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Dancing in the Dark: Sleep-dependent Motor Skill Memory Consolidation and Periodic Limb Movement Disorder

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Abstract

Periodic Limb Movement Disorder (PLMD) is a neurodegenerative disease characterized by repetitive limb movements during sleep and is suggested to be caused by striatal dopamine difficiency. PLMD can severely disrupt non-rapid eye movement (NREM) sleep. Motor skills learning and memory consolidation are dependent on striatal activation, the latter enhanced by NREM sleep. Therefore, we investigated whether individuals who experience PLMs had learning and sleep-related memory deficits, and whether this putative deficit was related to sleep quality or symptom severity. 14 adults with a PLM index >15/hr underwent two nights (baseline, training) of polysomnographic recording. 15 age-matched healthy controls underwent three nights (baseline, undisturbed training and disturbed training) of polysomnographic recording. On the training nights, participants learned an explicit motor sequence learning task and paired associates task at 8PM and were retested the following morning at 8AM. The healthy controls were then trained on a new sequence and a new word list and were retested at 8PM. Sleep quality was significantly worse at baseline in the PLM group compared to controls (e.g. sleep efficiency, awakenings, etc.). Training night sleep for the PLM group was less fragmented and the quality did not differ from the undisturbed night of controls despite the presence of elevated PLMs. The PLM group's motor sequence learning performance was significantly slower compared to the control group during the training session, but the overnight performance gains between two conditions did not differ. The results suggest that despite sleep disturbances and striatal dysfunction, the PLM group still yields overnight benefit to motor skill memory consolidation.

Keywords

Sleep, Sleep Quality, Sleep Architecture, Memory, Learning, PLMD, PLMs, Motor Sequence Learning, Paired Associates, Procedural Memory, Declarative Memory.

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List of Abbreviations

NREM – Non-Rapid Eye Movement sleep

REM – Rapid Eye Movement sleep

SWS – Slow Wave Sleep

PLMD – Periodic Limb Movement Disorders

PLMs – Periodic Limb Movements

MSL – Motor Sequence Learning

PA – Paired Associates

PVT – Psychomotor Vigilance Task

ES – Electrical (muscle) Stimulation

PLM – Periodic Limb Movement Condition

CTRL – sleep – Undisturbed training night of the control group

CTRL – ES - Disturbed by ES training night of the control group

CTRL – wake – Wake condition of the control group

MMS – Mini Mental State exam

Preface

The overall goal of this dissertation was to investigate sleep-dependent motor skill memory consolidation in people who experience Periodic Limb Movements (PLMs). Chapter 1 provides a general overview of sleep architecture, including a detailed description of the various stages of sleep and their importance. This is followed by a brief overview of memory systems and the process of memory consolidation. Next, memory consolidation in relation to sleep will be discussed. This is followed by a comprehensive overview of periodic limb movement disorder, as well as its prevalence, symptomatology and neural basis. Finally, the rationale and hypotheses for the current study will be discussed. Chapter 2 will explain the methodology of the current study, where the participants, equipment and protocol will be explained. Next, Chapter 3 will discuss the results of the experiment with the detailed reports on the behavioral and physiological testing. Finally, Chapter 4 will serve as a discussion where the new findings will be interpreted and further discussed in the light of the field's current literature.

Chapter 1: Introduction

1.1 Sleep architecture.

Views of the nature of sleep have changed dramatically in the past 50 years, particularly since the landmark discovery of REM sleep (Aserinsky & Kleitman, 1953; Jouvet & Michel, 1959). This pivotal discovery, which revealed that brain activity during sleep is paradoxically similar to wake, occurred at a time when sleep was viewed simply as a state of quiescence. This view is perhaps most apparent from the Scottish physician and surgeon, Robert MacNish, in his book *The Philosophy of Sleep* (1827) stated that: "*sleep is the intermediate state between wakefulness and death; wakefulness being regarded as the active state of all the animal and intellectual functions, and death as that of their total suspension*". The view that sleep was a state of oblivescence was not uncommon, and very little was known about sleep until the mid-1950's when the first polysomnographic overnight recording of sleep was collected (Aserinsky & Kleitman, 1953). The advent and availability of electroencephalography (EEG) and research that followed revealed that sleep is a dynamic, multifaceted, highly-organized, and active state, unique from wake. These recordings enabled researchers to classify two broadly distinct states of sleep: rapid eye movement (REM) sleep and non-REM sleep (NREM), with the latter further classified into increasingly deeper stages of sleep (NREM1, 2, & 3 or slow-wave sleep (SWS)). Over the course of the night, the brain cycles between NREM and REM states, repeating about every 90 minutes. The first part of the night is dominated by SWS and the later part of the night, by REM sleep, with the amount of NREM2 remaining relatively constant throughout, but making up about 50% of the night's sleep. The various stages of sleep and the neural, physiological and behavioural features that characterize these sleep states will be summarized in the following subsections and are necessary to describe and define the fundamental aspects of sleep that will be studied in latter chapters.

1.1.1 NREM1.

The very first and the "lightest" stage of sleep following wake is NREM1, and is considered the transition from wake to sleep. Typically, a healthy young adult spends

about 5% of the night in NREM1, however the amount spent in NREM1 may increase with age. Some evidence suggests an increase of 5% between the 2nd and 7th decades of life (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). The most predominant indicator of NREM1 is the reduction of alpha waves, which are maximal over occipital sites, and rolling eye movements. The disappearance of alpha is the defining feature of NREM1, when less than 50% of a 30-second epoch contains alpha waves (Iber, Ancoli-Israel, Chesson, & Quan, 2007). As brain oscillatory activity gradually slows during this stage, low voltage vertex sharp waves appear (Ogilvie, Wilkinson, & Allison, 1989).

1.1.2 NREM2.

During NREM2, the EEG becomes more synchronized, electromyogram (EMG) activity decreases and the arousal threshold for external stimuli (e.g. external noise) increases. NREM2 typically occupies about 50% of the night's total sleep. NREM2 tends to increase from middle-age onwards (Nicolas, Petit, Rompré, & Montplaisir, 2001; Ohayon et al., 2004), but some studies suggest that the increase in NREM2 only occurs in males (Ohayon et al., 2004). The main oscillatory markers of NREM2 are sleep spindles and K-complexes. Sleep spindles, are short bursts of sigma activity with a frequency of ~11-16 Hz (Iber et al., 2007), typically lasting between 0.25 and 3 seconds (Rechtschaffen, & Kales, 1968). Sleep spindles have been classically described to originate in the thalamus as evidenced by a complete disappearance of spindles in the case of thalamectomy (Villablanca, 2004), although, more recent evidence suggests cortical initiation and termination of spindles (Bonjean et al., 2011). Spindles are a result of the synaptic interactions between the mutually interconnected GABAergic inhibitory neurons of the reticular nucleus of thalamus and the thalamo-cortical neurons (Bazhenov, Timofeev, Steriade, & Sejnowski, 1999; Steriade, 1995).

There is evidence to suggest that there are two types of sleep spindles (Doran, 2003; Merica, 2000; Zeitlhofer et al., 1997), with distinct frequency ranges and topographies. Slow spindles are thought to be maximal over frontal sites and occur at a frequency of ~11-13.5 Hz, while fast spindles are maximal over parietal and central sites and occur at a frequency of ~13.5-16 Hz (De Gennaro, Ferrara, & Bertini, 2000). Sleep spindles are thought to serve several functions, such as protection from external stimuli (Cote, Epps,

& Campbell, 2000; Dang-Vu et al., 2011; Schabus et al., 2007; Steriade, 1994), as well as consolidation of procedural (e.g., skills, reasoning and rule-learning) and declarative (e.g., facts, figures and events) memory (Barakat et al., 2013; Fogel & Smith, 2006, 2011; Fogel et al., 2013; Gais, Mölle, Helms, & Born, 2002; Lafortune et al., 2014).

K-complexes also characterize NREM2, and appear as slow (<0.5sec), large amplitude (>100μV) cortical events that consist of a negative sharp wave, followed by a slower positive component (after ~350 to 550 ms), and terminate with a final negative peak occurring around 900ms (Rechtschaffen, & Kales, 1968). It has been suggested that it is the combination of sleep spindles and depolarizing component of the slow oscillation that lead to the production of K-complexes (Steriade & Amzica, 1998). Typically K-complexes are maximal over the anterior and superior frontal derivations (Roth, Shaw, & Green, 1956; Wennberg, 2010). They are thought to be generated in the thalamus (Bastien, Crowley, & Colrain, 2002), although their morphology and propagation across the scalp are influenced by cortical cells (Amzica & Massimini, 2002). While the function of K-complexes are still controversial, some studies suggest that K-complexes appear as partial arousals (Campbell, Bell, & Bastien, 1992; Davis, Davis, Loomis, Harvey, & Hobart, 1937; Roth et al., 1956), reflect auditory sensory processing during sleep (Cote, De Lugt, Langley, & Campbell, 2002; Dang-Vu et al., 2011; Hess, 1965), or an inhibitory process that protects sleep from external stimuli (Crowley, Trinder, Kim, Carrington, & Colrain, 2002).

1.1.3 SWS.

In young healthy adults, NREM3 or SWS typically occupies about 15% to 25% of total sleep time, and primarily appears in the first half of the night (Ohayon, Carskadon, Guilleminault, & Vitiello, 2003). During SWS, electromyogram activity remains low and the awareness of external environment is at its lowest. Slow Wave Activity (SWA), or delta waves, are the most prominent indicators of SWS and have a frequency of ~0.5-4 Hz and a large peak-to-peak amplitude of at least 75 μV (Iber et al., 2007). Delta waves are thought to reflect the thalamic large-scale synchronous firing of cortical neurons (Steriade, 2006). Some studies suggest that SWA serves to regulate synaptic homeostasis

and memory consolidation (Marshall, Helgadóttir, Mölle, & Born, 2006; Tononi & Cirelli, 2006).

1.1.4 REM sleep.

REM sleep is unique in that it is, paradoxically, characterized by wake-like, low amplitude, mixed-frequency EEG, including increases in alpha, beta, and gamma coupled to the theta range (Achermann & Borbély, 1998). The most characteristic features of REM sleep are rapid horizontal eye movements, which are apparent in the electrooculogram (EOG). REM sleep is also most commonly well known for its vivid and wake-like dream content (Aserinsky & Kleitman, 1953; Dement & Kleitman, 1957) although dreaming is now known to occur in all stages of sleep (Foulkes, 1993; Suzuki et al., 2004). While the EEG and eye muscles are more active than other stages of sleep, by contrast, REM sleep is accompanied by muscle atonia of the major muscle groups (Chase & Morales, 1990). This is an adaptive feature of REM sleep and is necessary in order to avoid physically enacting dreams. Studies have shown that lesions to the pons prevent muscle atonia during REM, and result in REM behaviour disorder, a neurodegenerative disease common in Parkinson's patients (Iber et al., 2007; Schenkel & Siegel, 1989).

REM is thought to occupy ~ 20% of total sleep, but there are inconsistent findings on the changes to REM sleep duration associated with increasing age (Darchia, Campbell, & Feinberg, 2003; Floyd, Janisse, Jenuwine, & Ager, 2007; Ohayon et al., 2004). The functions of REM are dissociable from NREM sleep, as REM has been linked to the consolidation of specific types of procedural memory, particularly when the learning involves the acquisition of an entirely new schema, rule, or skill (Fogel, Smith, & Cote, 2007; Nielsen et al., 2015; Smith, Nixon, & Nader, 2004; Smith & Smith, 2003). In addition, REM sleep has been implicated, in particular, in the processing of emotional content of memories (Groch, Wilhelm, Diekelmann, & Born, 2013; Hutchison & Rathore, 2015), and specifically, in disambiguating the emotional context from the memory itself (Nishida, Pearsall, Buckner, & Walker, 2009; Payne, Chambers, & Kensinger, 2012).

1.2 Memory systems.

In order to further discuss the sleep and memory literature, the following section will provide an overview of the memory systems and consolidation theories.

The traditional view of memory formation is as follows (for review see Rasch & Born, 2013; Walker & Stickgold, 2006); (1) acquisition of new information, (2) encoding of this information, (3) this encoding initiates molecular neurophysiological processes, collectively termed "consolidation", which convert the newly acquired information from a temporary memory form into its long-term, stable form, (4) a permanent memory trace is established enabling the individual to then retrieve the memory (i.e., the new information), and (5) potentially reconsolidate the trace (Nader, 2003a, 2003b; Winocur, Frankland, Sekeres, Fogel, & Moscovitch, 2009).

At the neuronal level, it is thought that the formation of a memory involves the strengthening of synaptic connections in the network representing the memory (Chapman et al., 1998; Ivanco & Racine, 2000; Trepel & Racine, 1998). This process is referred to as long-term potentiation (LTP). During LTP an increase in synaptic strength of potentiated neural pathways (depending on the memory being acquired or consolidated) may be observed (Gustafsson & Wigström, 1988). LTP can be observed during the encoding stage of memory formation and leads to two kinds of consolidation processes; synaptic consolidation and systems consolidation (Dudai, 1996). Synaptic consolidation, a process which may take up to few hours, refers to the strengthening of memory representations, which will lead to increased synaptic connection strength in local neuronal circuits (depending on the subtype of memory; Yadin Dudai, Karni, & Born, 2015). System consolidation, which may last hours, days or even years, involves the reorganization of newly acquired memory representations into long-term storage (e.g. to various brain locales, depending on the subtype of memory being formed; Diekelmann & Born, 2007).

At the systems level, memory can be classified into two, distinct systems described as *declarative* and *procedural* memory (Squire & Zola, 1996; Squire, 1992). Declarative memory consists of conscious facts and events, which can be retrieved or "declared",

whereas, procedural, or non-declarative memory, involves memory for actions, habits, procedures and skills which are usually acquired implicitly (i.e., without conscious knowledge). These memory systems were classified based on the pattern of cognitive deficits observed in patients with brain-injuries and neurodegenerative disease (for review see Gabrieli, 1998).

Declarative memory can be further subdivided into *episodic* (events i.e., autobiographical memories in a spatio-temporal context) and *semantic* memories (ideas and known facts independent of context; Tulving, 1983). Both episodic and semantic declarative memories can be learned quickly and with minimal exposure, even single-trail learning (for review see Wixted, 2004). Marr (1971) proposed the classical two-stage theory of declarative memory consolidation, suggesting that during the initial fast stage of consolidation, declarative memories are processed in the hippocampus, but are then transferred and stored in the neocortex. More recently, this theory has been supported by studies showing that patients with impaired hippocampal function, were no longer able to create new declarative memories, while older declarative memories remained intact (Corkin, 2002; for review see Frankland & Bontempi, 2005). Animal studies have also provided further support for the involvement of the medial temporal lobe in the consolidation of declarative memories (Cho, Beracochea, & Jaffard, 1993; Cho & Kesner, 1996; Wiig, Cooper, & Bear, 1996; Winocur, 1990; Winocur, Moscovitch, Fogel, Rosenbaum, & Sekeres, 2005) For example, brain lesions to the hippocampus created more severe memory impairment if they were administered closer to the initial training, compared to the cases with a longer time interval between training and lesion (Winocur, 1990). This was convincingly demonstrated in rats that had impaired recent, but spared remote spatial memory despite complete bilateral lesions to the hippocampus (Winocur, Moscovitch, Fogel, Rosenbaum, & Sekeres, 2005). Similar results were found when the lesions were administered to the thalamus (Winocur, 1990), the entorhinal cortex (Cho et al., 1993; Cho & Kesner, 1996) and the fornix (Wiig et al., 1996). Position emission tomography (PET) studies have provided evidence for the involvement of the hippocampus, cerebellum and the thalamus in the encoding and retrieval of episodic memories, specifically (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Together,

these findings suggest that the hippocampus, cerebellum and thalamus are involved in the acquisition, consolidation and retrieval of episodic and semantic declarative memories.

On the other hand, procedural memory, or non-declarative memory, can be further subdivided into *simple procedural* memory and *cognitive* (or complex) *procedural* memory based on the characteristics of the learning task (Smith, 1995, 2001). For example, simple procedural learning refers to tasks that are not cognitively complex and where performance improves with practice (e.g. Pursuit Rotor Task). However, cognitive procedural learning refers to more complex tasks that involve implicitly learning a rule or strategy to improve performance (e.g. Tower of Hanoi, or Mirror Tracing Task). Although there is little neuropsychological evidence to distinguish between these subtypes of procedural memory, the distinct learning-related changes in sleep suggest the involvement of different brain structures (Smith, 1995, 2001).

A number of studies have suggested the involvement of the striatum in implicit and explicit procedural motor skills formation and consolidation (Albouy et al., 2012, 2015; Doyon, Owen, Petrides, Sziklas, & Evans, 1996; Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Jueptner, Frith, Brooks, Frackowiak, & Passingham, 1997; Peigneux et al., 2000). There exist two experimental paradigms to investigate procedural motor learning mechanism: 1) the motor sequence learning task - to measure the acquisition of movements into a well-executed behaviour, and 2) the motor adaptation – to measure the capacity to compensate for the changes in the environment (Doyon et al., 1996; Flament, Ellermann, Kim, Ugurbil, & Ebner, 1996; Grafton, Hazeltine, & Ivry, 1995). The model by Doyon and Ungerleider (2002) proposes the existence of two systems, cortico-cerebellar and cortico-striatal, which contribute differently to motor sequence learning and motor adaptation, respectively. This system differentiation is most apparent during the reached asymptotic performance or during the reactivation of the skill during the retest session. There exist numerous studies which support this model with the evidence of greater cerebellar activation during the learning stage of the tasks (Doyon et al., 1996; Jenkins et al., 1994) and decreased cerebellar activity when the sequence becomes well-known (Grafton, Woods, & Tyszka, 1994; Jueptner et al., 1997). Furthermore, other evidence demonstrates a greater striatal activation when the motor skill performance

reaches the asymptotic level (Doyon et al., 1996; Jueptner et al., 1997) or during the retest session after a retention period (Grafton et al., 1994). For instance, a recent fMRI study demonstrated the initial activation of the cerebellar cortex during the learning phase of the motor sequence task, which gradually shifted into a striatal activation with extended practice (Doyon et al., 2002). A PET imaging study by Gafton et al. (1994) further suggests that during the acquisition of the simple motor procedure task (Pursuit Rotor Task) subjects demonstrated an activation in cerebellar structure, but next day at the retest session the activation was limited to bilateral putamen, bilateral parietal cortex, and left premotor cortex. Interestingly, neuroimaging studies also have shown that increased activity in the striatum during initial training on a motor sequence learning task, is specific to learning a certain sequence of motor movements and not due to unspecific finger movements (Orban et al., 2010; Seidler et al., 2005). Together suggesting that both the cerebellum and the striatum are central to procedural learning, but the striatal structure is also critical for the long-term storage of the well-learned movements.

