REMs can be influenced by instructional acoustic sound during REM sleep.

Chapter 7: Final Discussion

My thesis investigated sleep in menopausal women, a demographic group who is particularly at risk of sleep disturbances. Also, based on the findings that sleep plays an important role in cognition, I investigated the effects of sleep on memory and skill training and whether rapid eye movement (REM) during REM sleep are involved in the consolidation process.

The first chapter introduced the physiology and functions of sleep as well as how sleep changes across the lifespan. Also, circadian timing system (CTS) and sleep homeostatic interact with each other to influence sleep. The importance of sleep is uncontroversial. Slow wave sleep (SWS) is particularly vulnerable to aging as the amount of SWS declines as we grow older and by the age of 74 there is almost no SWS produced during sleep (Lewis, 2013; Mokhlesi et al., 2012; Van et al., 2000). Efforts have been made to artificially induce slow wave activations (SWA) by transcranial electrical stimulation (tES), Transcranial magnetic stimulation (TMS) and auditory stimulation. However, artificially induction of sleep is still at its infancy, future studies can explore different protocols and configuration of these brain stimulation methods as well as other innovative and novel methods.

The second chapter described the general methods in conducting polysomnography (PSG) and actigraphy experiments. More advanced mobile electroencephalogram (EEG) devices have become available which makes studying the physiology of sleep over a longer period of time possible. This opens new avenues for comparisons and cross validations between self-reported sleep questionnaires, sleep diary, and PSG.

The first chapter on the effects of menopause on sleep (chapter 3) provides a descriptive account of sleep in women experiencing menopausal related symptoms during menopause or the transition to menopause (42-59 years old), by using both subjective (sleep diary) and objective (actigraphy) measures over the course of two

weeks. Also, age-matched male subjects were included as a control group as this allows us to see whether menopause exerts an influence on sleep independent of age. The results show that a range of menopausal related symptoms but not menopausal status (marked by the cessation of menstruation for over one year) predict sleep quality. Thus, this functional, descriptive study provides a critical first step in understanding sleep in middle aged and menopausal women. On the other hand, higher somatic symptoms (e.g. hot flushes) were related to more restful sleep during the 5 hours of deepest sleep as assessed by actigraphy (L5). This means the more severe the somatic symptoms, the more likely the experience of awakenings during the middle of a night sleep, but somehow more restful sleep is achieved during the 5 hours of deepest stages of sleep. This could be our body's compensatory mechanism at work that tries to induce deeper sleep when sleep continuity is compromised. Despite deeper sleep may be induced due to compromised sleep continuity, sleep complaints are common in women during this age range (Shaver et al., 1998). This highlights the fact that sleep continuity is important for the subjective experience of a more restful sleep. These results provide clues about the best intervention strategies that can be adopted to improve sleep quality for this population of women, perhaps by aiming at alleviating menopausal related symptoms which would improve sleep continuity thus improving sleep quality.

Future studies may look at ways to improve sleep continuity in women of this age group by managing the severity of menopausal related symptoms. As mentioned in earlier chapters, menopausal related symptoms are caused by the reduction of female hormones (Al-Azzawi & Palacios, 2009). As hormone replacement therapy (HRT) has been shown to improve sleep quality in women who had menopausal vasomotor symptoms at baseline but not in women without these symptoms at baseline (see Cintron et al., 2017 for review). Perhaps, more ways to help to restore ovarian hormone level should be investigated. Also, PSG and self-reported studies have gathered

contradictory findings (Hachul et al., 2015; Kalleinen et al., 2008; Young et al., 2003), subjective reports of sleep complaints were accompanied by better sleep quality as measured by PSG (more SWS). More studies are needed to investigate the discrepancy or to establish the complementary relationship between subjective reports of sleep quality and sleep architecture measured by PSG or sleep EEG. With this view in mind, I designed my second laboratory experiment that investigated the sleep architecture of women of the same age range. It seems that menopausal women indeed had better sleep quality measured by PSG as they had more N2 sleep.

The second chapter of the effects of menopause on sleep and memory (chapter 4) addressed the question of whether there is a difference in sleep architecture between premenopausal and menopausal women during a nap and whether the nap helps to improve declarative memory performance. The results show that menopausal women performed significantly worse than premenopausal women in the memory task in both nap and non-nap conditions, despite having had more N2 sleep. These results demonstrate that the decline in memory performance during menopause is likely associated with poor memory encoding, instead of sleep-dependent memory consolidation. The decline in executive functions such as attention and working memory as a result of the reduction in ovarian hormone may affect memory encoding and retrieval in menopausal women.

