TRANSLATING SLEEP RESEARCH: DOES SLEEP PROMOTE LEARNING A FUNCTIONAL MOTOR TASK?

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Abstract

In rehabilitation, physical therapists are challenged to plan effective interventions that promote motor learning. Individuals who undergo rehabilitation need to learn new motor skills or relearn old motor skills. Motor learning improvements are achieved through the repetition of goal directed exercises. However, a growing body of evidence has demonstrated that sleep is a critical brain state for motor learning and memory consolidation in young adults. *Memory consolidation* refers to the conversion of memory traces from a labile state through the passage of time and without any additional practice (*off-line*) into a more permanent state. Evidence of sleep-dependent off-line motor learning has been demonstrated across a wide variety of motor tasks. However, to date, all of these tasks have been limited to relatively simple motor tasks conducted on a computer such as a finger-to-thumb opposition task and a serial reaction time task (SRTT). These tasks have limited implications in rehabilitation. It remains unclear whether a functional motor task that is clinically-relevant will benefit from sleep to produce off-line motor skill enhancement. Addressing this question was the purpose of this dissertation.

A novel walking task was used in Chapter 2 to assess the role of sleep in learning a functional motor task in young adults. Twenty-four young individuals were randomly assigned to either the sleep or the no-sleep group. The sleep group practiced the novel walking task in the evening and underwent retention testing the following morning, while the no-sleep group practiced the task in the morning and underwent retention testing in the evening. Results indicate that young participants who slept after practicing the novel walking task demonstrated a significant off-line improvement in performance on all walking outcome measures, while those participants who stayed awake failed to demonstrate off-line learning. The findings of this study demonstrate for the first time that sleep-dependent off-line learning

in young adults is not limited to simple motor tasks, but also extends to functional motor tasks that are complex and have direct implications for rehabilitation.

While mounting evidence has demonstrated that sleep is important for motor skill learning in young individuals, only a few recent studies have investigated sleep-dependent off-line motor learning in older adults. The findings of these studies offer mixed conclusions. Only one study has attempted to examine the role of sleep in motor learning in middle-aged adults. Furthermore, these studies all used simple computer-based motor tasks. Therefore, Chapter 3 examined sleep-dependent off-line learning of the novel walking task in middle-aged and older adults. Twenty middle-aged and 20 older individuals practiced the novel walking task and then either slept (sleep condition) or stayed awake (no-sleep condition) before retention testing. Only the middle-aged and older adults in the sleep condition demonstrated significant off-line improvement in performance on the novel walking task. However, when compared with the magnitude of off-line learning in young adults presented in Chapter 2, the results indicate that the magnitude of off-line improvement was less for middle-aged and older adults groups. These findings demonstrate for the first time that middle-aged and older adults are able to benefit from sleep to enhance motor skill learning of a functional task, but this ability diminishes with aging.

Many functions in everyday life require people to perform more than one task at a time such as walking and talking on the phone or walking while remembering a shopping list. However, sleep studies, almost exclusively, examined the role of sleep in motor learning using a single motor task. It is important to understand the role of sleep in learning functional tasks that include both a cognitive and a motor component. In Chapters 2 and 3 we found that sleep enhances the motor component of the functional task. In Chapter 4 the cognitive performance of the functional task was analyzed. The results reveal that in young, middle-aged, and older adults, cognitive performance improved only after a night of post-learning sleep. A similar period of wakefulness produced no improvement; in all age groups participants who stayed awake between practice and retention testing, demonstrated no improvement in cognitive performance. This study provides the first evidence that sleep enhances the cognitive aspect of a functional task.

In summary, this body of work indicates that sleep enhances learning a functional motor task that is clinically-relevant in young, middle-aged, and older adults. These findings suggest that clinicians should consider sleep as an important factor when structuring rehabilitation interventions. Different strategies need to be considered by clinicians to ensure the beneficial role of sleep on rehabilitation sessions. Therapy sessions may need to be conducted in the evening prior to sleeping or a nap may need to be encouraged between therapy sessions. To maximize the role of sleep in motor learning, emphasis should be placed on addressing sleep disorders and ensuring adequate sleep for individuals who undergo rehabilitation. Furthermore, the routine exam should include sleep quality assessment.