As well, other studies suggest that during motor sequence acquisition, different brain structures orchestrate the acquisition of motor sequence memory including rostro-dorsal, caudo-ventral and sensorimotor portions of the striatum (Lehéricy et al., 2004, 2005). Using PET imaging, Grafton and colleagues (1992) showed that the primary motor cortex, supplementary motor area and the pulvinar thalamus were more activated during learning of a simple motor procedure task (Pursuit Rotor Task), compared to a control group, which was instructed not to move their arm and to only follow the target with their eyes. Additional evidence from PET imaging studies suggest that the fronto-parieto-cerebellar network is involved during the practice of a visuomotor task (i.e., cognitive procedural learning; Balslev et al., 2002; Contreras-Vidal & Kerick, 2004; Ghilardi et al., 2000; Imamizu et al., 2000; Kakizaki et al., 2008; Shadmehr, 1997).

Finally, the evidence from patients with Parkinson's Disease (Jordan & Sagar 1994; Contreras-Vidal & Buch, 2003; Laforce & Doyon, 2002; Stoffers, Berendse, Deijen, & Wolters, 2002) supports the literature suggesting a role for the striatum in procedural learning in healthy, young individuals. Parkinson's disease is characterized by the degeneration of dopaminergic neurons in the nigrostriatal structure (Calabresi, Picconi,

Tozzi, & Di Filippo, 2007; Javoy-Agid et al., 1984; Lang & Lozano, 1998; Robertson & Robertson, 1988) as well as the main symptom of the disease being impaired motor skills, suggesting that Parkinson's Disease patients are the ideal candidates to investigate the consequence of striatal and substantia nigra dysfunction on procedural memory. Numerous studies demonstrated compromised performance of Parkinson's Disease patients on visuomotor sequence learning (Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Pascual-Leone et al., 1993), verbal serial reaction time (Westwater, McDowall, Siegert, Mossman, & Abernethy, 1998), initial learning of basal-ganglia-dependent classical conditioning pairs (Myers et al., 2003; Vriezen & Moscovitch, 1990), and probabilistic learning (Knowlton, Mangels, & Squire, 1996), thus contributing to the evidence suggesting the involvement of striatal structures in procedural memory. Together, these findings suggest that the cerebellum, striatum, primary and supplementary motor cortex, as well as thalamus are involved in the acquisition, consolidation and retrieval of simple and cognitive procedural memories.

1.3 Sleep & memory.

The idea that sleep supports learning and memory is not new, and can be traced back to pre-recorded history. However, scientific evidence to support the relationship between sleep and memory dates back to only the beginning of the 20th century, when it was demonstrated that between initial information acquisition and retrieval, a period of sleep may help to preserve memories better than an equivalent period of wake (Jenkins & Dallenbach, 1924). Since this time, a convincing body of scientific evidence in both humans and animals now supports the notion that sleep contributes to the consolidation of newly formed memories.

1.3.1 Declarative memory.

Early work in this field employed the "night-half paradigm" (Ekstrand, 1974). This paradigm was based on the fact that certain sleep stages dominate certain parts of the night (i.e., SWS predominates the first half of the night, while REM sleep predominates second half of the night). By requiring participants to sleep only during either the early or late part of the night, it was possible to distinguish whether SWS or REM sleep was

principally involved in the consolidation memory. These early studies, tended to focus on declarative learning and their results, as well as the more recent findings, suggest that declarative memories preferentially benefit from SWS (Barrett & Ekstrand, 1972; Fogel et al., 2007; Fowler, Sullivan, & Ekstrand, 1973; Gais & Born, 2004; Plihal & Born, 1995; Rasch, Büchel, Gais, & Born, 2007; Tilley & Empson, 1978; Tucker et al., 2006; Yaroush, Sullivan, & Ekstrand, 1971). More specifically, Yaroush and colleagues (1971) demonstrated that performance gains on a word pair recall task were specifically related to early sleep (i.e., more SWS) versus late sleep (i.e., more REM) or as compared to an equivalent amount of wake. However, these half-night studies overlooked the fact that NREM2 is rather equally distributed over the course of the night, and thus cannot rule out the involvement of NREM2 in declarative memory consolidation. Moreover, this type of paradigm does not take into account time-of-day differences, or the influence of prior sleep-wake state. Indeed, more recent evidence suggests that declarative memory consolidation is supported by NREM2 sleep, and specifically, related to sleep spindles (Clemens, Fabó, & Halász, 2005; Fogel & Smith, 2006; Milner, Fogel, & Cote, 2006; Nishida & Walker, 2007; Peters, Smith, & Smith, 2007; Schabus et al., 2004). Thus suggesting that when time-of-day and other confounds are taken into account, and the role of NREM2 considered, that the role of SWS in declarative memory consolidation is less clear.

1.3.2 Procedural memory.

The consolidation of procedural memory can be divided into two separate stages: stabilization and enhancement (Walker, 2005). Consolidation-based stabilization occurs irrespective of sleep or wake, and results in the acquired memory to become more resilient to external interference (Brashers-Krug, Shadmehr, & Bizzi, 1996). During this process, which may take up to a few hours, performance is asymptotic, reflecting memory stabilization (Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000; Walker et al., 2003, 2002). Shadmehr and Brashers-Krug (1997) found that after 6 hours of memory stabilization, different brain regions became more activated including pre-motor, parietal and cerebellar regions. On the other hand, consolidation-based enhancement occurs during sleep and, not only makes the memory more resistant to interference, but also

enhances it without further learning or practice (Albouy et al., 2015; Debas et al., 2010; Fogel, Ray, Binnie, & Owen, 2015; Huber, Ghilardi, Massimini, & Tononi, 2004; Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994; Tucker et al., 2006; Walker et al., 2002).

1.3.3 Cognitive procedural memory.

Evidence suggests that REM sleep is involved in sleep-dependent cognitive procedural memory consolidation (Plihal & Born, 1995, 1999; Smith et al., 2004; Wetzel, Wagner, & Balschun, 2003), while NREM2 is involved in simple procedural memory consolidation (Fogel & Smith, 2006; Laventure et al., 2016; Nishida & Walker, 2007; Smith & Macneill, 1994; Tweed, Aubrey, Nader, & Smith, 1999; Walker et al., 2002). The strongest evidence of REM sleep involvement in cognitive procedural memory consolidation comes from studies where a new language was learned (Koninck, Lorrain, Christ, Proulx, & Coulombe, 1989) or Morse code (Mandai, Guerrien, Sockeel, Dujardin, & Leconte, 1989). It has also been observed that the amount of REM sleep increases when participants learn a novel and complex pattern of motor movements and coordination such as those seen in trampolining (Buchegger, Fritsch, Meier-Koll, & Riehle, 1991; Buchegger & Meier-Koll, 1988) or learning the strategy or rule for completing the Tower of Hanoi task (Fogel et al., 2015; Smith, 1995; Smith et al., 2004). Perceptual studies, such as a visual texture discrimination task, have also demonstrated that the presence of uninterrupted REM and SWS promoted sleep-dependent memory enhancement, compared to an equivalent period of wake (Gais, Plihal, Wagner, & Born, 2000; Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994; Stickgold, James, & Hobson, 2000; Stickgold, Whidbee, et al., 2000).

1.3.4 Simple procedural memory.

Although REM sleep is required to consolidate complex procedural memories, the sleep-dependent simple procedural memory consolidation has been shown to be dependent on NREM2 (Fogel & Smith, 2006; Laventure et al., 2016; Nishida & Walker, 2007; Peters, Smith, & Smith, 2007; Smith & Macneill, 1994; Tweed et al., 1999; Walker et al., 2002). One of the first studies to investigate the relationship between simple procedural learning and sleep, was conducted by Smith and MacNeill (1994) and involved four sleep

conditions: REM sleep deprivation, NREM sleep deprivation, total sleep deprivation and late-sleep deprivation (i.e., a reduction in REM sleep). Their results suggested that participants who were late-sleep deprived (i.e., were not allowed to sleep during the last part of the night when both NREM2 and REM sleep occur) suffered the most impairment on the Pursuit Rotor Task. However, given that the REM sleep deprivation group performed normally on the task, and the NREM deprivation group was equally impaired, this pattern of results suggested that NREM2 played an important role in simple procedural memory consolidation. A similar study (Smith & Fazekas, 1997) provided further evidence suggesting that the consolidation of simple procedural memory cannot only be disrupted by NREM2 deprivation, but even by a slight interruption of NREM2 during the night. As well, Tweed and colleagues (1999) demonstrated that a disruption of NREM2 during the night impaired performance on a simple-tracing task but not on the mirror-tracing task. Similarly, deprivation of REM sleep weakened the performance gains for the mirror-tracing task, but not the simple-tracing task (Tweed et al., 1999). Taken together, these findings suggest the involvement of NREM2 in the consolidation of simple procedural memories, but suggest that NREM2 is not involved in the consolidation of cognitive procedural memories.

More recently, the relationship between NREM2 and simple procedural memory consolidation has been strengthened by studies suggesting that sleep-dependent performance gains on a motor sequence learning task were positively correlated with increased sleep spindle activity (e.g. frequency, amplitude, density; Fogel et al., 2015, 2007; Fogel & Smith, 2006, 2011a; Steffen Gais et al., 2002; Laventure et al., 2016; Nielsen et al., 2015) as well as an increases in fMRI blood-oxygen-level dependent (BOLD) signal in the striatum (Barakat et al., 2013; Fogel & Smith, 2011; Fogel et al., 2013). Further evidence from neuroimaging studies has shown that increased activation of the striatum during practice of a simple procedural task is enhanced following a night of sleep, compared to a period of wake (Debas et al., 2010; Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005). Together these findings suggest that both REM and NREM2 are necessary for the sleep-dependent consolidation of cognitive and simple procedural memories, respectively and that enhancement of the striatum, related to the action of sleep spindles may underlie memory consolidation.

1.4 Sleep & aging.

As people age, the quality and quantity of sleep are greatly reduced (for review, see Edwards et al., 2010; Ohayon, Carskadon, Guilleminault, & Vitiello, 2003; Zdanys & Steffens, 2015). With increasing age, the most striking and consistent changes in the neural oscillations of sleep are reduced SWA (Carrier, Land, Buysse, Kupfer, & Monk, 2001; Feinberg, Koresko, & Heller, 1967) and reduced sleep spindles (Martin et al., 2013; Peters, Ray, Fogel, Smith, & Smith, 2014); whereas REM sleep is strikingly preserved until the very late stages of life (Floyd et al., 2007). In general, sleep becomes increasingly lighter, and more fragmented with age (Guazzelli et al., 1986; Silva & Duffy, 2008; Wauquier, 1993), particularly for men (Redline et al., 2004) . There is also an increase in the electrophysiological signatures of wake, such as alpha activity intruding into sleep with increasing age (Dijk, Duffy, & Czeisler, 2001).

There are a number of indirect age related factors known to reduce sleep quality and duration. Some of these factors include medication intake (for review see Bliwise, 1993), health conditions such as dementia (Porter, Buxton, & Avidan, 2015), osteoarthritis (Pickering, Chapurlat, Kocher, & Peter-Derex, 2016), cardiovascular diseases (Badran, Yassin, Fox, Laher, & Ayas, 2015) as well as deterioration of pulmonary function (Phillips, Berry, Schmitt, Patel, & Cook, 1989) and sleep disorders such as Restless Leg Syndrome (RLS), Periodic Leg Movement Disorder (PLMD) and respiratory disorders such as sleep apnea (Roehrs, Zorick, Sicklesteel, Wittig, & Roth, 1983). The aforementioned sleep disorders, in particular, PLMD, have been documented to become increasingly prevalent with age (Pennestri et al., 2006) and are thought to be the result of neurodegeneration (for review see Anderson & Bradley, 2013). However, very little is known about the impact of these disorders on memory and cognitive functioning, or whether sleep disturbances are merely a symptom or are part of the etiology of the conditions themselves.

1.5 Periodic Limb Movement Disorder.

1.5.1 Characteristics.

Periodic Limb Movement Disorder (PLMD), originally termed nocturnal myoclonus, was first described in the 1950s by Symonds (Symonds, 1953) who initially proposed that PLMD was associated with epilepsy. This association was based on the nature of involuntary jerks during the night and given that many of his patients who experienced sleep-related limb movements tended to develop epilepsy in later years. Later work demonstrated that epileptic myoclonus is sporadic and involves spikes of cortical activity, whereas nocturnal myoclonus is periodic; occurring approximately every 15 to 30 seconds (Guilleminault, Raynal, Weitzman, & Dement, 1975; Lugaresi, Cirignotta, Coccagna, & Montagna, 1986). PLMD was subsequently described as a neurodegenerative disorder characterized by stereotyped, repetitive, and non-epileptiform movements of the lower limbs during sleep (Coleman, Pollak, & Weitzman, 1980). These muscle twitches, known as periodic limb movements (PLMs), are most frequently experienced in the lower limbs during NREM sleep. The tibialis interior is the most frequent initiating muscle although the upper limb muscles may also be involved (Provini et al., 2001; Weerd, Rijsman, & Brinkley, 2004). Periodic Arm Movements (PAMs), on the other hand, occur mostly during wakefulness or the lightest stage of sleep, happen less frequently than PLMs and do not seem to coincide with PLMs (Gabelia, Mitterling, Högl, Wenning, & Frauscher, 2014). PLMs, which are essentially contractions and expansions of various limb muscles, vary greatly between, as well as within, individuals and were found to vary in terms of muscles involvement and the order of muscle initiation (Bliwise, Carskadon, & Dement, 1988; Weerd et al., 2004). PLMs may start as early as NREM1 sleep, become most evident in NREM2 and SWS sleep, and are nearly absent in REM sleep (Iber et al., 2007).

PLMs are not to be confused with PLMD, a diagnosed clinical disorder; PLMs are only observed movements, and are very common below clinical diagnostic criteria. According to the American Association of Sleep Medicine Manual-III, in order for an adult to be diagnosed with PLMD, the frequency of PLMs should exceed 15 events per hour

averaged throughout the night and be accompanied by an associated sleep complaint (Iber et al., 2007).

1.5.2 PLM characteristics.

AASM sleep scoring guidelines specify that PLMs must be between 0.5 and 10 seconds in duration with a minimum amplitude increase of 8μV in leg EMG voltage compared to resting leg EMG to be counted. There also must be a series of at least 4 movements in the course of 90 seconds with a minimum interval of 5 seconds. Movements preceding or following an apnea or hypopnea by half a second are not to be counted as a PLM. If both legs experience a limb movement within 5 seconds, it is to be counted as a single movement.

1.5.3 PLM prevalence.

The first study to document the prevalence rates for PLMs using a large randomized sample of older adults (age range from 65 to 95 years old; 68 males) reported a 44% prevalence rate (>5 movements per hour, on average), whether accompanied by apnea or not (Ancoli-Israel, Kripke, Mason, & Kaplan, 1985). Subsequent research found the prevalence rate to be 45% past the age of 65 (Ancoli-Israel et al., 1991). Although prevalence is frequently reported to increase with age (Bixler et al., 1982; Mosko et al., 1988; Roehrs et al., 1983), and there is some evidence to suggest that PLM severity plateaus and no progressive worsening of PLMs is observed with increasing age after mid 60s (Gehrman et al., 2002). As for gender, the findings are equivocal as to whether PLMs are more likely to occur in men or in women (Bixler et al., 1982; Ohayon et al., 2004).

1.5.4 Neural basis of PLMs.

PLMD is a sensorimotor disorder that is closely related to Restless Leg Syndrome (RLS). RLS is a disorder in which patients intentionally move their limbs during the night or evening and experience feelings of restlessness (Walters, 1995). Importantly, the two conditions are thought to share similar underlying pathologies (Brodeur, Montplaisir, Godbout, & Marinier, 1988). Approximately 80% of patients experiencing RLS will also

experience PLMs, however not all PLMD patients will suffer from RLS (Montplaisir et al., 1997).

PLMs are more common in disorders with Lewy body pathology, such as Parkinson's Disease (Montplaisir, Michaud, Denesle, & Gosselin, 2000), and less common in disorders where excess dopamine has been observed, such as schizophrenia (Ancoli-Israel et al., 1999). Numerous studies have documented relief of RLS and PLMs symptoms and clinical improvement with medications that increase dopamine activity, including: Levodopa, Benserazide, and Bromocriptine (Benes et al., 1999; Boivin, Montplaisir, & Poirier, 1989; Brodeur et al., 1988; Chesson et al., 1999; Hening, Allen, Earley, Picchietti, & Silber, 2004; Montplaisir, Godbout, Poirier, & Bédard, 1986; Walters, Hening, Kavey, Chokroverty, & Gidro-Frank, 1988). Dopamine is a neurotransmitter that plays a major role in the regulation of wakefulness (Bagetta, De Sarro, Priolo, & Nisticò, 1988), and opiates have also been shown to subside PLMs (Montplaisir et al., 1986). Furthermore, both syndromes are worsened with the use of dopamine antagonists such as Pimozide (Akpinar, 1982; Montplaisir, Lorrain, & Godbout, 1991) and with the use of dopamine release blockers (Montplaisir et al., 1986).

It has been suggested that based on a treatment strategy with the use of dopamine agonists, PLMD patients might be hypo-dopaminergic (Kaplan, Allen, Buchholz, & Walters, 1993). Given that RLS and PLMD are comorbid in many cases, the majority of research attempting to understand the neural basis of PLMD have examined the patients with both disorders. Thus, the understanding of the neurological pathology of the PLMD is limited and current findings of structural differences of PLMD are clouded by the fact that the etiology of PLMD and RLS may be dissociable, however, much of the literature does not address this potential confound. It is important to note that PLMs and RLS are not necessarily associated with simply a lack of dopamine, but rather a reduction of dopaminergic activity in the central nervous system. For example, Montplaisir and colleagues (1985) found high levels of dopamine and homovanillic acid (a dopamine metabolite) in the cerebrospinal fluid of patients with RLS (Montplaisir et al., 1985). In fact, individuals who experience both PLMs and RLS are thought to suffer from a reduction in dopamine D2-receptor occupancy, which is worsened with the increase of

PLMs (Staedt et al., 1995), and lower mean binding to central dopamine D2-receptors (Staedt et al., 1993). Furthermore, patients with Parkinson's disease diagnosed with PLMD exhibit lower β-CIT striatal binding (Happe et al., 2003). Decline in D2 receptor stimulation is known to increase with age (Wong et al., 1984), corresponding with the increasing prevalence of PLMs in the elderly.