Future studies should investigate the effect of menopause on different aspects of memory, such as encoding, consolidation, retention, and retrieval, separately. This would help to illuminate the source of memory complaints and decline in menopausal women. Appropriate intervention strategy can then be developed to maximize the benefit of the intervention to improve targeted cognitive functions. For example, estrogen treatment has been found to improve executive functions instead of hippocampal dependent memory retention (Shanmugan and Epperson, 2014; Epperson et al., 2011; Krug et al., 2006). Also, the timing of treatment or intervention

needs to be considered as many studies have found that HRT administered only during perimenopause or the early years of postmenopause improved memory and other cognitive functions (Hara et al., 2015; Maki, 2013; Zhang et al., 2011; Verghese et al., 2000; Sherwin, 2009; Gibbs et al., 2003; Jacobs et al., 1998). Also, A 4-year follow up study of 2362 women in SWAN found verbal memory as measured by East Boston Memory Test, declined from premenopausal to perimenopausal stage but there was a rebound from perimenopausal to postmenopausal stage (Greendale et al., 2009). Future studies should consider the possibility of memory function rebound as the effect of hormone reduction becomes stabilised during later stage of menopause as this can also provide insights for intervention strategy targeting women during early years of menopausal transition who are affected the most. Perhaps male subjects can be included as a control group as testosterone level in healthy men decreases steadily as they age, there is no sudden disruption of production of testosterone in men like in women (Harman and Tsitouras, 1980; Sparrow et al., 1980). Lastly, although current study did not find any association between nap and memory performance in menopausal women, the beneficial effect of nocturnal sleep or afternoon nap on memory consolidation is well documented. As there is an increase in both sleep and memory complaints during menopause, a more comprehensive view can be formed when sleep and memory functions are studied together.

My third experiment (chapter 5) investigated the facilitating effects of sleep on cognitive training that involves higher order executive functions (task-switching, arithmetic, working memory, and visual search) or fluid intelligence, and the time course for cognitive training by using a commercial cognitive training mobile phone application. Subjects were trained either in the morning and then tested in the evening following 12 hours of wake period and then tested again in the following morning after 12 hours of sleep period or trained in the evening first then tested in the following morning after 12 hours of sleep and then tested again in the evening after 12 hours of wake period.

Results show that although the efficacy of the arithmetic task training is not apparent for short term training, training led to task-specific improvement on all other tasks, and sleep significantly facilitated the improvement in task-switching task. Thus, the best time for cognitive training would be in the evening before a night of sleep. The independent effect of sleep on task-switching task improvement has demonstrated that the consolidation effect of sleep for motor skills and other memories can be extended to higher-order executive function cognitive training.

Future studies should investigate the facilitating effect of sleep on higher-order cognitive training over a longer period of time. For example, Walker and colleagues (2003; 2002) trained participants on finger tapping task either 10 a.m. in the morning or 10 p.m. in the evening and then test them on the task 12 hours later and 24 hours later. They found that a night of sleep resulted in practice-independent improvement in task performance, and additional nights of sleep resulted in further practice-independent task improvement, whereas the equivalent amount of wake period had no influence on skill learning. Thus, after initial training and testing, further testing can be administered after several days or even weeks to find out the long term or cumulative facilitating effect of sleep on cognitive training. It is also possible to study the extend of importance of sleep in the early and later period of repeated cognitive training. For instance, newly formed memories are thought to be stored in hippocampus and these memories undergo consolidation and rearrangement into exiting knowledge in the neocortex over time (Alvarez and Squire, 1994). Sleep may play a differential role in the early and later period of skill training. Furthermore, PSG can be used to record sleep oscillations of different sleep stages (N1-N3, REM) during a nocturnal sleep or nap, and correlations can be drawn between the duration or the amplitude of specific sleep stages with different cognitive task improvement. Lastly, the main objective of cognitive training is that improvement in one task can be transferred to other tasks involving the same cognitive function or different cognitive functions. As sleep has been

found to help with integration of information (Durrant et al., 2013; Lewis and Durrant, 2011; Lau et al. 2011; Ellenbogen et al., 2006) as well as inspiring insights (Wagner et al., 2004) and creativity (Cai et al., 2009), sleep might play an important role in skill transfer. For example, the effects of training on working memory may be transferred to other cognitive skills such as problem solving and reasoning as working memory forms part of many complex cognitive functions (Engle et al., 1999; Shah and Miyake, 1999). Thus, more studies should investigate the effects of sleep on the transfer effects of cognitive training.

My last experiment (chapter 6) investigated whether direction, amplitude, and other quantitative characteristics of REMs during REM sleep are affected by previously learnt materials and whether they correlate with consolidation of declarative memory. This study provides the first evidence that REMs during REM sleep are affected by previously learnt materials prior to sleep and these REMs are related to improved memory performance. These results draw parallel to the neural substrates during the occurrence of REMs which are similar to learning prior to sleep, and which led to improved memory performance (Maquet et al., 2000; Peigneux et al., 2000; 2003). It also shows that REMs are not random, they may be involved in viewing dream imageries during dreaming as study of RBD patients showed eye movements imitated scanning of dream scenes (Leclair-Visonneau et al., 2010). As REMs are related to memory performance improvements, and other studies have found that previous waking experiences are replayed in dreams (Kusse et al., 2012; Oudiette et al., 2011; Fosse et al., 2003), I posit that REMs during REM sleep are involved in memory replay in the form of imitating scanning of dream scenes of prior waking experience, which then lead to improved memory performance upon awakening. These results provide evidence that REMs are not random, they are affected by preciously learnt materials prior to sleep, and are related to memory consolidation. REMs serve an important function in memory consolidation, and it is not simply a by-product of brain stem activity.