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Chapter 1

Introduction

1.1 Overview

Over the past decade, a growing body of evidence has demonstrated that sleep is a critical brain state for motor learning and memory consolidation in young, healthy adults[1-12]. *Memory consolidation* refers to the conversion of memory traces from a labile state through the passage of time and without any additional practice into a more permanent state[2, 13-20]. Memory consolidation that results in enhanced skill performance is termed *off-line motor learning*. Evidence of sleep-dependent off-line motor learning has been demonstrated across a wide variety of motor tasks[1-4, 7-12, 16, 21-27]. However, to date, all of these tasks have been limited to relatively simple motor tasks conducted on a computer such as a finger-to-thumb opposition task[11, 12], a serial reaction time task (SRTT)[28, 29], a sequential finger-tapping task[2, 3, 7, 20], a pursuit rotor task[22, 25, 26, 30], and a continuous tracking task[31, 32] (1.5. Sleep-Dependent Off-Line Motor Learning in Young Adults). Two studies have indicated that more complex tasks such as a more complex version of the finger-tapping task [33] and playing a video game[34] may benefit from sleep to enhance[33] and to stabilize[34] learning (1.10.Task Complexity and Sleep-Dependent Off-Line Motor Learning). There is a clear relationship between sleep and motor learning; however, data are limited for functional tasks that have significance to learning and relearning in healthy individuals and in people with neurological injuries. It remains unclear whether a functionally and clinically-relevant motor task (i.e., learning a novel walking task) will benefit from sleep to produce off-line motor skill enhancement.

The majority of studies examining sleep-dependent off-line motor learning have been conducted in young adults[1-4, 7, 8, 11, 12]. The few recent studies investigating sleep-dependent off-line motor learning in older adults have offered mixed conclusions[22, 28, 35-39] (1.9. Sleep-Dependent Off-Line Motor Learning in Healthy Older Adults). Furthermore, only one study has attempted to examine the influence of sleep on motor learning in middle-aged adults[38]. Considering that sleep changes with age[40] (1.8. Age Related-Sleep Changes), it is critical to understand the role of sleep in motor learning across the adult life span. *This work seeks to understand the role of sleep in learning a functional motor task in young, middle-aged, and older adults.* This study has important implications for clients who learn new or relearn motor skills during rehabilitation, such as a client with low back pain learning to perform a home exercise program properly, an athlete learning to pitch using proper mechanics following shoulder surgery, or client with a lower limb amputation learning to walk using a prosthesis. We believe that integration of sleep into motor training regimens and clinical interventions may hasten learning and motor recovery by allowing individuals to benefit from sleep-dependent off-line motor learning.

1.2. Overview of Memory

Memory formation is the process of acquiring information (such as facts, experiences, and skills), placing that information into storage, and modifying that information as needed over time[41]. Learning is considered the process for acquiring memory and defined as "a set of processes associated with practice or experience leading to relatively permanent changes in the capability for movement"[42]. Memory research in recent decades has led to significant progress in understanding the functions and neural substrates of memory systems. It is now widely accepted that "memory" is not a single entity but can be divided into separate systems supported by different neural circuits[43-47]. Human memory has been classified into two broad categories: declarative memory and nondeclarative memory (Figure 1.1)[48 44-47]. Declarative memory is the conscious memory of events and facts[48]. Episodic and semantic memories are two distinct types of declarative memory[49]. Episodic memory refers to memory of events that have a particular spatial and temporal context, whereas semantic memory refers to general knowledge of facts about the world[46, 49]. On the other hand, nondeclarative memory has been defined as " a heterogeneous collection of nonconscious learning capacities that are expressed through performance"[45]. There are three main classes of nondeclarative memory: simple conditioning, priming, and procedural memory[15, 16, 44-46]. For the purpose of this work, we are most interested in procedural memory, which refers to the unconscious memory of skills[46, 47].