The aforementioned dopamine deficiency in patients with PLMs or RLS is thought to occur primarily in the striatum, with the putamen being more affected than the caudate (Michaud, Soucy, Chabli, Lavigne, & Montplaisir, 2002; Ruottinen et al., 2000; Staedt et al., 1995).

1.5.5 PLMs, arousals and sleep disturbances.

PLMs are often accompanied by an alpha-arousal in the EEG, although their exact relationship is unclear due to vast inter-individual variability (Karadeniz, Ondze, Besset, & Billiard, 2000). Some studies using subjective sleep reports suggest that PLMs do not cause sleep or mood disturbances regardless of their severity (Dickel & Mosko, 1990; Mosko et al., 1988). Surprisingly, no significant relationships have been found between PLM index and subjective complaints in regards to sleep quality (Carrier et al., 2005; Hornyak, Riemann, & Voderholzer, 2004; Mendelson, 1996; Pennestri et al., 2006; Youngstedt, Kripke, Klauber, Sepulveda, & Mason, 1998) or between PLMs and daytime sleepiness (Coleman et al., 1982; Nicolas, Lespérance, & Montplaisir, 1998). However, patients who experience insomnia accompanied by PLMs may be more affected as they have more awakenings with prolonged sleepless periods after the limb movements (Rosenthal et al., 1984; Saskin, Moldofsky, & Lue, 1985). However, the aforementioned studies have only taken into account subjective self-reports of sleep quality, thus may have overlooked clinically and functionally important aspects of sleep disruption that only overnight polysomnography (PSG) could detect. In order to obtain a more complete picture on this issue, objective measures of sleep quality during PLMs should be considered. Employing psychomotor vigilance measures yielded no difference in reaction times between the PLMs population and the healthy controls (Sivertsen et al., 2008). However, studies employing overnight polysomnography show that PLMs cause frequent arousals, sleep fragmentation, and sleep stage shifts (Bastuji & García-Larrea, 1999;

Rosenthal et al., 1984; Staedt et al., 1995) as well as lower sleep efficiency (Hilbert & Mohsenin, 2003), longer sleep onset, and shorter sleep length in general (Saskin et al., 1985). Due to frequent arousals, the overall sleep of individuals with PLMs was about 100 minutes shorter as compared to healthy controls, which equates to a loss of an entire sleep cycle (Ancoli-Israel et al., 1985; Kales et al., 1967). Based on objective sleep evaluations, these findings suggest that PLMs might contribute to reduced sleep efficiency in the face of no subjective sleep quality complaints.

1.5.6 PLMs & memory

The possible underlying pathophysiology of PLMs and resulting sleep fragmentation would suggest a link between PLMs and poor consolidation of motor memory skills, which are sleep dependent, and rely on the striatum for optimal consolidation (Albouy et al., 2012, 2015; Doyon et al., 1996; Jenkins et al., 1994; Jueptner et al., 1997; Peigneux et al., 2000). Another essential component for this type of memory consolidation, is uninterrupted and good quality sleep, specifically NREM2 (Fogel & Smith, 2006; Laventure et al., 2016; Nishida & Walker, 2007; Smith & Macneill, 1994; Tweed, Aubrey, Nader, & Smith, 1999; Walker et al., 2002). Individuals who experience PLMs not only experience striatal dopamine deficits but also fragmented sleep and arousals during sleep caused by the limb movements. Consequently, people who encounter PLMs may experience memory deficits which are specific to motor skills, however there are no studies investigating this possibility. Furthermore, if they do experience memory deficits, it is unclear whether these deficits are caused by the neural basis of PLMs or the sleep disturbances that are associated with PLMs.

1.6 Current Study

The main purpose of the current study was to examine the relationship between PLMs and memory. There are currently no studies investigating the consequences of PLMs on memory, and to our knowledge, no work has been done specifically exploring the impact of PLMs on sleep-dependent consolidation of motor skill memory. Given that PLMs are most prominent during NREM2 sleep (Iber et al., 2007) and have been shown to have a negative impact on sleep quality (Bastuji & García-Larrea, 1999; Hilbert & Mohsenin,

2003; Rosenthal et al., 1984; Saskin et al., 1985; Staedt et al., 1995), it remains to be investigated if memory consolidation for memory tasks that are dependent on NREM2 sleep (e.g. motor sequence learning task and the paired associates) are impaired in people who experience PLMs. Moreover, it is not clear whether any related impairment in memory consolidation would be due to disrupted sleep per se, or independent of this type of sleep disruption (i.e., periodic, brief arousals), or rather, related to other iatrogenic factors, such as neurodegeneration of the brain regions that support motor memory consolidation, such as the striatum. The objective of the study is to, not only examine whether PLMs have any effect on motor skills memory consolidation, but also to disentangle two plausible reasons why this might happen: the ongoing sleep disturbance throughout the night caused by PLMs or other putative explanations, such as the neural basis of PLMs themselves.

Here, we investigated the impact of PLMs on motor skill memory consolidation in a sample of individuals who experience PLMs compared to healthy, aged-matched controls under either normal sleep conditions, or by disrupting the sleep of normal controls by inducing leg movements using mild electrical stimulation of the muscles, similar to the PLMs. Furthermore, in order to probe whether memory deficits were specific to striatal-dependent motor memory consolidation, we have also employed a declarative paired associates memory task, which is known to be hippocampus-dependent (Corkin, 2002; Gilbert, 2001; Persson, Kalpouzos, Nilsson, Ryberg, & Nyberg, 2011; Winocur, 1985). We hypothesize that: 1) people who experience naturally occurring PLMs will demonstrate sleep-dependent motor skills consolidation deficits in comparison to the healthy controls (whether with disturbed or undisturbed sleep); 2) the control group will only exhibit motor sequence learning task performance gains if the retention period between the training and the retest session involves undisturbed sleep (wake or disturbed by induced leg movements sleep); 3) there will be no difference on paired associates task performance gains between the PLM and the control group’s disturbed sleep condition.

Chapter 2: Method

2.1 Participants.

Forty-eight participants age 30 to 65 years old were enrolled in the study. The participants were recruited via flyers posted in public places such as the university campus, community centres, cafes, dance and yoga studios, as well as via newspaper advertisements and online classified ads.

All participants were in good health, normal BMI (<30), right-handed, non-smokers, did not consume excessive caffeine (<2/day) or alcohol (<14/week), described themselves as subjectively "good" sleepers, non-shiftworkers, had regular sleep between the hours of 10 pm to 9 am, free from sleep disorders, free from medication known to interfere with sleep, with no history of chronic pain, seizures, head injury, depression, anxiety and had normal mobility of the hands and fingers. Professional typists or trained musicians were excluded. The initial eligibility was determined through a telephone screening interview (**Appendix A**). Eligible participants visited the sleep laboratory for an overnight PSG to screen participants for signs of any sleep abnormalities or sleep disorders (see Procedure section for further detail).

We excluded 19 participants in total: eight participants for poor sleep quality (sleep efficiency < 90%), five participants who experienced respiratory events (> 10 events/hour) and two participants for not complying with the experimental protocol. Finally, four participants voluntarily dropped out of the study following their first night in the laboratory. The final sample consisted of 22 females and 7 males aged between 30 and 62 years (M = 46.38, SD = 11.35). The demographics for the sample are presented in **Table 1**.

	Conditions	
	Control (N=15)	PLM (N=14)
Age *M (SD)*	42.2 (13.0)	50.8 (7.4)
# males	2	5
# females	13	9
Beck's Depression Scale *M (SD)*	3.3 (3.3)	3.5 (2.6)
Beck's Anxiety Scale *M (SD)*	4.4 (3.5)	6.5 (6.19)
Epworth Questionnaire Score *M (SD)*	6.7 (3)	6.5 (2.3)
Sleep Disorders Questionnaire – Sleep Apnea *M (SD)*	18.6 (6.8)	22.7 (5.5)
Sleep Disorders Questionnaire – PLMD *M (SD)*	12.3 (3.7)	13.1 (3.9)
Sleep Disorders Questionnaire – PSY *M (SD)*	15 (3.1)	14 (3.2)
MMS – *M (SD)*	29 (0.8)	28 (1.3)

Table 1. Demographic details of the control and PLM groups.

2.2 Ethics approval.

All participants provided written consent prior to participation (**Appendix B)**. At the conclusion of the study, participants were given financial remuneration and debriefed. This research was approved by the Western University Health Science Research Ethics Board.

2.3 Polysomnographic recording.

Embla Titanium (Natus, San Carlos, CA, USA) 24 channel EEG systems were used to perform in-laboratory PSG recordings. The EEG was recorded at a sampling rate of 512 Hz, with a high pass filter = 0.1 Hz and low pass filter = 220 Hz. EEG (F3, F4, Fz, C3, C4, Cz, P3, P4, Pz and Oz) and EOG (placed on the temples) referential recordings (reference Fpz), were re-referenced offline to averaged mastoid derivations (M1 and M2), placed according to the international 10-20 electrode placement system (Iber et al., 2007). Submental EMG channel was recorded from as a bipolar derivation. Leg movements were recorded with the use of two bipolar channels placed on tibialis anterior muscles. RemLogic analysis software (Natus, San Carlos, CA, USA) was used to sleep stage score the recordings according to standard criteria (Iber et al., 2007). The sleep variables of interest obtained from the PSG recording nights included the total sleep time (TST), sleep efficiency (SE), number of awakenings (NA), wake after sleep onset (WASO), percentage of time spent in wake, NREM1, NREM2, SWS and REM, plus limb movements with arousals and limb movements without arousals. TST was calculated as the total time spent asleep between “lights off” and “lights on”. SE was calculated as a percentage of the total time spent in bed between “lights off” and “lights on” divided by the time spent in bed actually sleeping. NA was defined as any 30-sec epoch, following sleep onset, that was scored as wake due to either: (1) occipital EEG alpha activity occurring for more than 50% of the epoch or (2) a body movement as well as alpha activity occurring for part of the epoch (even <50% of the epoch) (Iber et al., 2007). WASO was defined as epochs following sleep onset that were scored as wake. Sleep stage percentages were calculated as the percentage of time between “lights off” and “lights on” scored as wake, NREM1, NREM2, SWS and REM divided by TST. A limb movement was scored if it was between 0.5 and 10 seconds in duration with a minimum amplitude increase of 8μV in leg EMG voltage (compared to resting leg EMG). The limb movements must also have occurred in a series of at least 4 movements in the course of 90 seconds with a minimum interval of 5 seconds between them. An arousal was scored with a limb movement if there was a minimum of a 3 second burst of alpha activity following the limb movement.

2.3.1 Screening night.

EEG was recorded from Fz, Cz, Pz and Oz scalp locations, respiration effort was measured using thorax and abdomen respiratory effort belts, electrocardiographic activity was recorded from the left and right clavicle, leg muscle EMG recordings were recorded from two electrodes placed on each anterior tibialis muscle and blood oxygen saturation was recorded from an infrared finger probe sensor on index finger. The screening night recording was visually scored according to the clinical guidelines established by the American Academy of Sleep Medicine (Iber et al., 2007) by a Registered Polysomnographic Technologist. Participants experiencing above 10 respiratory events per hour, any RLS events, or control subjects with poor sleep quality (sleep efficiency < 90%) were excluded from the study (refer to the Participants section). During this visit, participants were instructed to fill out the Sleep Disorders Questionnaire **(Appendix C)** to screen out people with poor sleep quality and potential sleep disorders, the Napping Behaviour Questionnaire (**Appendix D)** to classify the participants into nappers or non-nappers, the Beck Depression (**Appendix E**; Beck et al., 1974) and Anxiety Inventories (**Appendix F**; Beck et al., 1988) to screen out people who exhibit signs of depression or anxiety, the Epworth Sleepiness Scale (**Appendix G**; Johns, 1991) to measure participants' fatigue. The Horne-Ostberg Circadian Rhythm Questionnaire (**Appendix I**) was used to classify participants into the morningness or eveningness type (Horne and Ostberg, 1976), and the Edinburgh Handedness Inventory (**Appendix J**; Oldfield, 1971) to screen out people whose dominant hand was not right. Finally, all participants completed the Mini Mental State exam (**Appendix K**; Folstein, Folstein, & McHugh, 1975) to screen out dementia. Participants who scored higher than 10 on the Beck's Depression and Anxiety scales, as well as those who scored above normal values for either sleep apnea or a psychiatric sleep disorder on the Sleep Disorders Questionnaire and any participant scoring above normal on the Mini Mental State exam was excluded from further participation in the study. Furthermore, participants were excluded if they did not keep a regular sleep-wake schedule according to the instructions given (bed time between 10pm and 1am; and rise time between 7am and 9am).

2.4 Electrical muscle stimulation.

Transcutaneous electrical muscle stimulation (ES) was used to induce periodic limb movements in individuals who do not naturally experience them at clinically significant levels (e.g. <15 PLMs/hour; Iber et al., 2007). This condition will be referred to as CTRL-ES from now on. The low-voltage electrical current stimulation was delivered via a GRASS SD9 stimulator. Two electrodes were applied with adhesive tape onto the participant's right leg directly over the tibialis muscle (about 3-4 inches apart). To induce a brief muscle contraction, the stimulator was set as follows: frequency 0.1 PPS, delay 0.1ms and duration 6ms, according to stimulation parameters known to induce mild muscle contractions. The final voltage of the electrical stimulation that was delivered during sleep was determined based on the individual threshold determined by raising the voltage gradually until stimulations produced a visible leg twitch, mimicking a limb movement of the participants with naturally occurring PLMs (PLM condition). The adjustment and the setting of the voltage strength were administered while receiving feedback from the participant to avoid causing pain or discomfort. Because the number of PLMs differs depending on the time of night, the frequency of the stimulations was varied according to age norms reported by NREM cycle (Sforza, Jouny, & Ibanez, 2003). In addition, the frequency and number of stimulations was varied to simulate 3 PLMs severities: severe, moderate and mild (see **Table 2**).

Condition	Sleep Cycle 1	Sleep Cycle 2	Sleep Cycle 3	Sleep Cycle 4	# of Participants in Each Condition
Severe	80/hr	60/hr	40/hr	30/hr	5
Moderate	60/hr	40/hr	30/hr	30/hr	6
Mild	40/hr	30/hr	10/hr	10/hr	4

Table 2. The stimulation within each condition varied according to the amount of NREM2 and SWS each participant received. Each participant was randomly assigned to one of the ES severity conditions.

The shocks were only administered while the participants were in sleep stage NREM2 or SWS, as previous literature demonstrates that PLMs are most likely to occur then (Carrier et al., 2005; Haba-Rubio, Staner, Krieger, & Macher, 2004; Saletu et al., 2002; Sforza et al., 2003). PLMs have been known to occasionally occur in NREM1, however, the administration of shocks during NREM1 was avoided, as it would likely wake participants and prevent them from progressing to the next stage of sleep. After the 4th sleep cycle was complete the muscle stimulation was terminated.

2.5 Objective vigilance – PVT.

In order to access the objective vigilance, the Psychomotor Vigilance Task (PVT) was completed before and after each behavioural testing session. The PVT is a computerized task which presents the participant with a focal point in the centre of a black screen. At random intervals, the focal point will change to a timer. The objective of the task is to press the keyboard as quickly as possible when the timer becomes visible. The PVT sessions included 100 trials each and the variable of interest obtained from the PVT data was the reaction time (measured in milliseconds).

2.6 Behavioral tasks.

2.6.1 Motor Sequence Learning task.

The motor sequence learning task used was an adapted version of the finger-tapping task (Karni et al., 1995). A numeric keypad was used with 4 buttons in an ergonomic configuration for the left hand (**Figure 1**).

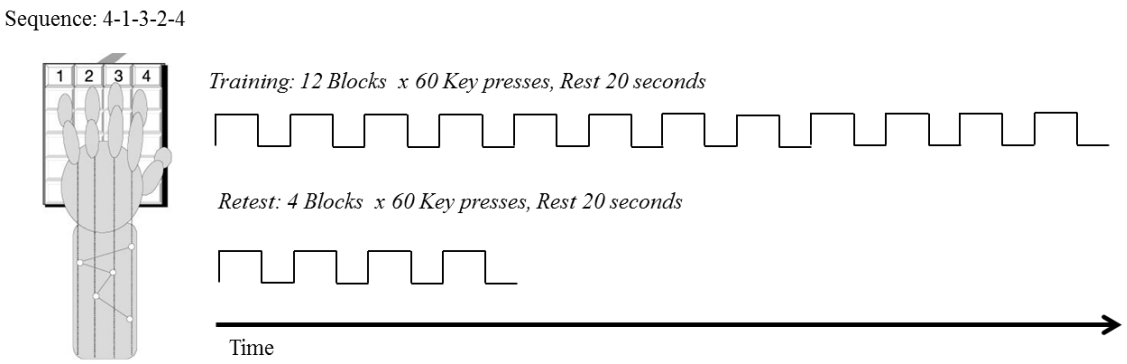

Figure 1. The task was subdivided into three stages: "Verification", "Practice" and "Training". First, during the "verification" phase, subjects were instructed to execute the sequence 1-2-3-4 (where 1 corresponds to the index finger, and 4 corresponds to the little finger) slowly and accurately to ensure that the equipment and software was operating normally and the subject was using the keypad as instructed. Next, during the "practice" phase, participants were instructed to execute a 5-item sequence (for example "4-1-2-3-4") slowly and accurately until the sequence was reproduced three times in a row without making any errors. This procedure was intended to verify that the participant had explicitly learned the sequence and could execute the sequence consistently without errors. During the "training" phase, participants were instructed to execute the sequence learned in the "practice" phase as quickly and as accurately as possible. The session consisted of 12 blocks (indicated by a green cross in the middle of a black screen) and 12 rest periods between the training blocks (marked by a red cross in the middle of a black screen). Each block comprised 60 key presses and each rest period lasted for 20 seconds. Participants were instructed to start at the beginning of the 5-item sequence in the event of an error. The morning re-test session was identical to the training session with the exception that it included only 4 blocks (60 key presses each) and 4 resting periods (20 seconds each). Three equivalent sequences were randomly assigned to the participants: '4-1-3-2-4', '2-3-1-4-2' and '3-4-2-1-3' (Karni et al., 1995; Walker et al., 2005). Figure adapted and modified from Walker et al., 2003.