Future studies may look into the functions of REMs by incorporating fMRI as well as dream reports to form a more conclusive view about how REMs are affected by prior waking experience. Also, since REMs can be influenced by prior waking experience, the next step is to look at whether REMs can be affected by direct stimuli during REM sleep. A recent study that used repeated exposure of acoustic noise during different stages of sleep and found that REM sleep is especially conducive in the formation of new acoustic memories whereas SWS supresses the formation of new memories during sleep (Andrillon et al., 2017). This suggests new memories can be formed during sleep and REM sleep is receptive to external stimuli. It would be interesting to find out whether dreaming is involved in the formation of these new memories during REM sleep and whether REMs can be influenced by instructional acoustic sound during REM sleep. For example, if an audio description about the location of an object is played during the occurrence of REMs, the direction of REMs can be studies to see whether they coincide with the location of the object. This helps to see whether REMs are random or whether they follow the directions of dream imageries. Lastly, REM sleep has been found to play an important role in emotional memory consolidation (Groch et al., 2013; Nishida et al., 2008; Wagner et al., 2006), and regulation of emotions (Mauss et al., 2013; Minkel et al., 2012; Yoo et al., 2007), evidence show that people with depression tend to have more REM sleep and most antidepressant drugs have the effect of reducing REM sleep (see review, Palagini et al., 2013). The finding that REMs are affected by previously learnt materials opens new avenues of research on interventional strategies that may alleviate depression. Perhaps it is possible to induce memory replay of positive information after viewing and learning positive stimuli which may then regulate mood and depressive symptoms upon awakening.

In conclusion, this thesis investigated the effects of sleep on wellbeing with particular interest in the middle-aged women population that is especially at risk of sleep disturbances and dissatisfaction. I found that sleep disturbances in these women are

likely affected by menopausal related symptoms as a result of the reduction of ovarian hormones. The disruption in memory functions in these women is more likely the results of poor encoding as their executive functions such as attention and working memory are affected by the hormonal changes. But the effects of poor sleep on memory performance cannot be ruled out. The thesis also investigated the effects of sleep on cognition especially in cognitive training as well as how memories are consolidated. Sleep has been found to play an important role in cognitive training of the executive functions also known as fluid intelligence. REMs during REM sleep have also been found to be affected by previously learnt materials and contribute to memory consolidation possibly in the form of memory replay.

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Chapter 1

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Chapter 3

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Chapter 4

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Chapter 5

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Acronyms

American Academy of Sleep Medicine (**AASM**)

Analysis of variance (**ANOVA**)

Band Limit Power (**BLP**)

Body Mass Index (**BMI**)

Chronic sleep restriction (**CSR**)

Circadian Timing System (**CTS**)

Delayed Sleep Phase Syndrome (**DSPS**)

Dorsolateral prefrontal cortex (**DLPFC**)

Electroencephalogram (**EEG**)

Electromyography (**EMG**)

Electrooculography (**EOG**)

Epworth Sleepiness Scale (**ESS**)

Eye movement (**EM**)

Evoked response potential (**ERP**)

Functional magnetic resonance imaging (**fMRI**)

Hertz (**Hz**)

Hormone replacement therapy (**HRT**)

Intergeniculate Leaflet (**IGL**)

Interdaily Stability (**IS**)

Intradaily Variability (**IV**)

Interstimulus interval (**ISI**)

Karolinska Sleep Diary (**KSD**)

Karolinska Sleepiness Scale (**KSS**)

Massachusetts Institute of Technology (**MIT**)

Medial temporal lobe (**MTL**)

Medial prefrontal cortex (**mPFC**)

Menopausal Rating Scale (**MRS**)

Non-rapid eye movement (**NREM**)

N-methyl-D-aspartate (**NMDA**)

Oestrogen Level Assessment Questionnaire (**OLA**)

Paradoxical sleep (**PS**)

Phase response curve (**PRC**)

Pittsburgh Sleep Quality Index (**PSQI**)

Polysomnography (**PSG**)

Positive and Negative Affect Scale (**PNAS**)

Ponto-geniculo-occipital (**PGO**)

Prefrontal cortex (**PFC**)

Rapid eye movement (**REM**)

REM sleep behaviour disorder (**RBD**)

Relative Amplitude (**RA**)

Repeated transcranial magnetic stimulation (**rTMS**)

Retinohypothalamic tract (**RHT**)

Reaction time (**RT**)

Slow wave activity (**SWA**)

Slow wave sleep (**SWS**)

Sleep deprivation (**SD**)

Sleep efficiency (SE)

Sleep onset latency (**SOL**)

Sleep Quality (**SQ**)

Standard deviation (**SD**)

Standard error of mean (**SEM**)

Suprachiasmatic nucleus (**SCN**)

Transcranial direct current stimulation (**tDCS**)

Transcranial electrical stimulation (**tES**)

Transcranial magnetic stimulation (**TMS**)

Total sleep time (**TST**)

Wakefulness (**W**)

Wake after sleep onset (**WASO**)