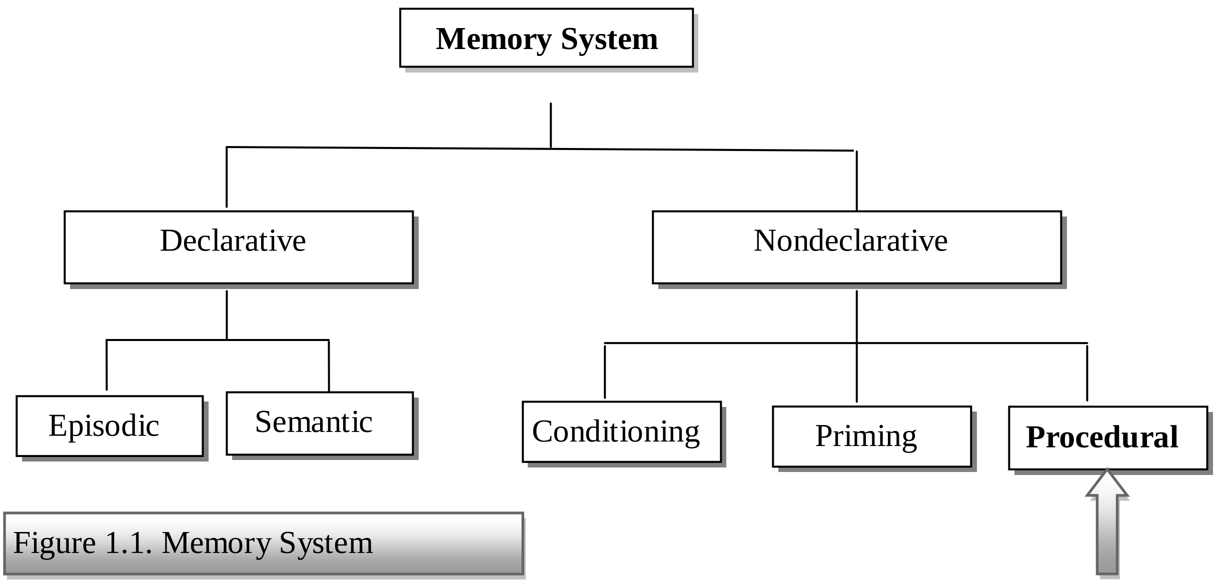


Figure 1.1. Memory System

In addition to the differences in their functions, declarative and procedural memories are neuro-anatomically different[43-47, 49]. By using modern brain imaging techniques such as fMRI, researchers were able to identify the neural mechanisms mediating these types of memory in humans. Many studies have confirmed the critical importance of the medial temporal lobe, including the hippocampus, for learning and formation of declarative memory[14, 15, 19, 43, 44, 49]. In contrast, the neural structures supporting procedural learning are more distributed and involve both cortical and subcortical networks (including in particular the sensorimotor cortex, the cerebellum, and the basal ganglia)[50-53]. Some of the evidence which supports that declarative and procedural memories rely on different neural systems comes from the study of people with amnesia who have bilateral damage to the medial temporal lobe[43-47]. Studies found that patients with amnesia usually perform normally on tasks that assess skills and habit learning. However, those patients are severely impaired on tests that examine declarative memory.

Many studies have confirmed the beneficial effect of sleep on declarative[54-61] and procedural[1, 2, 7, 9, 11, 12, 62] memories. A period of post-learning sleep enhances retention of declarative information[54-61] and improves procedural skills performance when compared with a wake interval of equal length[1, 2, 7, 9, 11, 12, 62]. In this study we will explore the role of sleep in learning a functional motor task that is complex and related to everyday life activities in young adults (Chapter 2), and middle-aged and older adults (Chapter 3). Therefore, nondeclarative memory, and more specifically procedural motor memory, will be the main focus of this work.

1.3. Stages of Procedural Memory Formation

The new skills formation is a multi-step process occurring on a time scale of minutes, hours, days, and even weeks. Memory formation appears to develop over time in several stages (Figure 1.2)[43]. The first stage is encoding or acquisition which describes an initial engagement with an object or performing an action. Successful acquisition results in attaining a certain level of task ability which leads to the rapid formation of a memory representation within the brain. Following encoding, memory consolidation occurs. Memory consolidation refers to the process by which a memory becomes resistant to interference from competing factors. Recent studies have indicated that consolidation can result not only in stabilizing memories, but further enhancing them[4, 15, 19]. Accordingly, Walker et al[15, 19] differentiate two distinct stages of consolidation in procedural memory formation: stabilization and enhancement[15, 19]. During memory stabilization, motor skill performance maintained over time. While during memory enhancement, motor skill performance improved without further task practice.

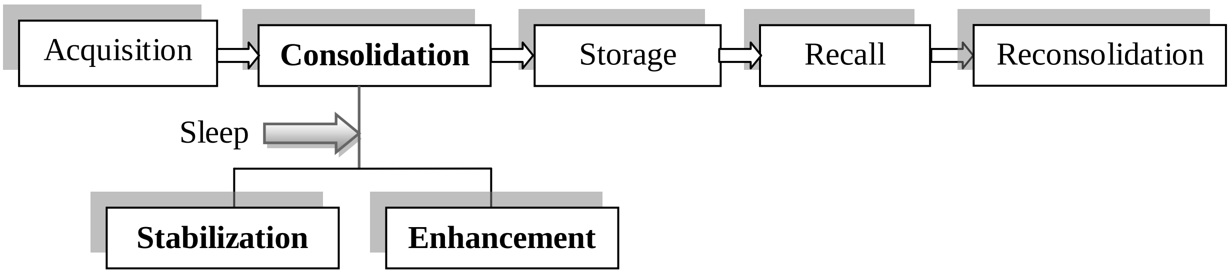


Figure 1.2. Stages of memory formation

The third step in memory processing is storage, in which memory is maintained in the brain over time. Recall is the final step of memory formation in which the stored memory is able to be called back when needed for use. Following memory recall, the memory representation has been found to destabilize. Therefore, reconsolidation has been found to convert the labile memory into restabilized form[4, 14, 15, 63-65].