The measurement of performance on the motor sequence learning task was the averaged time between each consecutive key press during the correct sequences per block.

2.6.2 Paired Associates task.

Participants were randomly presented one of three lists of 40 unrelated word pairs. The word lists were adapted from Payne et al (2012) and Fogel et al (Fogel et al., 2007). The participants were instructed to memorize the word pairs to the best of their ability, by visually relating the words to one another using mental imagery (**Figure 2**).

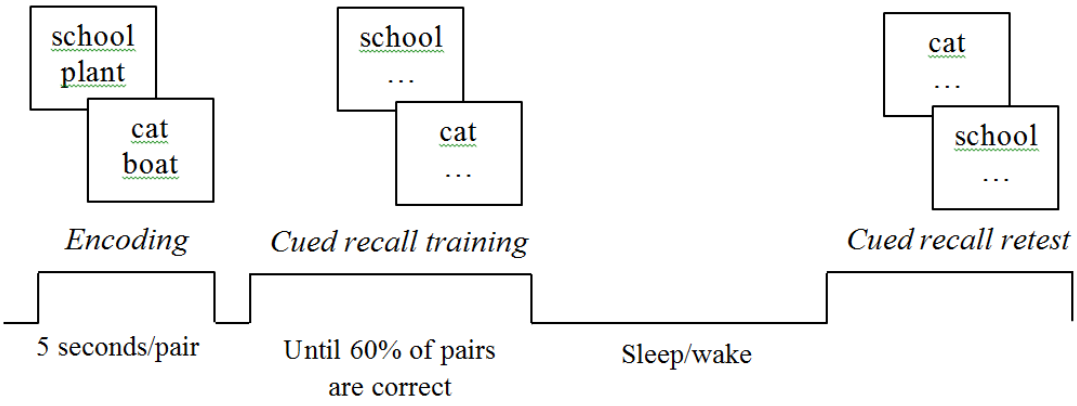

Figure 2. Paired Associates task. Each participant was presented one word pair at a time for 5 seconds to memorize the pair. Each word pair presentation was followed by a 5 second rest period with a fixation point in the centre of the screen. The order of word pairs was randomized to avoid any order effects. Following this, the participants were presented with one word from the pair (cue) and asked to type in the corresponding word (target). Feedback was provided such that if the target word was incorrect, the participant was presented with the correct pair, allowing for ongoing relearning. A learning criterion of 60% correct answers was determined, and if participants failed to achieve this criterion, the list was randomized and presented again. The training was terminated when 60% learning criterion was achieved. In the morning, the participants were tested on the same list of words (randomized once again) with no feedback provided.

The performance gains on paired associates task were calculated as the change in the number of words correctly recalled from training to retest, e.g. % Correct at Retest - % Correct at Training (Payne, Tucker, et al., 2012).

2.7 Procedure

The first night of PSG recording (**Figure 3**) served as an acclimatization and sleep disorder screening night.

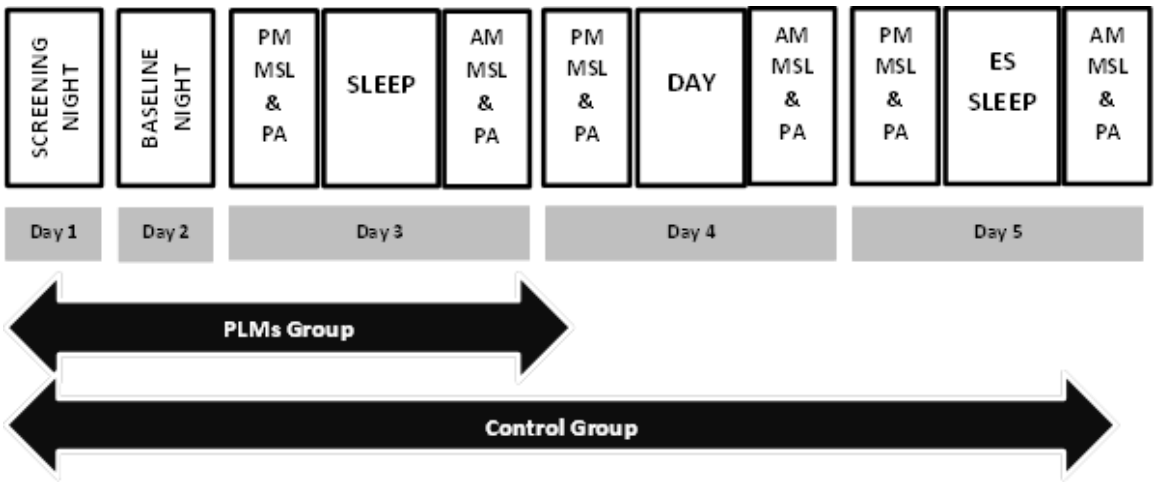

Figure 3. Experimental protocol. Subjects first underwent an overnight screening and acclimatization night to screen for signs of sleep disorders or poor quality sleep, to categorize subjects into the PLM or CTRL condition, and to ensure that the following night a representative baseline recording could be obtained. The PLM group then underwent motor sequence learning and paired associates training in the evening (PM), followed by overnight PSG, and subsequent retesting the following morning (AM). The Control group underwent the same procedure, but in addition were trained on a novel sequence and word list in the morning on day 4, and then retested after an interval filled with wake in the evening. This was followed by training on another novel sequence and word list, however, sleep was disrupted experimentally by inducing leg movements to mimic PLMs. Finally subjects were retested the following morning after a night of disrupted sleep. Abbreviations: Motor Sequence Learning (MSL); Paired Associates (PA); Electrical Muscle Stimulation (ES) during sleep to induce periodic leg movements (PLMs).

The screening night was used to assign participants into one of the two experimental conditions: PLM group (people, who experience clinically significant levels of PLMs, e.g. <15 PLMs per hour) and control group (people who have very few or no PLMs). Participants were given a log to keep track of their daily activities and sleep habits (**Appendix L**), and an 'Actiwatch' (Philips-Respironics Inc.; a wrist-worn accelerometer, to measure sleep-wake-related limb movements) to wear for the length of their participation in the study. Participants were excluded if they did not keep a regular sleep-wake schedule according to the instructions given (bed time between 10pm and 1am; and rise time between 7am and 9am).

Participants returned to the sleep laboratory 4 to 7 days following the screening night for an overnight baseline recording for a normal, undisturbed night of sleep. Participants returned to the sleep laboratory 1 to 4 days later for the experimental night. Prior to each behavioural testing session, participants performed the Psychomotor Vigilance Task (PVT; Dinges & Powell, 1985) to measure their objective sleepiness. This was followed by two tasks: the paired associates task and the motor sequence learning task, where the order of administration was counterbalanced across participants. Upon completion of the tasks, participants were allowed to sleep between the hours of 11pm and 7am at which time their sleep was recorded and monitored throughout the night from the adjacent control room via online PSG, video and audio recordings. At least 30 minutes after awakening (to allow sufficient time for sleep inertia to dissipate (Silva & Duffy, 2008), participants were asked to perform the PVT, followed by retesting on the paired associates and motor sequence learning tasks. The condition in which the control group had undisturbed sleep will be referred to as CTRL-sleep from now on.

Following the AM retest session, the control group was then trained on a novel set of paired associates words and novel motor sequence in the AM testing session, and following an interval filled with daytime wakefulness, were retested the following evening (at 8 PM) and trained on another set of words and sequence prior to overnight PSG sleep recording where they were exposed to the mild electrical muscle stimulation (ES) to mimic PLMs. The condition when the control group's retention period happened over wake period from now on will be referred as CTRL-wake. The order of the two experimental nights, the task order, the word lists and the sequences were all counterbalanced across participants.

Chapter 3: Results

3.1 Motor Sequence Learning task.

3.1.1 Training Session (fast learning phase: blocks 1-8).

CTRL conditions: A repeated-measures 2 (CTRL-sleep, CTRL-wake) x 8 (practice blocks) ANOVA was used to determine if performance during the evening training session differed from the morning training session in healthy controls, to ascertain if time-of-day impacted learning on the task. The results revealed that there was a significant main effect of practice block $F(7, 98) = 11.55$, $p < .001$, and no significant difference between the conditions, $F(1, 14) = 1.10$, $p = .312$, or significant (practice block x condition) interaction, $F(7, 98) = 2.31$, $p = .121$ (**Figure 4**). This indicated that both conditions improved performance across blocks with practice, and that there was no time-of-day effect.

Next, a repeated-measures 2 (CTRL-sleep, CTRL-ES) x 8 (practice block) ANOVA was used to compare performance across the first 8 blocks prior to the disturbed and undisturbed nights in the healthy controls. The results revealed that there was a significant main effect of block, $F(7, 98) = 23.07$, $p < .001$, but no significant difference between the conditions, $F(1, 14) = 1.18$, $p = .296$, or significant (practice block x condition) interaction, $F(7, 98) = .800$, $p = .443$ (**Figure 5**). Thus, performance improved over the course of practice blocks during the training session for all CTRL conditions, but did not differ between control conditions.

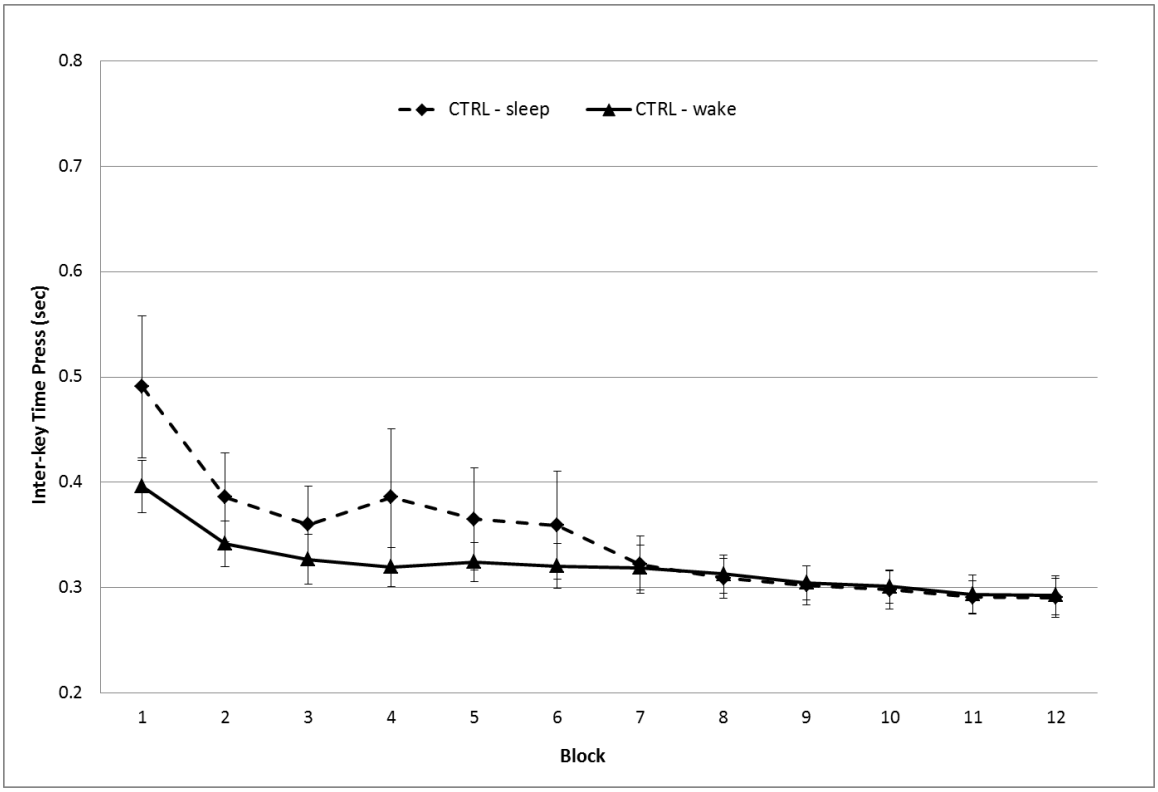

Figure 4. Performance of the control group on motor sequence learning task during the undisturbed night (CTRL-sleep) and daytime (CTRL-wake) during the 12 blocks of practice (+/-SE). Performance improved over the course of the training blocks (1-8) in both conditions.

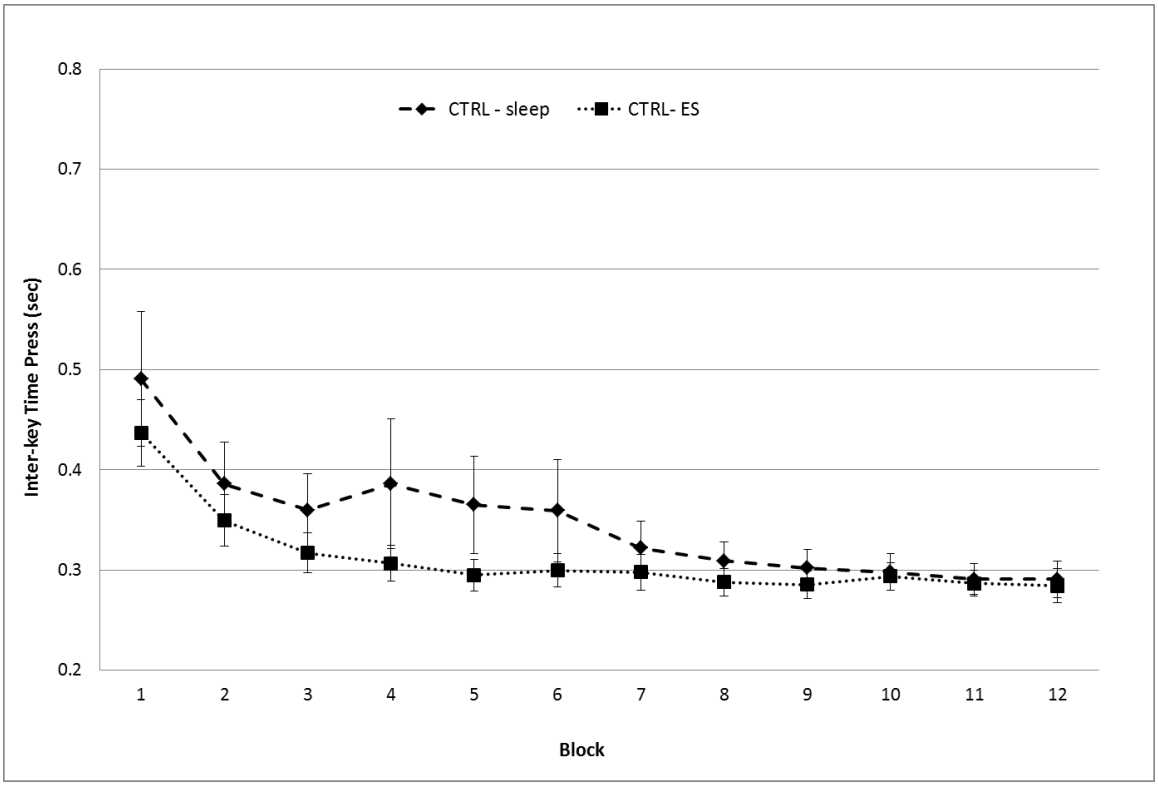

Figure 5. Performance of the control group on the motor sequence learning task during the undisturbed night (CTRL- sleep) and the EMS night (CTRL-ES) during the 12 blocks of practice (+/-SE). Performance improved over the course of the training blocks (1-8) in both conditions.

PLM vs. CTRL conditions: A mixed-design 2 (PLM, CTRL-sleep) x 8 (practice block) ANOVA was used to test for changes in performance over the course of the training session, between PLM and the normally rested CTRL condition. The results revealed a main effect of condition, $F(1,27) = 4.26$, $p = .049$, main effect of block, $F(7, 189) = 29.09$, $p < .001$ but no significant condition by block interaction, $F(7, 189) = 2.729$, $p = .065$ (**Figure 6**). Suggesting that both conditions improved with practice but the PLM group was slower overall.

Similarly, a mixed-design 2 (PLM, CTRL-ES) x 8 (practice block) ANOVA was used to compare performance over the course of the training session between the PLM and

disrupted sleep CTRL condition. The results revealed a main effect of condition, $F(1,27) = 16.99$, $p < .001$, a significant effect of practice block, $F(7, 189) = 64.78$, $p < .001$, and a significant (practice block x condition) interaction, $F(7, 189) = 4.42$, $p = .013$ (**Figure 7**). Thus suggesting that performance in the CTRL-ES condition was faster overall, and improved to a different extent as compared PLM condition during the training session.