Sleep may impact each stage of procedural memory processing differently. However, the focus of the majority of studies has been to understand the role of sleep in memory consolidation. Many studies have confirmed the beneficial role of sleep on procedural memory consolidation[1-4, 7, 11, 20, 22]. It has been argued that stabilization may be primarily time-dependent while enhancement may be sleep-dependent[19]. However, studies have found that sleep also benefits the stabilization of learning[34, 62]. Interestingly, to date, studies have focused almost exclusively on examining the consolidating effect of sleep using simple motor tasks, such as a finger-to-thumb opposition task[11, 12], a serial reaction time task[28, 29], and a sequential finger-tapping task[2, 3, 7, 20]. No studies have assessed the effect of sleep on a functionally relevant task. Therefore, this work attempts to understand whether sleep enhances learning a functional task that is more complex and related to real-life activities by examining the role of sleep in learning a novel walking task.

1.4. Overview of Normal Sleep

Based on patterns of electrical activity in the brain (measured using electroencephalogram, EEG), eye movements (measured using electro-oculography, EOG), and muscle tone (measured using electromyography, EMG), sleep is defined as a specific behavior during which the organism adopts a recognizable posture and demonstrates reduced motor activity and decreased response to external stimulation[66]. Sleep cannot be considered a homogenous state. Instead, it has been broadly divided into two different stages and named according to its main distinctive features[67]. The first phase, characterized by the presence of rapid eye movement in spite of muscular atonia, is referred to as rapid eye movement (REM) sleep. REM sleep is also referred to as paradoxical sleep (PS) as the high-frequency pattern of the EEG recording during REM sleep resembles the EEG pattern of wakefulness. REM sleep is associated with the "phasic endogenous wave forms" occurring in the pons, genculate nuclei of the thalamus, and the occipital cortex, referred to as "PGO waves".[68]

The other main sleep stage is known as non-rapid eye movement (non-REM) sleep. According to the recent American Academy of Sleep Medicine (AASM) scoring manual[69], non-REM sleep is subdivided into 3 characteristic sub-stages corresponding to increasing depth of sleep. Stage 1 involves the transition from wakefulness to sleep (corresponds to light sleep) and is characterized by sinusoidal alpha wave activity. Stage 2 is characterized by K complexes and sleep spindles. The amount of slow oscillations increases as sleep deepens, leading to Stage 3 which is called slow-wave sleep (SWS) and is characterized by high-amplitude slow delta waves (Table 1.1).

Sleep Stages		Electrophysiology	Time Spent (Young adults)
REM		Increased EEG frequency PGO waves	20-25%
Non-REM			
	Stage 1	Sinusoidal alpha wave activity	1-5%
	Stage 2	K-complexes and sleep spindles	50-60 %
	Stage 3 (SWS)	High- amplitudes slow delta Waves	15-25%

Table 1.1. Sleep stages and main features of each stage

Functional brain imaging has been used in humans to characterize brain activity associated with different sleep stages. PET and fMRI studies have reported a decreased brain activity during non-REM sleep. Reductions in brain activity were found in the subcortical (brainstem, thalamus, basal ganglia, and basal forebrain) and the cortical (prefrontal cortex, anterior cingulate cortex, and precuneus) regions[70-73]. The reduction in brain activation during non-REM may explain the restorative function of sleep needed for energy recovery. On the other hand, recent fMRI studies demonstrate that non-REM sleep is accompanied by a brief increase in brain activity in specific cortical and subcortical areas involved in the generation and modulation of non-REM sleep oscillations[61, 74 75]. For example, an fMRI study by Schabus et al[61] found that sleep spindles were associated with increased brain activity in the lateral and posterior aspect of the thalamus, anterior cingulate cortex, insula, and the superior temporal gyrus[76]. Increases in brain activity were also reported during slow wave sleep in the brainstem, cerebellum, ventral prefrontal cortex, and posterior cingulate cortex[75, 76]. These neural activity patterns indicate that non-REM sleep is an active brain state and might point to the important role that sleep has in memory consolidation (see Section 1.5 for more discussion about the role of sleep in memory consolidation).

Patterns of brain activity associated with REM sleep are considerably different from the patterns associated with non-REM sleep. These brain activities are not significantly different from the patterns associated with wakefulness. Many brain regions increase their activity (pontine tagmentum, thalamus, basal forebrain, amygdala, hippocampus, anterior cingulated cortex, and temporal-occipital areas). Other brain structures decrease their activity (dorsolateral prefrontal cortex, posterior cingulate gyrus, precuneus, and inferior parietal cortex) during REM sleep[70-73].