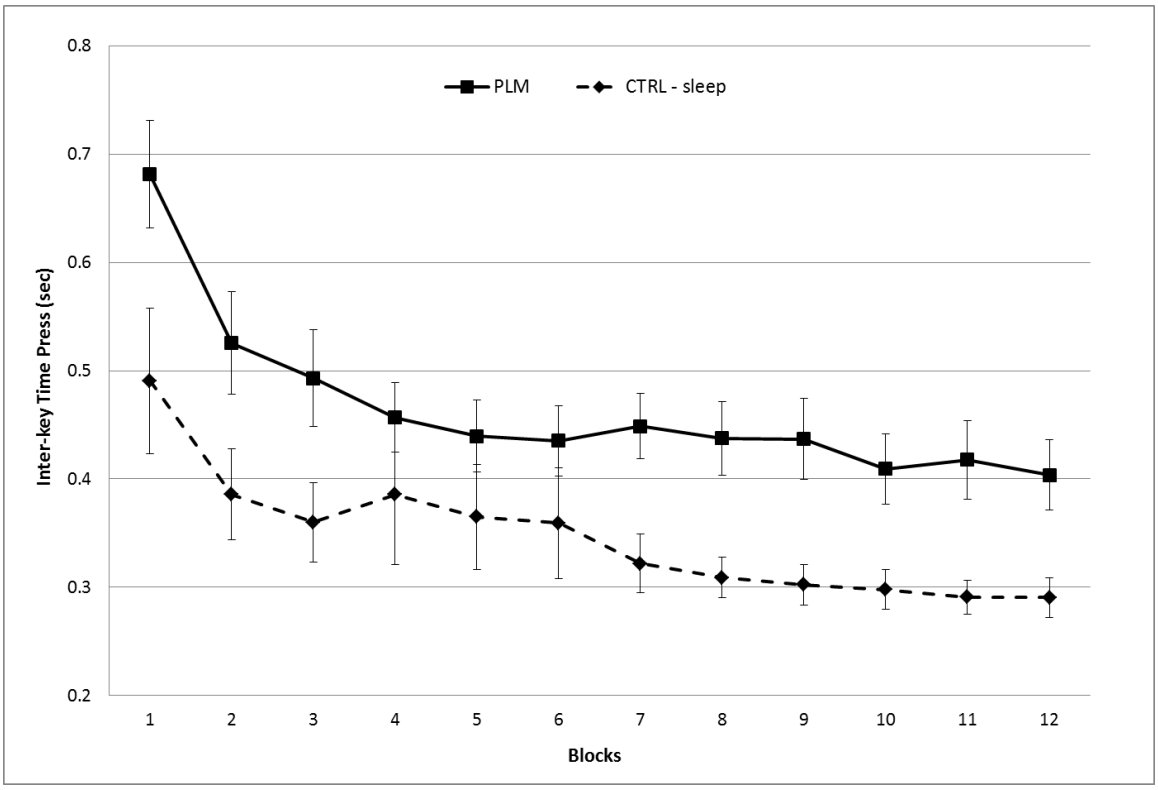

Figure 6. Performance of the PLM group (PLM) and the control group on the motor sequence learning task during the undisturbed night (CTRL-sleep) during the 12 blocks of practice (+/-SE). Performance improved over the course of the training blocks (1-8) in both conditions, although performance was slower overall in the PLM group.

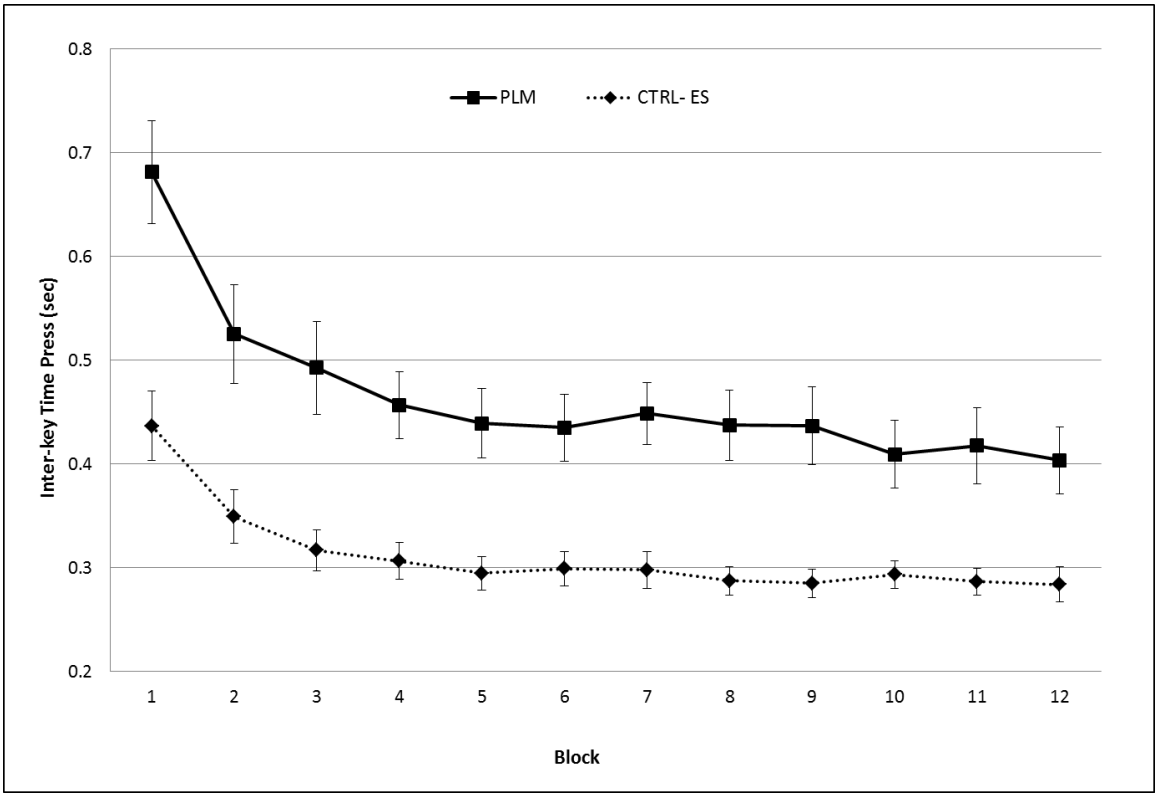

Figure 7. Performance of the PLM group (PLM) and the control group on the motor sequence learning task during the disturbed night (CTRL-ES) during the 12 blocks of practice (+/-SE). Performance improved over the course of the training blocks (1-8) in both conditions, although performance was slower overall in the PLM group.

3.1.2 Training session (slow learning phase: blocks 9-12).

CTRL conditions: A repeated-measures 2 (CTRL-sleep, CTRL-wake) x 4 (block) ANOVA was used to investigate whether performance across the last 4 blocks differed between the evening and the morning in the control conditions. The results revealed that there was no significant main effect of block $F(3, 42) = 2.402$, $p < .081$, no significant effect of condition, $F(1, 14) = .063$, $p = .805$, or block x condition interaction, $F(3, 42) = .004$, $p = .994$ (**Figure 4**). This suggests that performance was asymptotic at the end of the training session, and there was no time-of-day related difference in performance between the evening and morning training at the end of the training session.

Next, a repeated-measures 2 (CTRL-sleep, CTRL-ES) x 4 (practice block) ANOVA was used to assess performance over the last 4 blocks of training prior to the disturbed and non-disturbed nights in healthy controls. The results revealed no significant main effect of block, $F(3, 42) = .657$, $p = .583$, no main effect of condition, $F(1, 14) = .463$, $p = .520$, or significant (practice block x condition) interaction, $F(3, 42) = .726$, $p = .470$ (**Figure 5**). Thus a similar pattern of asymptotic performance was observed at the end of the training session for both normal and undisturbed sleep in the CTRL condition.

PLM vs. CTRL conditions: In order to test whether performance had become stable and asymptotic by the end of the training session, a mixed-design 2 (PLM, CTRL-sleep) x 4 (practice block) ANOVA was used to compare performance between the PLM and CTRL-sleep over the course of the last 4 blocks of practice. The results revealed no significant difference in performance across blocks, $F(3, 81) = 2.55$, $p = .076$, which suggests that there was no further improvement during the last 4 blocks of the training. However, there was a statistically significant main effect of condition, $F(1, 27) = 10.84$, $p = .003$ but no significant (practice block x condition) interaction, $F(3, 81) = .874$, $p = .440$. These results suggest that the PLM condition demonstrated no performance improvement on the last 4 training blocks and performed slower overall than the CTRL-sleep at the end of the training session (**Figure 6**).

Similarly, a mixed-design 2 (PLM, CTRL-ES) x 4 (practice block) ANOVA was used to compare performance between the CTRL-ES and the PLM condition over the course of the last 4 blocks of training. The results revealed that there was no significant effect of block, $F(3,81) = 1.19$, $p = .318$, suggesting that there was no improvement during the last 4 blocks of the training. However, there was a main effect of condition, $F(1, 27) = 13.68$, $p = .001$, but no significant (block x condition) interaction, $F(3, 81) = 1.56$, $p = .206$. Thus, the PLM condition performed slower compared to the CTRL-ES condition at the end of the training session, and demonstrated similar pattern of asymptotic performance on the last 4 blocks of training (**Figure 7**).

Taken together, these results suggest that the PLM group was slower at the last 4 training blocks compared to the rest of the overnight conditions, and all conditions reached asymptotic performance at the end of the training session.

3.1.3 Between session, offline gains in performance.

Control conditions: One-sample *t*-tests examining % change in performance between sessions in CTRL-sleep, CTRL-ES and CTRL-wake conditions were conducted in order to determine whether sleep (disturbed or undisturbed) had an effect on between-session offline gains in performance in healthy controls (**Figure 8**). As expected, the results demonstrated significant performance gains in CTRL-sleep condition, $t(14) = 2.34$, $p = .035$. Contrary to our predictions and the previous literature, the results revealed gains in the CTRL-wake condition $t(14) = 3.24$, $p = .006$. However, as predicted, the CTRL-ES condition did not significantly derive a benefit from sleep, $t(14) = 1.82$, $p = .090$. These findings suggest that performance on motor sequence learning task improved irrespective of whether the retention period contained either sleep or wake, but the gains were attenuated with disrupted sleep from induced limb movements in healthy controls.

PLM condition: A one-sample t-test was used in order to test whether PLM had an effect on motor memory consolidation. Surprisingly, and contrary to our hypotheses, the results demonstrated that the participants in the PLM condition had significant off-line gains on motor sequence learning performance, $t(13) = 3.37$, $p = .005$.

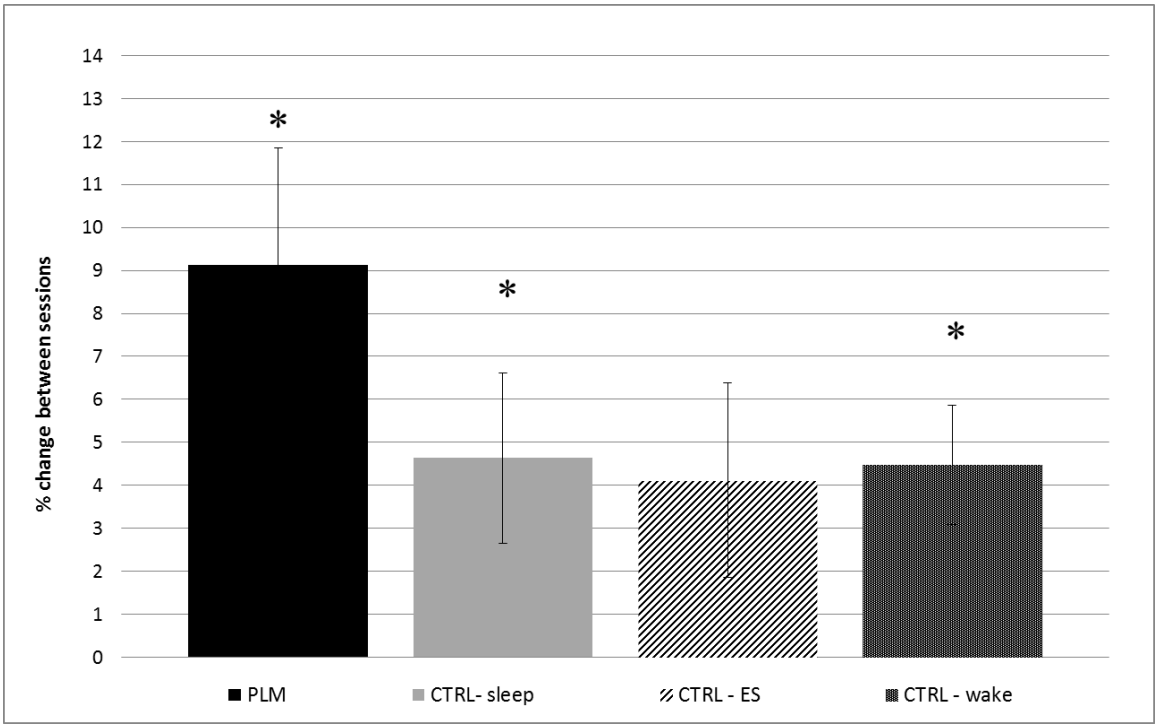

Figure 8. % change in mean (+/-SE) performance between sessions for the PLM, undisturbed night of the control group (CTRL-sleep), disturbed night of the control group (CTRL-ES) and wake period of the control group (CTRL-wake). Note: * indicates significant gains from one-sample *t*-tests at $p < 0.05$.

3.2 Paired Associates task.

Control conditions: A similar analysis strategy was employed to explore gains in performance for the paired associates task. One-sample *t*-tests were conducted on % change of recalled words for CTRL-sleep, CTRL-ES and CTRL-wake conditions to analyze whether sleep (disturbed or undisturbed) had an effect on consolidation of declarative memory in healthy controls. This revealed that all three conditions, CTRL-sleep ($t(14) = .544$, $p = .595$), CTRL-ES condition ($t(14) = 1.95$, $p = .071$) and CTRL-wake ($t(14) = -1.06$, $p = .305$) did not exhibit significant gains on the paired associates task (**Table 3**). These findings suggest that there was no significant improvement on the paired associates task performance whether the retention period contained wake, undisturbed or disturbed sleep.

These findings suggest % change in recalled words did not significantly differ in the undisturbed night and day conditions, as well as in the undisturbed and disturbed night conditions. However, it is worth noting that performance deteriorated (i.e., exhibited forgetting) in the CTRL-wake condition (**Table 3**), whereas all sleep-filled intervals exhibited improvements across the interval.

	Performance on the paired associates task (% recalled at the training - % recalled at the retest)	
Condition	*M*	*SD*
PLM	2.50	10.05
CTRL-sleep	1.00	7.12
CTRL-ES	4.17	8.27
CTRL-wake	-2.67	9.70

Table 3. Mean % change (SD) of recalled words of the paired associates task for PLM, CTRL-sleep, CTRL-ES and CTRL-wake conditions.

PLM condition: A One-sample *t*-test was used to determine whether sleep was beneficial for declarative memory consolidation in the PLM condition. This test demonstrated that the PLM condition ($t(12) = .897$, $p = .387$) did not show significant improvement on the paired associates task. These findings suggest that sleep did not benefit declarative memory consolidation in the PLM group or the CTRL conditions on the paired associates task.

3.3 Sleep related data.

3.3.1 PVT.

The PVT was used to assess whether objective sleepiness varied across day and night control conditions and between PLM and control conditions to ascertain whether sleepiness was a factor that might explain changes in performance on the memory tasks from training to retest sessions, or between experimental conditions (**Table 4**).

A mixed-design 2 (PLM, CTRL-sleep) x 2 (training, retest session) ANOVA was used in order to establish whether the participants from both conditions were at the same level of alertness before the training and the retest sessions. The results revealed that the groups did not significantly differ on their PVT reaction times from training to retest, $F(1, 27) = .126$, $p = .725$. There was also no statistically significant main effect of condition, $F(1, 27) = .000$, $p = .983$, or significant session by condition interaction $F(1, 27) = .616$, $p = .439$, suggesting that the two groups did not differ on their objective alertness between the sessions.

	Condition			
PVT(ms) *M(SD)*	PLM	CTRL-sleep	CTRL-ES	CTRL-wake
PVT training	3.11 (.41)	3.13 (.25)	3.15 (.19)	3.12 (.36)
PVT retest	3.14 (.37)	3.12 (.36)	3.13 (.57)	3.18 (.25)

Table 4. Mean PVT scores (SD) for the training and retest sessions in the PLM, CTRL-sleep, CTRL-ES and CTRL-wake conditions.

Similarly, a mixed-design 2 x 2 ANOVA was used to compare the PVT reaction times for the PLM group and the control group (EMS night) for their evening training and morning retest sessions. The results revealed that the groups did not differ on their PVT reaction

times from training to retest, $F(1, 27) = .033$, $p = .858$. There was also no statistically significant main effect of condition, $F(1, 27) = .009$, $p = .924$, or significant session by condition interaction $F(1, 27) = .162$, $p = .690$, again suggesting that the two groups did not differ on their objective alertness between the sessions.

A repeated-measures 2 (CTRL-sleep, CTRL-wake) x 2 (training, retest session) ANOVA was used to analyze whether there was a time-of-day effect on PVT reaction times for the control group. The results revealed no significant main effect of condition, $F(1, 14) = 2.541$, $p = .133$, no significant session main effect, $F(1, 14) = 2.541$, $p = .133$ and no significant (condition x session) interaction, $F(1, 14) = .578$, $p = .460$. This suggests that there was no time-of-day effect on psychomotor vigilance reaction time.

Finally, a repeated-measures 2 (CTRL-sleep, CTRL-ES) x 2 (training, retest session) ANOVA was conducted to measure the alertness level in the healthy controls between the training and the retest sessions for the disturbed and non-disturbed nights. The results revealed that there was no significant main effect of condition, $F(1, 14) = .065$, $p = .802$, no significant session main effect, $F(1, 14) = .047$, $p = .832$ and no significant (condition x session) interaction, $F(1, 14) = .000$, $p = .999$. These results suggest that the control group did not differ in their level of alertness between the training and the retest sessions whether the night was disturbed or not.

Taken together these results suggest that any differences in the motor sequence learning task performance may not be attributed to the different levels of vigilance or psychomotor performance related to time-of-day, sleep disruption, preceding sleep-wake state, or whether subjects suffered from PLMs.

3.3.2 Sleep architecture.

Baseline night: Independent samples *t*-tests were used to test whether individuals with PLMs had reduced sleep quality as compared to the CTRL group on the baseline night. Consistent with the extant literature, the PLM group has significantly less TST ($t(27) = 3.41$, $p = .002$), lower SE ($t(27) = 2.75$ $p = .013$), a greater number of awakening ($t(27) = -2.46$, $p = .024$), more WASO ($t(27) = -2.63$, $p = .017$), and spent more time awake

during the night ($t(27) = -2.67$, $p = .016$) than controls on the baseline night. In addition the PLM group had a greater number of total leg movements ($t(27) = -6.94$, $p < .001$), leg movements with arousals ($t(27) = -8.36$, $p < .001$) and leg movements without arousals ($t(27) = -4.86$, $p < .001$) as compared to controls on the baseline night (**Table 4**). Thus, individuals who met the criteria for the PLM condition had more leg movements during sleep and reduced sleep quality.