During a night of sleep, young adults have a specific pattern of sleep stages. Young adults start sleep by entering non-REM sleep followed by REM sleep. Throughout the night non-REM and REM sleep phases alternate repeatedly every 90-110 minutes with a total of 4 to 6 cycles[66]. During the night the non-REM sleep to REM sleep ratio changes. SWS dominates in the first half of the night. In the second half, the proportions of REM sleep and Stage 2 sleep increase[66, 67 77]. Non-REM sleep accounts for 75-80 % of sleep time in young adults (Stage 2 sleep accounts for approximately 50-60%, SWS accounts for 15-20 %, and Stage 1 accounts for 1-5%)[66, 67]. REM sleep, on the other hand, accounts for 20-25 % of sleep time (Table 1.1). Furthermore, a healthy young adult has approximately 90% sleep efficiency (i.e., less than 5% of the total time in bed is spent awake) [67], immediate sleep onset, and few and brief awakenings during night[67].

1.5. Sleep-Dependent Off-Line Motor Learning in Young Adults

A large body of evidence indicates that delayed gains in performance occurred following a period of sleep, but not following an equivalent period of wakefulness in young adults[1-4, 7-17, 19, 22, 26]. Sleep has been shown to play an important role in the consolidation of a variety of motor tasks involving a finger-to-thumb opposition task[11, 12], a serial reaction time task[28, 29], a sequential finger-tapping task[2, 3, 7, 20], and a pursuit rotor task[22, 25-27]. For example, Walker et al[3] introduced a sequential finger-tapping task to subjects, requiring them to repeat a five-element sequence "4-1-3-2-4" as quickly and accurately as possible by pressing keys with the non-dominant hand for a period of 30 s. After a night of sleep, the researchers found significant increases in motor speed without loss of accuracy, while no benefits were observed after an equal period of wakefulness. Fischer et al[11] confirmed these results by Walker et al[3] and demonstrated that sleep on the first night following motor task training is critical for the sleep-dependent off-line motor learning process. Studies by Smith et al[25] and Maquet et al[26] demonstrated that sleep deprivation on the first night following the practice of a simple motor task (rotary pursuit) impaired performance at retest (one week later) as compared with a group of individuals not deprived of sleep.

While the influence of circadian rhythm cannot be eliminated as a potential contributing factor to learning and memory consolidation, sleep is thought to be a more crucial element[11, 20]. A study by Fischer et al[11] has reported that after practicing a finger-to-thumb opposition task, sleep enhanced the speed of sequence performance and reduced the error rate to the same extent after 8 hours of night sleep or 8 hours of day sleep, compared with corresponding intervals of wakefulness[11]. Furthermore, studies have demonstrated that naps offered at different times of the day produced off-line motor skill enhancement[10, 20, 78 79-81]. Korman et al[10] showed that a 90-min nap after training elicited performance gains similar to those achieved after a night of sleep. Nishida et al[81] support the findings by Korman et al[10] and also found significant correlation between the amount of off-line improvement and stage-2 non-REM sleep. Further, this later study[81] indicated that sleep spindles, the prominent feature of Stage 2 non-REM sleep, are important for simple motor procedural memory consolidation. These nap studies provide further evidence that sleep rather than circadian rhythm factors produce off-line motor skill enhancement.

The role of sleep in motor learning enhancement is not without controversy. Sleep-dependent off-line motor learning is not reported under all circumstances and seems to be associated with several factors, including an individual's awareness about the task regularities[7, 28, 36] and the type of task utilized[20, 31]. In a recent study, Siengsukon and Al-Sharman[31] demonstrated that sleep enhances learning an explicit discrete task but not an explicit continuous task. The authors proposed that the differences in motor control and differences in task complexity support sleep-dependent off-line enhancement of discrete tasks but not continuous ones. A study by Doyon et al[20] found sleep-dependent off-line consolidation for a finger-tapping sequence task, but found no sleep-dependent off-line consolidation for a visuomotor adaptation task in young, healthy adults. Doyon et al[20] suggest that task-related differences may explain the different outcomes. For example, the visuomotor adaptation task requires a strong perceptual component since subjects learn to adjust their movement in response to visual feedback. This differs from the finger-tapping task that does not include visual feedback. Interestingly, few studies have indicated that sleep preferentially enhances learning tasks that are more complex[33, 34] and tasks that are relevant to future behavior[82] (for more details see Section 1.10. Task Complexity and Sleep-Dependent Off-Line Motor Learning).