Training night: Independent samples t-test were used to compare sleep quality on a training night between the PLM and the CTRL-sleep conditions. Two groups significantly differed on TST ($t(27) = 2.37$, $p = .028$, total limb movements ($t(27) = -6.82$, $p < .001$), limb movements with arousals ($t(27) = -6.29$, $p < .001$) and limb movements without arousals ($t(27) = -5.904$, $p < .001$).

The same approach was used to test for differences between the PLM and the CTRL-ES conditions. The results revealed that two groups differed for TST ($t(27) = 2.18$, $p = .038$ only.

These findings suggest that despite the PLM condition having a significantly poorer sleep quality during the baseline night as compared to the control condition, aside from the PLMs control condition having had less total sleep time, the ES condition had similar sleep quality characteristics as compared to the PLM condition.

Baseline vs Training nights in CTRL condition: A repeated-measures ANOVA was used to compare the sleep variables for the control group across all three nights (i.e., CTRL-baseline, CTRL-sleep, CTRL-ES). This analysis revealed that the control group did not significantly differ on the sleep architecture variables between the three conditions except for the total limb movements ($F(2, 1.05) = 116.28$, $p < .001$), limb movements with arousals ($F(2, 1.15) = 45.84$, $p < .005$) and limb movements without arousals ($F(2, 1.01) = 79.67$, $p < .001$). Pairwise post-hoc comparisons revealed that the number of total limb movements significantly differed between the CTRL-ES and CTRL-baseline conditions ($t(14), = 10.91$, $p < .001$), the CTRL-ES and CTRL-sleep conditions ($t(14), = -10.84$, $p < .001$), but not between the CTRL- baseline and CTRL-sleep ($t(14), =-2.03$, $p = 0.61$). The number of limb movements with arousals significantly differed

between the CTRL-ES and CTRL- baseline conditions ($t(14)$, = 7.05, $p < .001$), and between the CTRL-ES and the CTRL-sleep conditions ($t(14)$, = -6.78, $p < .001$), but not between the CTRL- baseline and CTRL-sleep ($t(14)$, =-2.01, $p = 0.61$). Finally, the limb movements without arousals significantly differed between the CTRL-ES and the CTRL-baseline conditions ($t(14)$, = 8.98, $p < .001$) and between the CTRL-ES and the CTRL-sleep conditions ($t(14)$, = -8.90, $p < .001$) , but not between the CTRL- baseline and CTRL-sleep ($t(14)$, =-1.92, $p = 0.75$) (**Table 4**). These findings suggest that the experimentally induced limb movements successfully mimicked PLMs in control subjects, but these movements did not appear to have altered sleep architecture and sleep quality.

Baseline vs. Training nights in PLM condition: Paired samples t-tests were used to compare sleep architecture for the PLM condition across baseline and training nights. Interestingly, the results revealed that the PLM condition had significantly less limb movements with arousals after the training, $t(13) = 2.22$, $p = .045$. Thus, suggesting that the post training sleep of the PLM condition was less fragmented. No other sleep architecture variables differed between the baseline and training night for the PLM condition.

In summary, as expected and consistent with the extant literature, these findings indicate that the participants in the PLM condition had significantly worse sleep quality in comparison to the CTRL condition on the baseline night. While the control group did not differ in terms of sleep quality between the baseline and the undisturbed training nights, their sleep was significantly disturbed due to the arousals associated with the induced limb movements during the ES night. Surprisingly, the PLM condition experienced significantly less sleep fragmentation after training on the memory tasks and their sleep quality was similar to the undisturbed night of the control group. Finally, aside from the decreased total sleep time of the PLM group, the sleep quality of the PLM group on the training night was not significantly different from the disturbed training night of the control group.

	Conditions				
	PLM		Control		
Sleep Characteristic *M (SD)*	Baseline	Training	Baseline	CTRL-Sleep	CTRL-ES
Total sleep time (hr)	6.33 (.71)	6.43 (.65)	7.17 (.62)	6.90 (.35)	6.45 (1.84)
Sleep efficiency (%)	87.37 (8.77)	90.93 (6.32)	94.39 (3.96)	94.31 (3.68)	94.20 (4.80)
# of awakenings	21.93 (11.78)	19.43 (10.83)	13.47 (5.40)	13.47 (6.80)	13.13 (7.29)
Wake after sleep onset (min)	49.02 (38.55)	32.57 (26.19)	19.62 (16.74)	16.62 (14.05)	20.36 (17.35)
% NREM 1	5.25 (3.78)	4.14 (2.94)	3.06 (2.05)	2.76 (2.49)	2.95 (1.74)
% NREM 2	54.56 (8.87)	51.47 (9.57)	53.54 (9.25)	50.74 (8.33)	54.49 (12.79)
% NREM 3	20.77 (5.76)	23.33 (7.43)	21.49 (8.66)	22.99 (6.51)	20.98 (7.57)
% NREM (total)	80.58 (5.77)	78.94 (6.49)	78.06 (4.12)	76.49 (4.55)	78.43 (8.76)
% REM	19.42 (5.77)	21.06 (6.49)	21.91 (4.09)	23.51 (4.55)	21.57 (8.76)
% wake	15.61 (12.48)	10.52 (8.38)	6.13 (4.71)	6.19 (4.32)	6.44 (5.95)
# limb movement	165.50 (87.54)	163.29 (84.08)	2.47 (7.47)	8.07 (14.10)	163.13* (58.48)
# limb movements with arousals	62.93 (27.62)	54.86* (29.11)	1.00 (2.45)	4.40 (7.55)	39.80* (21.43)
# limb movements without arousals	102.57 (77.66)	108.43 (66.06)	.20 (.69)	3.67 (6.94)	123.33* (53.77)

Table 5. Sleep architecture for the baseline night, undisturbed night (CTRL-sleep) and disturbed sleep (CTRL-ES). Note: * indicates a significant change from baseline night at $p < 0.05$.

Chapter 4: Discussion

The current study aimed to investigate the impact of PLMs on motor skill learning and memory consolidation. We investigated this question in a sample of individuals with PLMs compared to healthy, aged-matched controls under either normal sleep conditions, or with sleep disruption as a result of induced leg movements using ES. Results of the current investigation revealed that: **1)** similar to previous studies, individuals with clinically significant PLMs had reduced sleep quality as compared to controls, **2)** they also exhibited slower performance than controls when learning a procedural motor skills task, **3)** these deficits appear to be specific to motor learning, as no impairment was observed for a declarative memory task, and no differences in psychomotor reaction time were observed, however, **4)** contrary to our hypotheses, surprisingly, people who experienced PLMs showed overnight motor sequence learning task performance gains, and, **5)** sleep quality for the PLM condition was improved following motor sequence learning.

4.1 PLMs and memory.

Here we found for the first time that individuals with clinically significant PLMs had overall slower performance compared to controls during the training session for a simple motor procedural skill task. Given that there were no differences in psychomotor reaction time, this difference in motor sequence learning performance cannot be easily attributed to increased sleepiness and fatigue, due to impoverished sleep quality associated with the PLMs (Rosenthal et al., 1984; Saskin et al., 1985). Moreover, the slower performance in motor sequence learning during the training session was specific to motor skills and not a global memory deficit, as the PLM group's performance on the paired associates task did not differ from controls. Additional support for the notion that this deficit was not due to

more global cognitive deficits is supported by the fact that there were no signs of mild cognitive impairments on the MMS questionnaire. Together these findings suggest that individuals who experience PLMs demonstrated deficits specifically in the speed performance of the simple procedural memory but not in declarative memory learning or in general cognitive domains.

There are several potential explanations for why individuals with PLMs may have impaired motor skills learning. First, literature suggests in the patients who suffer from both RLS and PLMD, limb movements are caused by dysfunctions in the striatal structures of the brain, with the putamen affected to a greater extent than the caudate (Michaud et al., 2002; Ruottinen et al., 2000; Staedt et al., 1995). Given that motor sequence learning is dependent on the putamen (Barakat et al., 2013; Debas et al., 2010; Fogel & Smith, 2011; Fogel et al., 2013; Grafton et al., 1995; Jenkins et al., 1994; Jueptner, Frith, Brooks, Frackowiak, & Passingham, 1997b; Penhune & Doyon, 2002; Walker et al., 2005), it is not surprising that individuals with PLMs do not perform as well as controls, and suggests that functional/structural differences in the putamen may underlie impaired motor sequence learning in individuals who experience PLMs. Secondly, individuals with PLMs experience fragmented sleep and reduced sleep quality as a result of limb movements during sleep (Rosenthal et al., 1984; Saskin et al., 1985). However, this does not result in excessive daytime sleepiness, suggesting that sleep disruption associated with PLMs may not impact memory performance as a result of excessive daytime sleepiness. Consistent with this notion, objective sleepiness as assessed by the PVT did not differ between PLM and control conditions, which is consistent with the previous literature (Sivertsen et al., 2008). Thus, our results suggest that slower performance on motor sequence learning in people who experience PLMs may be due to neurodegeneration in the striatum, rather than be attributable to the reduced sleep quality that may affect daytime performance. However, one major shortcoming of the present study was that we did not directly assess whether slower performance on motor sequence learning was mediated by structural or functional striatal abnormalities in individuals with PLMs. Additionally, the research on structural deficits in the individuals who experience exclusively clinical PLMs with no accompanied comorbidities is rather limited. Therefore, this could be an important area for future

research, especially considering that the participants in the current study were *de novo*, and only exhibited clinically significant signs of PLMs, but were neither aware of their condition, nor ever sought or received diagnosis or treatment. Thus, slower performance on motor sequence learning may serve as a behavioural early warning sign for the development of PLMD.

While sleep disruption caused by PLMs does not necessarily results in excessive daytime sleepiness, it would be expected that these sleep disruptions would interfere with the functions that sleep support, such as memory consolidation. Surprisingly, however, the PLM group demonstrated sleep-related off-line gains on the motor sequence learning task in the face of clinically significant levels of PLMs. While this may seem counter-intuitive, interestingly, studies in animal models have suggested that physical exercise stimulates the synthesis of dopamine leading to motor performance improvement (for review, see Sutoo & Akiyama, 2003). This is also supported by human studies that showed elevated levels of dopamine following aerobic exercise (Koch, Johansson, & Arvidsson, 1980). In addition, Parkinson's patients, who took a part in a 3-week exercise program, showed significant movement initiation and reaction time improvements in a simple reaction time task (Stefaniwsky & Bilowit, 1973). Other studies of Parkinson's Disease patients have shown that goal-based exercises (e.g., Tai Chi, dancing, boxing, etc.) that involve repetitive movements lead to improvements in motor performance (for review, see Petzinger et al., 2013). Although, these studies employed larger muscle groups compared to the current experiment, these findings suggest that physical training on the motor sequence learning task may have led consequently to the elevated dopamine levels, resulting in the improvement on the motor sequence learning task in the PLM condition. However, this possibility is speculative and remains to be directly investigated in future studies. Furthermore, motor procedural memory consolidation has been found to be associated with an increase in post-learning sleep spindles during NREM sleep (Fogel, Nader, Cote, & Smith, 2007; Fogel, Ray, Binnie, & Owen, 2015; Fogel & Smith, 2006; Gais, Mölle, Helms, & Born, 2002; Laventure et al., 2016). Learning-related changes in sleep spindles have been found to be correlated with post-learning changes in striatal activation (Barakat et al., 2013; Fogel et al., 2013), which is thought to reflect a reactivation of the memory trace during post-learning sleep. Thus, suggesting that motor

learning may afford preferential benefit for sufferers of PLMs via stimulation of the striatum during sleep leading to improved sleep quality and enhanced memory consolidation. Another possible explanation for these findings is that motor sequence learning practice in the PLM group may have had a beneficial impact on post-learning sleep. Previous research has found that sleep architecture is radically altered and reorganized following intense periods of motor skills learning (Fogel & Smith, 2006; Peters et al., 2007). Consistent with these results, we found that post-training sleep architecture and sleep quality improved in the PLM condition from the baseline night when compared to the controls. This improved sleep quality was marked by a reduction in the number of PLMs associated with arousals. At present, the only treatment available to treat PLMD is with the use of dopamine agonist medications (Benes et al., 1999; Boivin et al., 1989; Brodeur et al., 1988; Chesson et al., 1999; Hening et al., 2004; Montplaisir et al., 1986; Walters et al., 1988). However, while speculative, this study suggests that by simply activating the striatum prior to sleep through training on novel tasks that rely on the striatum, such as motor sequence learning, this may have a beneficial impact on sleep quality, by reducing the number PLM-related arousals during subsequent sleep. This novel and unexpected pattern of results however remains to be investigated employing an experimental approach specifically designed to test such a hypothesis. Nonetheless, this could represent a potential avenue for non-pharmacological treatment of PLMD but remains to be directly investigated.

4.2 Limitations of the current study.

Contrary to previous research, and our predictions, the control group demonstrated performance gains on motor sequence learning after both an undisturbed night of sleep and after an equivalent period of daytime wake. Thus suggesting that offline gains in performance on motor sequence learning task occurred irrespective of sleep or wake. Unlike the current study which examined offline gains after long retention periods (~12 hours), much of the recent research that provides evidence of sleep being more beneficial for motor skills memory consolidation employed considerably shorter retention periods (~90 mins) often over a short daytime nap (Albouy et al., 2015; Doyon et al., 2009; Nishida & Walker, 2007; Ribeiro Pereira, Beijamini, Vincenzi, & Louzada, 2015;

Verweij, Onuki, Van Someren, & Van der Werf, 2016). Moreover, there is evidence to suggest that a daytime nap condenses motor skill consolidation (Korman et al., 2007) whereby equivalent consolidation was observed between sleep and wake over long intervals, but significantly faster consolidation was observed during a nap versus same time spent awake (Korman et al., 2007). Thus, in order to study the relative benefits of napping in PLM vs. controls, it may be necessary to study this phenomena in a daytime napping protocol which may be more sensitive to detecting the beneficial impact of sleep on memory processes. Moreover, recent evidence suggests that sleep only stabilizes newly learned motor sequence skills, but does not necessarily enhance performance (Nettersheim, Hallschmid, Born, & Diekelmann, 2015). Finally, a recent meta-analysis suggests that sleep may not afford a clear enhancement to for offline gains when controlling for various potentially confounding effects across studies, such as calculation of pre-post gain scores, inhibition during training, time of testing, training duration, and age (Pan & Rickard, 2015). Thus, this remains to be investigated using other procedural tasks where sleep has been clearly shown to enhance consolidation, and are not confounded by recently identified extraneous factors. Together, these findings suggest that while there was no differentiation between sleep and wake related gains on motor sequence learning task, there was however a reduction in gains in controls following experimentally induced PLMs, thus suggesting that normal healthy sleep supports offline gains in performance.

Unlike previous research, the present experiment also did not observe sleep-dependent improvements on the paired associates task in comparison to a period of daytime wake. Previous studies demonstrated that sleep facilitates consolidation of declarative memory, normally observed as a reduction in forgetting. The current study did not demonstrate sleep-dependent declarative memory consolidation enhancement in comparison to wake in the healthy control condition. One plausible explanation of this finding is the age range of the current sample. Previous studies tend to study memory in young adult populations, which generally experiences more SWS than older adults (Ohayon et al., 2004). The participants from the current study may have not exhibited sleep-related off-line gains in the performance of the PA task due to diminished SWS, or other age-related changes in sleep. However, congruent with previous literature (Plihal & Born, 1997; Tucker et al.,

2006), it was observed that the individuals tended to forget more words during the day in comparison to the night. Similar to motor sequence learning, this cannot be attributed to general cognitive deficits psychomotor reaction time between day and night conditions.

4.3 Future directions.

The results from the current study provide a starting point for several potentially promising directions for the future research. While it is speculated that striatal degeneration may underlie PLMD, evidence for this possibility is not yet conclusive, and here, we did not quantify biological markers of impaired striatal functioning in participants who experience PLMs. Thus, the current findings can only infer the slower performance of the motor skill task to deficits in striatum in the PLM group. Future research could address this directly with the use of the neuroimaging techniques such as PET or fMRI to further investigate whether the memory deficits observed here are related to a reduction of striatal activation during learning. Furthermore, using a combined EEG-fMRI, it would be possible to investigate post-training neural activation during sleep as compared to wake to examine any sleep-related differences in brain activation after training.

Previous studies have shown that sleep spindles (including frequency, amplitude and density), are enhanced after learning a motor sequence task (Fogel, Nader, Cote, & Smith, 2007; Fogel, Ray, Binnie, & Owen, 2015; Fogel & Smith, 2006; Gais, Mölle, Helms, & Born, 2002; Laventure et al., 2016). One of the roles of sleep spindles is for sleep maintenance in the face of external stimulation (Cote et al., 2000; Dang-Vu et al., 2011; Schabus et al., 2007; Steriade, 1994a). Moreover, learning-related changes in sleep spindles have been found to be correlated with post-learning changes in striatal activation (Barakat et al., 2013; Fogel et al., 2013). Investigation of post-training spindle activity may reveal insight into why offline gains were observed in the PLM group, and in combination with MRI techniques could shed light on the neural correlates of this potential link between sleep and memory in individuals who suffer from PLMs.

Furthermore, given the focus on procedural motor skills in the present investigation, the possibility remains that other cognitive deficits may be associated with PLMs, and the present study suggest that this may be an important area for future investigation.

4.4 Conclusions.

At present, while relatively much is known about the prevalence, biological basis and sleep disturbances in PLMD, very little is known about any associated cognitive and memory deficits in this condition. The present study is an important first step in understanding cognitive deficits in people who experience PLMs. The current results suggest that individuals who experience PLMs, while they do exhibit improvement with practice on motor skills learning, they exhibit slower performance overall, and do not reach the same level of performance as normally rested age-matched controls. This slower performance in procedural learning is specific to simple motor procedural memory, as declarative memory learning was not impaired, nor were there signs of mild cognitive impairment, or evidence to suggest that performance deficits on the motor sequence learning task were due to excessive daytime sleepiness. Thus, suggesting that deficits in motor sequence learning may be related to the underlying neural deficits known to be responsible for PLMs, however, this possibility remains to be directly investigated. Interestingly, individuals with PLMs showed an offline improvement in performance on motor sequence learning task, similar to the healthy control group. Following motor sequence learning, sleep quality was improved in the PLM condition as indicated by a reduction of PLM-associated arousals, suggesting that motor sequence learning may have had a therapeutic effect, although this possibility remains contentious and requires further confirmation. In summary, this study suggests that PLMs may not simply have negative consequences for sleep quality, rather, one of the core clinical features of PLMs may be cognitive. Finally, this research may lead to promising avenues for identifying early warning signs of neurodegeneration and novel non-pharmacological management of PLMD.