An individual's awareness about the task regularities before or during practice (explicit vs. implicit) has emerged as an important factor in determining whether off-line motor learning is related to sleep or simply the passage of time. Robertson et al[7] found that participants in the implicit condition (i.e., who had no awareness of the sequence to be learned) demonstrated improvement in their performance after a 12-hour interval regardless of whether or not it contained a period of sleep. In contrast, participants in the explicit condition (i.e., who were instructed on the sequence pattern to be learned) demonstrated an improvement in performance only if the training was followed by a period of sleep. The findings of this study by Robertson et al[7] and many other studies [2-4, 11] [2-4, 11] suggest that sleep preferentially enhances the learning of explicitly learned motor tasks. However, there is less agreement on whether implicitly learned tasks benefit from sleep or from the passage of time to enhance learning. While few studies revealed that sleep enhances learning implicit motor tasks[23, 26, 83, 84], other studies have found different results[7, 28, 30, 32, 85-87]. Comparing the results between these studies is very difficult as different tasks and methods were utilized.

Few studies have examined whether sleep enhances only a certain characteristic of motor tasks[11, 28, 32, 86, 88]. For example, using the serial reaction time, Cohen et al[88] found that only the goal or spatial regularity of the task was enhanced by sleep following practice, whereas the motor pattern was enhanced over the day without sleep. This suggests that different mechanisms of off-line learning support distinct aspects of motor memory. Few studies have also assessed the role of sleep in promoting general motor skill learning compared to sequence-specific motor skill learning[28, 86]. These studies found that sleep does not have a critical role in off-line learning of either general skill or sequence-specific motor skill learning. Recently, Al-Sharman and Siengsukon[32] confirmed these results and found that that both general skill learning and sequence-specific skill learning of an implicitly learned motor task improve off-line, regardless of whether participants slept or stayed awake between practice and retention testing.

In summary, despite the accumulating evidence supporting sleep-dependent off-line motor learning, sleep may not be necessary to consolidate all forms of motor learning and seems to be associated with many factors. As we mentioned previously, the majority of tasks which have been used to examine sleep-dependent consolidation are simple computer-based tasks. Performing these tasks requires pushing buttons or controlling a joystick. Importantly, these tasks have limited applications to daily life activities and rehabilitation (i.e., not relevant to an individual's life). No study has attempted to examine the role of sleep in learning a functional motor task that is more complex and resembles a typical daily task. In this work, we attempt to add to the body of work and explore the role of sleep in learning a novel functional walking task.

1.6. Stages of Sleep and Procedural Memory Consolidation

A longstanding line of research indicates that procedural memory requires Stage 2 non-REM and/or REM sleep for consolidation[3, 11, 22, 27]. Walker et al[3] found that overnight improvement on a finger-tapping task was positively correlated with the amount of Stage 2 non-REM sleep. Whereas, a study by Fischer et al[11] found that overnight improvement of a motor task is correlated with REM sleep. Emerging evidence suggests that REM sleep is important for consolidating a procedural motor task that is complex and requires a new cognitive strategy; whereas, Stage 2 sleep is dedicated to the consolidation of simple motor tasks[25, 27, 89]. Fogal et al[90] and Peter et al[22] support the hypothesis that Stage 2 sleep and more specifically sleep spindles are important for simple motor procedural memory consolidation. Using four types of simple motor tasks, Fogal et al[90] found that overall off-line improvement of motor tasks was positively correlated with increases in density of sleep spindles.

Interestingly, using a pursuit rotor task, Peter et al[21] found that individuals' initial skill level is an important variable that needs to be considered to determine which stage is important for procedural motor tasks consolidation. The results of this study[21] support the literature that indicate Stage 2 non-REM and/or REM are important for procedural memory consolidation. However, different neural processes were associated with off-line learning in low- and high-skilled individuals. In high-skilled participants, there was a significant increase in Stage 2 spindles density after learning. A significant correlation was found between the spindles density that occurred after learning and improved performance on the pursuit rotor task at retest, one week later. In contrast, in low-skilled participants there was a significant correlation between increased REM density and improved performance on the pursuit rotor task at retest.

In summary, the sleep stages REM and Stage 2 non-REM sleep are associated with the neural processes underling the consolidation of newly encoded procedural memories. However, factors such as the cognitive load and an initial skill level of the learner seem to affect which stage is important for a given procedural memory.

1.7. Brain Reorganization During and After Sleep

In addition to behavioral data, neuroimaging has contributed to understanding the relationship between sleep and learning. Studies found that several brain areas activated during motor learning are more activated during sleep in subjects who trained on the task[23, 87, 91, 92]. Maquet and colleagues[23] have shown that several brain areas activated during practice on the probabilistic SRTT were active during post-training REM sleep in subjects who practiced the task as opposed to subjects without prior SRTT practice. The authors concluded that the cerebral reactivation during post-training REM sleep reflects the “reprocessing” of the memory traces formed during SRTT practice. Additionally, the authors found that the connectivity between areas already active during learning was enhanced during post-training REM sleep as compared to the REM sleep of untrained subjects. The reactivation of brain areas and the alteration of functional connectivity during post-training sleep describe the off-line processing of recent memories and likely explain improved performance the next morning.