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Appendix A: Telephone Recruitment Survey.

Brain & Mind Institute Sleep Research Laboratory
Telephone Recruitment Survey

I. Script

1) Hello, may I please speak with {insert the name of the potential participant}.
If the potential participant is not home ask if there is a better time to call. Do not leave a message as it may be a confidential matter you are calling about that may not be apparent to you
If they are home, continue with the conversation
2) Hi, {insert the name of the potential participant} this is {insert your name} calling from the Brain and Mind Sleep Research Laboratory.
I am calling today to ask if you are interested in a research study that we are conducting. The study is being conducted by Dr. Adrian Owen and will look at the relationship between
sleep and learning. The study would involve you first completing a series of general questions to verify that you are eligible to participate. If eligible, you will be asked to sleep in the laboratory for a maximum of 4, non-consecutive nights where your brain activity will be recorded via electrodes placed on the surface of your scalp and face. Before bed-time on the 3nd through 4th nights, you will be asked to complete a simple, visual-motor task and two memory tasks which you will again complete the following morning. For your participation in the study, you would receive either $80 or $105 honourarium, depending on how many nights you spend in the lab. Would you be interested in hearing more about this study?
If no, thank them for their time and say good-bye
If yes, continue to explain the study details to them based on the letter of information
3) If you have a few minutes, I am now going to read you the letter of information.
At this point, read the letter to them
4) Do you have any questions?
If yes, answer their questions to the best of your ability
5) Are you still interested in participating in this study?
If yes, continue with the inclusion criteria questions
If no, thank them for their time and say good-bye
6) I have a few questions for you to make sure you are eligible for the study. You are free to ask questions or discontinue at any time.

II. Pre-Screening Questions (Inclusion criteria noted in square brackets)
Subject ID: _____ Date (dd/mm/yy): _____ Time: _____ am / pm
General Questions
1. How old are you? [30-65]: _____
2. Are you a smoker or non-smoker? [non-smoker]: smoker / non-smoker
3. How many caffeinated drinks do you typically have in a day? [≤2]: _____
4. How many alcoholic drinks do you typically have in a week? [≤14]: _____
5. Are you right or left handed? [right]: left / right

6. Are you a trained, or professional musician? [no]: yes / no
7. Are you a trained, or professional typist? [no]: yes / no
8. Are you willing and able to abstain from caffeine, nicotine, drugs and alcohol, at least 3 days prior to and throughout participating in this study? [yes]: yes / no

Sleep Questions

1. What is your usual bedtime? [10pm to 1am]: _____
2. What is your usual wake time? [6am to 9am]: _____
3. Are you willing and able to go to bed between 10pm and midnight and wake between 7am and 9am, at least 3 days prior to and throughout participating in this study? [yes]: yes / no
4. Do you work nights or shift-work? [no, in past month]: yes / no
5. Have you taken a trans-meridian trip in the last month? [no]: yes / no
6. Do you have difficulty falling asleep at night? [no]: yes / no
7. Do you wake up often during the night and are unable to return to sleep? [no]: yes / no
8. Would you describe yourself as excessively tired during the day? [no]: yes / no
9. Have you ever been diagnosed with a sleep disorder? [no]: yes / no
10. Do you know, or has anyone ever told you that you stop breathing while asleep? [preferably no]: yes / no
11. Do you know, or has anyone ever told you that you snore? [preferably no]: yes / no

Health Questions

1. Are you presently in good health? [yes]: yes / no
2. Are you pregnant? [no]: yes / no
3. Are you presently taking any medications? [preferably no]: yes / no
4. Do you have a history of chronic pain? [no]: yes / no
5. Do you have a history of anxiety or depression? [no]: yes / no
6. Have you ever suffered any kind of head trauma? [no]: yes / no
7. Have you ever suffered any kind of seizure? [no]: yes / no
8. Have you ever been diagnosed with any neurological or psychiatric condition?[no]: yes/no
9. What is your weight? _____; and your height? _____

BMI = (Weight in Pounds / (Height in inches x Height in inches)) x 703
BMI = (Weight in Kilograms / (Height in Meters x Height in Meters))
BMI [≤25]: _____

10. Do you have any mobility problems with your hands or fingers? [no]: yes / no

III. Contact Information

Name*****: _____
Telephone number(s)*****: _____
E-mail*****: _____
Date of testing: _____

*** IMPORTANT NOTE:** The subject's contact information (indicated by *) and ID are to be entered into a separate password-protected, name-ID key database, containing only their

name, telephone number, email (i.e., information that could be used to identify the participant) and ID to prevent their identity from being linked to their data, without the key. The remaining information collected in **Section II and Section III**, is to be immediately entered into a password-protected database, using only the subject's unique ID (i.e., no name, telephone number or email) to identify each record. Once this information is entered into the database, the paper version of **Section III** is to be destroyed, and **Section II**, is to be filed in a secure location (e.g., locked filing cabinet, in a locked office).

Appendix B: Letter of Information and Consent Form.

Project Title: Sleep-Dependent Motor Sequence Memory Consolidation in People Who Experience Periodic Limb Movements.

Principal Investigator:
Adrian Owen, PhD
Department of Psychology, Brain & Mind Institute, Western University

Letter of Information

1. **Invitation to Participate**

   Because you meet the general selection criteria we have defined for healthy individuals, you are invited to participate in this research study that investigates sleep-dependent memory in adults who may be experiencing limb movements while sleeping.

2. **Purpose of the Letter**

   The purpose of this letter is to provide you with information required for you to make an informed decision regarding participation in this research.

3. **Purpose of this Study**

   The purpose of this study is to investigate the relationship between the post-sleep memory consolidation of motor skills in healthy adults and sleep-related involuntary periodic limb movements.

4. Inclusion Criteria

Individuals who are in good health, between 20 and 65 years of age, have a normal BMI (<25), are right-handed, are non-professional musician/typists, non-smokers, do not consume excessive caffeine (< 2 servings/day) or alcohol (< 14 servings/week), describe themselves as subjectively "good" sleepers, are non-shift-workers, keep regular sleep schedules (sleep between 10pm and 9am), have no history of sleep disorders, are relatively free from medication, have no history of chronic pain, seizures, head injury, depression, anxiety and have normal mobility of the hands and fingers are eligible to participate in this study.

5. Exclusion Criteria

Individuals who do not meet the inclusion criteria described above who are unable to adhere to a regular sleep schedule and abstain from excessive caffeine, nicotine, drugs or alcohol 3-days prior to and throughout participation are not eligible to participate in this study.

6. Study Procedures

If you agree to participate, and meet the inclusion and exclusion criteria, you will be asked to complete a series of screening questionnaires. If eligible, you will be asked to wear wristwatch (that measures the movement of your arm to track your sleep-wake cycle), to complete an aptitude test and keep a daily log of your activity and sleepiness for the length of your participation in the study. You will also be asked to spend either three or four nights in the sleep lab, depending on your condition, where your brain waves will be recorded via electrodes placed on your scalp and face. You will also be asked to perform a simple, visual-motor memory task before and after each night in the laboratory. After the last night at the lab, you will be asked to return in the evening for one last

testing session. For the nights, you will be asked to arrive at the lab for the night sleep session by 8pm and you will leave the lab the next morning around 9am. For the last session, you will be asked to arrive at 5-6 pm in the evening and you will leave within the hour. The task(s) will be conducted at the Brain & Mind Sleep Research Laboratory. There will be up to a total of 3 participants (including you) run per session for a total study size of 30 participants.

7. Possible Risks and Harms

The only known possible risks or discomfort to you may experience, if you have sensitive skin, include a temporary, slight skin irritation caused by the exfoliant used to gently clean the surface of the skin where the electrodes are applied. You might also experience a mild tingling sensation on the leg during the nap sleep session.

8. Possible Benefits

Participants will be shown how valuable sleep is toward maximizing intellectual function and efficient learning. The potential benefits to society would include that the results will emphasize the importance of sleep for learning, memory and intellectual function.

9. Compensation

You will be compensated $10 for the screening night, $25 for the baseline and testing night, and $20 for the final testing session and completion of the study, for a total of $80-$105, depending which group you will be assigned to. If you do not complete the entire study, you will be compensated on a per-session basis.

10. Voluntary Participation

Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future academic status. You do not waive your legal rights by signing this form. You do not waive your legal rights by signing this form.

11. Confidentiality

All data collected will remain confidential and accessible only to the investigators of this study. The master list (identifying your name, phone number and email and corresponding unique ID) will be stored electronically in a password-protected database on a hard drive within the local network of the locked sleep laboratory, and backup copies in the PI's on-campus office, stored on local password-protected hard drives. Under no circumstances will your data be stored with personal information that could be used to identify you. The data will be stored indefinitely and will be accessible only to the investigators of this study. If the results are published, your name will not be used. Representatives of The University of Western Ontario Health Sciences Research Ethics Board may contact you or require access to your study-related records to monitor the conduct of the research.

12. Contacts for Further Information

If you require any further information regarding this research project or your participation in the study you may contact the project Team Leader, Dr. Stuart Fogel, ext. 80506, sfogel@uwo.ca or Valya Sergeeva, vsergee@uwo.ca.

If you have any questions about your rights as a research participant or the conduct of this study, you may contact The Office of Research Ethics (519) 661-3036, email: ethics@uwo.ca.

13. Publication

If the results of the study are published, all data will be pooled and your name will not be used. If you would like to receive a copy of any potential study results, please contact Valya Sergeeva, vsergee@uwo.ca.

This letter is yours to keep for future reference.

Consent Form

Project Title: Sleep-Dependent Motor Sequence Memory Consolidation in People Who Experience Periodic Limb Movements.

Study Investigator's Name: Adrian Owen, PhD

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

Participant's Name (please print): _____

Participant's Signature: _____

Date: _____

Person Obtaining Informed Consent (please print): _____

Signature: _____

Date: _____

Appendix C: Sleep Disorders Questionnaire.

1

Sleep Disorders Questionnaire (SDQ)

Instructions: In answering the questions, consider each question as applying to the **past six months** of your life. In the next section, the questions are simple statements. You answer by circling a number from 1 to 5. If you strongly disagree with the statement, or if it never happens to you, answer "1". If the statement is always true in your case, or you agree strongly with it, answer "5". You may also choose "2; rarely", "3; sometimes", or "4; usually" as your answer. Notice that an "answer key" appears at the bottom of each page to remind you what is meant by the numbers. Please answer all of the questions.

1 NEVER (strongly disagree)	2 RARELY (disagree)	3 SOMETIMES (not sure)	4 USUALLY (agree)	5 ALWAYS (agree strongly)

3.	I have trouble getting to sleep at night.	1 2 3 4 5
4.	I wake up often during the night.	1 2 3 4 5
6.	At bedtime, thoughts race through my mind.	1 2 3 4 5
7.	At bedtime, I feel sad and depressed.	1 2 3 4 5
12.	When falling asleep, I have "restless legs" (a feeling of crawling, aching, or inability to keep legs still)	1 2 3 4 5
21.	I am told that I snore loudly and it bothers others.	1 2 3 4 5
22.	I am told I stop breathing ("hold my breath") in sleep.	1 2 3 4 5
23.	I awake suddenly gasping for breath, unable to breathe.	1 2 3 4 5
24.	At night my heart pounds, beats rapidly, or beats irregularly ("palpitation").	1 2 3 4 5
25.	I sweat a great deal at night.	1 2 3 4 5

2

1 NEVER (strongly disagree)	2 RARELY (disagree)	3 SOMETIMES (not sure)	4 USUALLY (agree)	5 ALWAYS (agree strongly)

31. My sleep is disturbed by “restless legs” (a feeling of crawling, aching, or inability to keep legs still) 1 2 3 4 5

33. My sleep is disturbed by sadness or depression. 1 2 3 4 5

38. I have a lot of nightmares (frightening dreams). 1 2 3 4 5

43. I have been unable to sleep <u>at all</u> for several days. 1 2 3 4 5

45. I feel that I have insomnia. 1 2 3 4 5

71. I have high blood pressure (or once had it). 1 2 3 4 5

84. I am unhappy about loving relationships in my life. 1 2 3 4 5

89. I have considered or attempted suicide. 1 2 3 4 5

101. Someone in my family has been hospitalized for a psychiatric illness or “nervous breakdown”. 1 2 3 4 5

108. I smoke tobacco within two hours of bedtime. 1 2 3 4 5

139. I have a problem with my nose blocking up when I am trying to sleep. 1 2 3 4 5

141. My snoring or my breathing problem is much worse if I sleep on my back. 1 2 3 4 5

142. My snoring or my breathing problem is much worse if I fall asleep right after drinking alcohol. 1 2 3 4 5

3

Instructions: In the next section, please circle the item (numbered 1 to 5) that best matches your answer.

154. How long is your longest wake period at night?

1) less than 5 minutes 2) 6 to 19 minutes 3) 20 to 59 minutes

4) 1 to 2 hours 5) more than 2 hours

155. How many times in a night do you get up to urinate?

1) None 2) one 3) two

4) three 5) four or more times

163. What is your current weight in lbs.?

1) 134 or less 2) 135 to 159 3) 160 to 183

4) 184 to 209 5) 210 or more

170. How many years were you a smoker?

1) None 2) one 3) 2 to 12

4) 13 to 25 5) 26 or more

173. How old are you now?

1) 25 or under 2) 26 to 35 3) 36 to 44

4) 45 to 50 5) 51 or older

For test administrator use only-

SubID: _____ Date: _____

*See separate page for scoring instructions

Appendix D: Napping Questionnaire.

Napping Behaviour Survey 1

Instructions: For questions #1 to #7, check the **one** answer that **best** describes:

1. Given the opportunity to nap, would you take a daytime nap?
   ___ Yes
   ___ No

Instructions: If you responded 'yes' to #1, continue to answer questions #2 to #7. If you responded 'no' to #1, skip to question #8.

2. How often do you nap?
   ___ Every day
   ___ Once or twice a week
   ___ Once or twice a month
   ___ Less than once a month

3. How long do your naps usually last?
   ___ Less than 10 minutes
   ___ 10 - 20 minutes
   ___ 20 - 30 minutes
   ___ 30 - 60 minutes
   ___ More than 60 minutes

4. How long does it take you to fall asleep?
   ___ Less than 5 minutes
   ___ 5-10 minutes
   ___ 10-20 minutes
   ___ 20-60 minutes
   ___ More than 60 minutes

5. Do you ever fall asleep unintentionally during the day?
   ___ Yes
   ___ No

6. Do you nap because you:

___ Can no longer stay awake (e.g., due to a medical condition or excessive daytime sleepiness)?
___ Did not get enough sleep the night before?
___ Anticipate having to stay up late the following night?
___ Simply enjoy napping?

7. Upon awakening from a nap, do you feel:
___ Irritable
___ Groggy
___ Relaxed
___ Alert / Rested

Instructions: If you responded 'yes' to #1, do not respond to question #8.

8. You avoid taking daytime naps because:

For administrative use only-

SubID: _____ Date: _____

Appendix E: Beck Depression Inventory II.

1

Beck Depression Inventory II

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick the **one statement** in each group that best describes the way you have been feeling during the past **two weeks**, including today. Circle the number beside the statement you picked. If several statements in the group seem top apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. **Sadness**
   - 0 I do not feel sad.
   - 1 I feel sad much of the time
   - 2 I am so sad all the time.
   - 3 I am so sad or unhappy that I cannot stand it.

2. **Pessimism**
   - 0 I am not discouraged about my future.
   - 1 I feel more discouraged about my future than I used to be.
   - 2 I do not expect things to work out for me.
   - 3 I feel my future is hopeless and will only get worse.

3. **Past Failure**
   - 0 I do not feel like a failure.
   - 1 I have failed more than I should have.
   - 2 As I look back, I see a lot of failures.
   - 3 I feel I am a total failure as a person.

4. **Loss of Pleasure**
   - 0 I get as much pleasure as I ever did from the things I enjoy.
   - 1 I don't enjoy things as much as I used to.
   - 2 I get very little pleasure from the things I used to enjoy.
   - 3 I can't get any pleasure from the things I used to enjoy.

5. **Guilty Feelings**
   - 0 I don't feel particularly guilty.
   - 1 I feel guilty over many things I have done or should have done.
   - 2 I feel quite guilty most of the time.
   - 3 I feel guilty all of the time.

6. **Punishment Feelings**
   - 0 I don't feel I am being punished.
   - 1 I feel I may be punished.
   - 2 I expect to be punished.
   - 3 I feel I am being punished.

7. **Self-Dislike**
   - 0 I feel the same about myself as ever.
   - 1 I have lost confidence in myself.
   - 2 I am disappointed in myself.
   - 3 I dislike myself.

8. **Self-Criticalness**
   - 0 I don't criticize or blame myself more than usual.
   - 1 I am more critical of myself then I used to be.
   - 2 I criticize myself for all of my faults.
   - 3 I blame myself for everything bad that happens.

9. **Suicidal Thoughts or Wishes**
   - 0 I don't have any thoughts of killing myself.
   - 1 I have thoughts of killing myself, but I would not carry them out.
   - 2 I would like to kill myself.
   - 3 I would kill myself if I had a chance.

10. **Crying**
   - 0 I don't cry any more than I used to.
   - 1 I cry more than I used to.
   - 2 I cry over every little thing.
   - 3 I feel like crying, but I can't.

11. **Agitation**
    0 I am no more restless or wound up than usual.
    1 I feel more restless or wound up than usual.
    2 I am so restless or agitated that it's hard to stay still.
    3 I am so restless or agitated that I have to keep moving or doing something.

12. **Loss of Interest**
    0 I have not lost interest in other people or activities.
    1 I am less interested in other people or things than before.
    2 I have lost most of my interest in other people or things.
    3 It's hard to get interested in anything.

13. **Indecisiveness**
    0 I make decisions about as well as ever.
    1 I find it more difficult to make decisions than usual.
    2 I have greater difficulty in making decisions than I used to.
    3 I have trouble making any decisions.

14. **Worthlessness**
    0 I do not feel I am worthless.
    1 I don't consider myself as worthwhile and useful as I used to be.
    2 I feel more worthless as compared to other people.
    3 I feel utterly worthless.

15. **Loss of Energy**
    0 I have as much energy as ever.
    1 I have less energy than I used to have.
    2 I don't have enough energy to do very much.
    3 I don't have enough energy to do anything.

16. **Changes in Sleeping Pattern**
    - 0 I have not experienced any change in my sleeping pattern.
    - 1a I sleep somewhat more than usual.
    - 1b I sleep somewhat less than usual.
    - 2a I sleep a lot more than usual.
    - 2b I sleep a lot less than usual.
    - 3a I sleep most of the day.
    - 3b I wake up 1-2 hours early and can't go back to sleep.

17. **Irritability**
    - 0 I am no more irritable than usual.
    - 1 I am more irritable than usual.
    - 2 I am much more irritable than usual.
    - 3 I am irritable all the time.

18. **Changes in Appetite**
    - 0 I have not experienced any change in my appetite.
    - 1a My appetite is somewhat less than usual.
    - 1b My appetite is somewhat greater than usual.
    - 2a My appetite is much less than usual.
    - 2b My appetite is much greater than usual.
    - 3a I have no appetite at all.
    - 3b I crave food all the time.

19. **Concentration Difficulty**
    - 0 I can concentrate as well as ever.
    - 1 I can't concentrate as well as usual.
    - 2 It's hard to keep my mind on anything for very long.
    - 3 I can't concentrate on anything.

20. **Tiredness or Fatigue**
    - 0 I am no more tired or fatigued than usual.
    - 1 I get more tired or fatigued more easily than usual.
    - 2 I am too tired or fatigued to do a lot of the things I used to.
    - 3 I am too tired or fatigued to do most of the things I used to.

5

21. **Loss of Interest in Sex**

0 I have not noticed any recent change in my interest in sex.
1 I am much less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

For test administrator use-

SubID: _____ Date: _____

TOTAL SCORE (add up scores for all 21 items)**:** _____

Appendix F: Beck Anxiety Inventory.

1

Beck Anxiety Inventory

Instructions: Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom **during the past month, including today**, by circling the number in the corresponding space in the column next to each symptom.

Rating scale:
Not At All
Mildly: "it didn't bother me much"
Moderately: "it wasn't pleasant at times"
Severely: "it bothered me a lot"

	Not At All	Mildly	Moderately	Severely
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding / racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3

2

	Not At All	Mildly	Moderately	Severely
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot / cold sweats	0	1	2	3

For administrative use only-

SubID: _____ Date: _____

TOTAL SCORE (add up scores for all items)**:** _____

Appendix G: The Epworth Sleepiness Scale.

The Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to how you are feeling **today only**. Even if you have not done some of these things today, try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:
0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	**Chance of Dozing**
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (e.g. a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____

For administrative use only-

SubID: _____ Date: _____

TOTAL SCORE (add up scores for all items)**:** _____

Appendix H: The Stanford Sleepiness Scale.

The Stanford Sleepiness Scale

Last time asleep (hh:mm AM/PM): _____

Last time awoke (hh:mm AM/PM): _____

Instructions: Circle the scale rating that best describes how you feel **right now**.

Degree of Sleepiness	Scale Rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

For administrative use only-

SubID: _____ Date: _____

Appendix I: Circadian Rhythms Questionnaire.

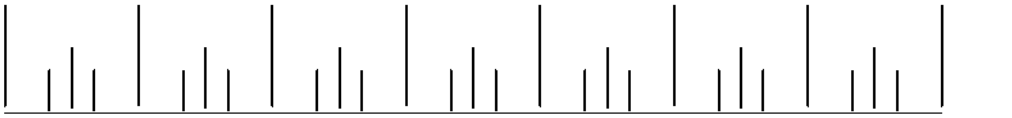
Circadian Rhythms Questionnaire

Instructions:

1. Please read each question very carefully before answering.
2. Answer ALL the questions.
3. Answer each question in numerical order.
4. Each question should be answered independently of others. Do NOT go back and check your answers.
5. All questions have a selection of answers. For each question, place and "X" alongside ONE answer only. Some questions have a scale instead of a selection of answers. Place an "X" at the appropriate point along the scale.
6. Please answer each question as honestly as possible. Both your answers and the results will be kept in strict confidence.
7. Please feel free to make any comments in the section provided below each question.

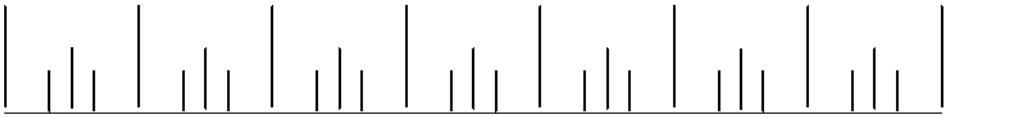
Questions:

1. Considering only your own "feeling best" rhythm, at what time would you get up if you were free to plan your day?



5 AM 6 7 8 9 10 11 12 PM

2. Considering only your own "feeling best" rhythm, at what time would you go to bed if you were entirely free to plan your evening?



8 PM 9 10 11 12 AM 1 2 3 AM

3. If there is a specific time at which you have to get up in the morning, to what extent are you dependent on being woken up by an alarm clock?

___ Not at all dependent
___ Slightly dependent
___ Fairly dependent
___ Very dependent

4. Assuming adequate environmental conditions, how easy do you find getting up in the morning?

___ Not at all easy
___ Not very easy
___ Fairly easy
___ Very easy

5. How alert do you feel during the first half hour after having woken in the morning?

___ Not at all alert
___ Not very alert
___ Fairly alert
___ Very alert

6. How is your appetite during the first half hour after having woken in the morning?

___ Very poor
___ Fairly poor
___ Fairly good
___ Very good

7. During the first half hour after having woken in the morning, how tired do you feel?

___ Very tired
___ Fairly tired
___ Fairly refreshed
___ Very refreshed

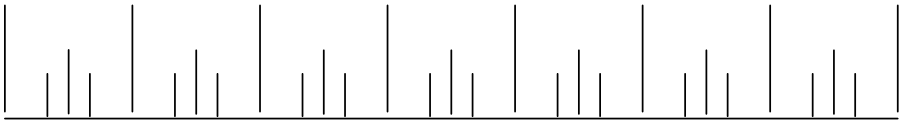
8. When you have no commitments the next day, at what time do you go to bed compared to your usual bedtime?

___ Seldom or never later
___ Less than one hour later
___ One to two hours later
___ More than two hours later

9. You have decided to engage in some physical exercise. A friend suggests that you do this one hour twice a week and the best time for him/her is between 7 and 8 AM. Bearing in mind nothing else but your own "feeling best" rhythm, how do you think you would perform?

___ Would be on good form
___ Would be on reasonable form
___ Would find it difficult
___ Would find it very difficult

10. At what time in the evening do you feel tired and, as a result, in need of sleep?



8 PM 9 10 11 12 AM 1 2 3 AM

4

11. You wish to be at peak performance for a test which you know is going to be mentally exhausting and lasting for two hours. You are entirely free to plan your day and considering your own “feeling best” rhythm, which ONE of the four testing times would you choose?

___ 8 to 10 AM
___ 11 AM to 1 PM
___ 3 to 5 PM
___ 7 to 9 PM

12. If you went to bed at 11 PM, at which level of tiredness would you be?

___ Not at all tired
___ A little tired
___ Fairly tired
___ Very tired

13. For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which ONE of the following events are you most likely to experience?

___ Will wake up at usual time and will NOT fall back to sleep
___ Will wake up at usual time and will doze thereafter
___ Will wake up at usual time but still fall asleep again
___ Will NOT wake up until later than usual

14. One night you have to remain awake between 4 and 6 AM in order to carry out a night watch. You have no commitments the next day. Which ONE of the following alternatives will suit you best?

___ Would NOT go to bed until watch was over
___ Would take a nap before and sleep after
___ Would take a good sleep before and nap after
___ Would take ALL sleep before watch

5

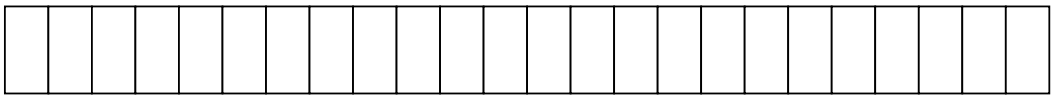
15. You have to do two hours of hard physical work. You are free to plan your day and considering only your own "feeling best" rhythm, which ONE of the following times would you choose?

___ 8 to 10 AM
___ 11 AM to 1 PM
___ 3 to 5 PM
___ 7 to 9 PM

16. You have decided to engage in hard physical exercise. A friend suggests that you do this for one hour twice a week and the best time for him/her is between 10 and 11 PM. Bearing in mind nothing else but your own "feeling best" rhythm, how well do you think you would perform?

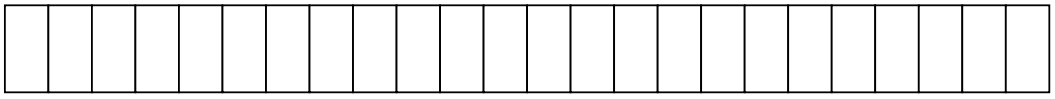
___ Would be on good form
___ Would be on reasonable form
___ Would find it difficult
___ Would find it very difficult

17. Suppose you can choose your own work hours. Assume that you work a FIVE hour day (including breaks) and that your job was interesting and paid by results. Which FIVE CONSECUTIVE HOURS would you select? (mark them in the scale below)



12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12
MIDNIGHT NOON MIDNIGHT

18. At what time of day do you think that you reach your "feeling best" peak? (Please choose one hour only)



12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12
MIDNIGHT NOON MIDNIGHT

6

19. One hears about “morning” and “evening” types of people. Which one of these types do you consider yourself to be?

___ Definitely a “morning” type
___ Rather more a “morning” type than an “evening” type
___ Rather more an “evening” type than a “morning” type
___ Definitely an “evening” type

For administrative use only-

SubID: _____ Date: _____

Appendix J: Edinburgh Handedness Inventory.

Edinburgh Handedness Inventory

Instructions: Please indicate your preferences in the use of hands in the following activities **by putting a check in the appropriate column**. Where the preference is so strong that you would never try to use the other hand, unless absolutely forced to, **put 2 checks**. If in any case you are really indifferent, **put a check in both columns**.

Some of the activities listed below require the use of both hands. In these cases, the part of the task, or object, for which hand preference is wanted is indicated in parentheses. Please try and answer all of the questions, and only leave a blank if you have no experience at all with the object or task.

Activity	Left	Right
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking Match (match)		
10. Opening box (lid)		

For test administrator use only-

SubID: _____ Date: _____

TOTAL SCORE (add up all checks in each column)**:** _____

Cumulative total (left + right) _____

Difference (right – left) _____

Index [(difference/cumulative total)*100] _____

Appendix K: Mini Mental State (MMS) Exam.

Mini Mental State (MMS) EXAM

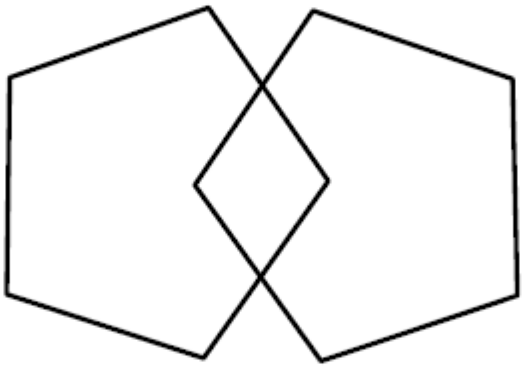
Q1. Orientation in time	
"What year is it?"	☐ correct ☐ incorrect or no response
"What season is it?"	☐ correct ☐ incorrect or no response
"What is today's date?"	☐ correct ☐ incorrect or no response
"What is the day of the week?"	☐ correct ☐ incorrect or no response
"What is the month?"	☐ correct ☐ incorrect or no response
	TOTAL (max 5): _____
Q2. Orientation in space	
"What country are we in?"	☐ correct ☐ incorrect or no response
"What province are we in?"	☐ correct ☐ incorrect or no response
"What town/city are we in?"	☐ correct ☐ incorrect or no response
"What building are we in?"	☐ correct ☐ incorrect or no response
"What floor are we on?"	☐ correct ☐ incorrect or no response
	TOTAL (max 5): _____
Q3. Registration	
Ask the subject to repeat the following words (e.g.: apple, penny, table). Note the number of words on the **first trial**, and the **number of trials** *(max 5 – n.b., not included in total score)*.	Number of words repeated on the first trial: 0 1 2 3 Number of trials: 1 2 3 4 5
	TOTAL (max 3): _____
Q4. Attention and calculation *(n.b., include only a or b in total score)*	
4a. Ask the subject to count backwards from 100 by subtracting 7 (e.g., 93, 86, 79, 72, 65). Score 1 point for each correct. Stop at 5 responses.	Number of correct results: 0 1 2 3 4 5
4b. Ask the subject to spell the word "WORLD" forward and then backwards. Score 1 point for each letter in correct order (DLROW = 5, DLORW = 3).	Number of letters in the correct order: 0 1 2 3 4 5
	TOTAL (max 5): _____
Q5. Recall	
"Please repeat the names of the 3 objects given to remember in Q3." Score 1 point for each correctly recalled word, irrespective of the order.	Number of words recalled: 0 1 2 3
	TOTAL (max 3): _____

Q6. Language	
Show the subject a "PENCIL" and a "WATCH". Have the person name them as you point to each object. Score 1 point for each correct answer.	Number of correct responses: 0 1 2
Ask the subject to repeat the phrase: "NO IFS, ANDS or BUTS".	☐ correct ☐ incorrect or no response
Have the person follow a 3 stage command: Take the paper in your right/left hand. Fold it in half once with both hands. Put it on the floor. Score 1 point for each part correctly executed.	Number of correctly executed commands: 0 1 2 3
Read and follow the message. They do not have to read aloud.	Execution of message ☐ yes ☐ no
Ask the subject to write a sentence of his/her own choice. The sentence should contain a subject and an object to make sense. Ignore spelling mistakes.	☐ correct ☐ incorrect or no sentence
	TOTAL (max 8): _____
7. Praxis	
Ask the subject to copy the design. Score 1 point if all sides and angles are preserved and the intersecting side form a quadrangle.	☐ correct ☐ incorrect or no drawing
	TOTAL (max 1): _____
TOTAL (max 30):	

Interpretation of the MMSE

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

CLOSE YOUR EYES



Appendix L: Sleep Diary.

Brain & Mind Sleep Diary

	To be completed in the morning...						To be completed at the end of the day...			
	I went to bed last night at:	I got out of bed this morning at:	Last night, I fell asleep in:	I woke up during the night:	When I woke up for the day, I felt:	Last night I slept a total of:	My sleep was disturbed by:	I consumed caffeinated drinks in the:	I exercised at least 20 minutes in the:	Approximately 2-3 hours before going to bed, I consumed:	Medication(s) I took during the day:	About 1 hour before going to sleep, I did the following activity:
DAY 1	___:___ PM/AM	___:___ PM/AM	_____ Minutes	_____ Times	☐ Refreshed ☐ Somewhat refreshed ☐ Fatigued	_____ Hours		☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Alcohol ☐ A heavy meal ☐ None		
YY/MM/DD:												
DAY 2	___:___ PM/AM	___:___ PM/AM	_____ Minutes	_____ Times	☐ Refreshed ☐ Somewhat refreshed ☐ Fatigued	_____ Hours		☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Alcohol ☐ A heavy meal ☐ None		
YY/MM/DD:												
DAY 3	___:___ PM/AM	___:___ PM/AM	_____ Minutes	_____ Times	☐ Refreshed ☐ Somewhat refreshed ☐ Fatigued	_____ Hours		☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Alcohol ☐ A heavy meal ☐ None		
YY/MM/DD:												
DAY 4	___:___ PM/AM	___:___ PM/AM	_____ Minutes	_____ Times	☐ Refreshed ☐ Somewhat refreshed ☐ Fatigued	_____ Hours		☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Alcohol ☐ A heavy meal ☐ None		
YY/MM/DD:												
DAY 5	___:___ PM/AM	___:___ PM/AM	_____ Minutes	_____ Times	☐ Refreshed ☐ Somewhat refreshed ☐ Fatigued	_____ Hours		☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Alcohol ☐ A heavy meal ☐ None		
YY/MM/DD:												
DAY 6	___:___ PM/AM	___:___ PM/AM	_____ Minutes	_____ Times	☐ Refreshed ☐ Somewhat refreshed ☐ Fatigued	_____ Hours		☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Alcohol ☐ A heavy meal ☐ None		
YY/MM/DD:												
DAY 7	___:___ PM/AM	___:___ PM/AM	_____ Minutes	_____ Times	☐ Refreshed ☐ Somewhat refreshed ☐ Fatigued	_____ Hours		☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Morning ☐ Afternoon ☐ Within 3 hours of going to bed ☐ None	☐ Alcohol ☐ A heavy meal ☐ None		
YY/MM/DD:												

Curriculum Vitae

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Brock University
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2010-2013 H.B.A.

The University of Western Ontario
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2014-present M.A.

Honours and Awards:
Dean's Honour List, Brock University
2013

NeuroXchange Conference Oral Presentation Award
2013

Western Graduate Research Scholarship
2014-2016

Reva Gerstein Fellowship for Masters Study in Psychology
2014

Province of Ontario Graduate Scholarship
2015-2916

Related Work Experience
Research Assistant, Brain & Mind Sleep Research Laboratory
The University of Western Ontario
2014-2016

Teaching Assistant
The University of Western Ontario
2014-2016

Publications:

Sergeeva, V., Viczko, J., Fogel, S, & Carrier, J. (in press) Chapter on Sleep Oscillations and Aging. In Dang-Vu, T. & Courtemanche, R. (Eds.). Neuronal Oscillations of Wakefulness and Sleep. New York, NY: Springer.

Cote, K.A., Mondloch, C.J., **Sergeeva, V**., Taylor, M., and Semplonius, T. (2014). Impact of Total Sleep Deprivation on Behavioural and Neural Processing of Emotionally Expressive Faces. Experimental Brain Research, 232(5), 1429-1442.

Fang, Z., **Sergeeva, V**., Ray, L.B., Viczko, J., Owen, A.M. & Fogel, S.M. (in review). Sleep spindles and intellectual ability: Epiphenomenon or intrinsically linked? Journal of Cognitive Neuroscience.