In addition to approaches that measure the reactivation of brain areas during post-training sleep, other neuroimaging studies have focused on memory performance and related brain activity following sleep or sleep deprivation. Using fMRI, Maquet et al[26] have investigated changes in brain activity associated with learning a procedural motor task after normal sleep versus sleep deprivation. As expected, the behavioral results of this study by Maquet et al[26] demonstrate a performance gain in the sleeping group, as indicated by the decreased time on target, compared to the sleep-deprived group. Importantly, fMRI data revealed that sleeping subjects experience more brain activity in the superior temporal sulcus (STS), the area involved in the evaluation of complex motion patterns. In addition, increased functional connectivity was observed between the supplementary eye field (SEF) and the frontal eye field (FEF), regions known to participate in improved control of eye movements. In contrast, no such brain activities were observed in the sleep-deprived group, suggesting that sleep deprivation hampered the process of plasticity and consolidation.

Fischer et al[93] found that sleep-dependent improvement on a sequential finger-tapping task at retention was associated with a reduction in brain activation in the left prefrontal cortex, right lateral premotor, and left primary motor areas. The authors suggest that the reduction of brain activity in these areas probably indicates a reduced need for “conscious monitoring” of finger movements by the action of sleep. On the other hand, stronger involvement was found in the left superior parietal cortex, the structure that supports performance automation. Interestingly, the fMRI data from a study by Walker et al[13] show different brain activation patterns. In the later study[13], post-practice sleep was associated with increased brain activations in the right primary motor cortex, medial prefrontal lobe, hippocampus, and left cerebellum. The researchers suggest that these changes support improved motor performance and “more precise mapping of key-press movements”. In addition, Walker et al[13] identified decreased brain activations in the parietal cortices, the left insular cortex, the temporal pole and the fronto-polar region. The authors explain these reductions in brain activation with a reduced need for conscious monitoring and a decreased emotional task load.

In summary, using different neuroimaging techniques, studies were able to confirm the behavioral data about the relationship between sleep and off-line motor learning.

1.8. Age -Related Sleep Changes

Sleep changes with advancing age[66, 67, 77, 94]. Aging is associated with both qualitative and quantitative changes in sleep quality, pattern, and distribution[22, 36, 77, 95-102]. Numerous studies reported important changes in sleep architecture with age[66, 67, 77, 103-105]. (Table1 summarizes the percent of time spent in each sleep stage for young, middle-aged, and older adults). Reviews assessing changes in sleep architecture across the human lifespan demonstrate that as people age, time spent in Stages 1and 2 increases[40, 77, 100, 104]. Significant increases in these stages have been found between young and middle-aged adults and between middle-aged and older adults[77, 100, 104].In contrast, the time spent in REM sleep and SWS decreases with aging[40]. The percentage of SWS decreases at a rate of approximately 2% per decade up to 60 years of age and then stabilizes through the mid-90s[77, 96]. The percentage of REM sleep also diminishes, although the decline is more subtle[67]. The major decrement in REM sleep occurs between young and middle adulthood, after which little change is noted[96, 106].

Stage of sleep	Time Spent (Young adults)	Time spent (Middle- aged)	Time spent Older adults)
REM	**20-25%**	**18%**	**18-15%**
Non-REM			
Stage 1	**1-5%**	**11%**	**8-15%**
Stage 2	**50-60 %**	**62%-68%**	**60-80%**
Stage 3 (SWS)	**15-25%**	**3.4-8%**	**0-5%**

Table 1.2. Percent of time spent in each sleep stage for young, middle-aged, and older adults.

In addition to the global changes in sleep structure, several studies have examined the changes that occur in sleep microstructure[94, 101, 107]. Crowley and colleagues[107] have reported an age-related reduction in sleep spindles number, density, and duration, as well as decreases in the number and density of K-complexes[40]. These findings are interesting as, recently, it has been suggested that sleep spindles represent an important mechanism of sleep-dependent off-line memory improvement[108-112]. Studies have found that sleep spindles contribute to the synaptic plasticity that facilitates memory consolidation and Long-Term Memory (LTM) formation[108, 113, 114].

Recently, a few studies have reported that sleep does not enhance motor learning in older adults who are healthy[21, 28, 35-37]. These studies propose that changes in sleep architecture associated with normal aging, in particular changes occurring in sleep spindles, limit the possible benefits of sleep to produce off-line memory enhancement. The apparent lack of sleep-dependent off-line motor learning in older adults is discussed in more detail in Section 1.9. (Sleep-Dependent Off-Line Motor Learning in Healthy Older Adults).

Along with the changes in sleep architecture, many older adults report a decrease in sleep quality[94]. In a survey of more than 9,000 older adults aged 65 years and older, more than half reported at least one sleep problem, such as waking during the night and waking without feeling rested in the morning[115]. Only 12% of the sample reported no sleep complaints[115]. Studies have found that both total sleep time and sleep efficiency continue to decrease with age[116]. Moreover, evidence suggests that sleep becomes more fragmented with age; that is, older subjects experience more frequent arousal from sleep[66, 77, 95, 96, 103]. A meta-analysis by Floyd and colleagues[117] on age-related changes in the initiation and maintenance of sleep (i.e., insomnia) confirmed that waking frequency and duration increased with aging.

However, the question remains whether these changes in sleep quality are simply part of the aging process or if they are secondary to other co-morbidities that arise with advancing age such as arthritis and depression. Much of the evidence shows increased support for the latter[118, 119]. In a study by Ohayon et at[118] age-related increases of insomnia are eliminated when controlling for activity status and social life satisfaction. These results are further supported by Foley et al[120] who concluded, using data from the National Sleep Foundation Survey (2003) of people aged 55 to 84 years, that sleep complaints are often secondary to chronic diseases. These results suggest that sleep complaints common in older adults are often secondary to their co-morbidities and not to the normal aging process.

Considering the large number of older adults in the United States and the large number of Medicare patients who are treated annually in inpatient rehabilitation facilities (IRF) across the United States, it is critical to investigate factors that might impact learning in older adults[121, 122]. If sleep is important for the memory formation underlying learning in older adults, then it is reasonable to suggest that sleep could influence the effectiveness of rehabilitation interventions for those individuals.

1.9. Sleep-Dependent Off-Line Motor Learning in Healthy Older Adults

Few studies have investigated sleep-dependent off-line motor learning in older adults[22, 28, 35-39]. Using a continuous tracking task, Siengsukon et al[36, 37] found that older adults fail to benefit from sleep to enhance their performance. The authors[37] suggest that changes in sleep architecture such as the reduction in sleep spindles associated with aging limit the potential benefits of sleep. Spencer et al[35] have found that, compared to young adults, older adults demonstrate a lack of sleep-dependent improvement on both an explicit and implicit version of a SRTT. However, the authors assessed a wide age range (between 45 and 80 years of age) without distinguishing between middle-aged and older adults. Considering that sleep parameters change across age, and that there are differences in sleep parameters between middle-aged and older adults, it is difficult to determine which age group actually experiences impairment in sleep-dependent consolidation and at which age sleep-dependent consolidation starts to diminish. Recently, Wilson et al[38] designed a study to address this issue by examining off-line changes in performance using a SRTT in young, middle-aged, and older healthy adults. The researchers found that, compared to young participants who showed a significant sleep-dependent off-line learning, middle-aged adults demonstrated a decline in sleep-dependent off-line motor learning on a SRTT. Further, older adults failed to benefit from sleep to enhance performance suggesting, as did Spencer et al[35], that aging is associated with decrement in sleep-dependent off-line motor learning.

Unlike these studies which detected no sleep-dependent off-line improvement in older adults[35, 37], Peter et al[22] found both young and older adults experienced significant off-line improvement on the pursuit rotor task after a 1-week delay. However, a larger improvement was observed in the young group compared to the older group. Furthermore, in a recent study by Tucker et al[39] 16 older and 15 young adults were assessed using a sequential finger-tapping task before and after a night of sleep. By assessing both "immediate off-line improvement” (i.e., performance at the first 3 retest trails - performance at the last 3 training trails) and “plateau off-line improvement” (i.e., performance at the last 3 retest trails - performance at the last 3 training trails) the authors found that elderly participants maintained their performance at the beginning of the retest session and demonstrated a significant improvement by the end of the retest session. Conversely, after 12 hours of daytime wakefulness older adults showed 22% decline in performance at the beginning of the retest session and a slight non- significant improvement at the end of the retest session.

Taken together, studies conducted in older adults have provided mixed results and the influence of sleep on off-line motor learning in older adults remains an active topic of debate. Despite the fact that sleep architecture begins to change during midlife, only one study by Wilson et al[38] has examined the role of sleep in middle-aged adults. A common feature between previous studies that were conducted on older and middle-aged adults is that all have utilized simple tasks. In young adults it has been found that sleep enhances learning tasks that are more complex[33, 34] and tasks that are relevant to an individual’s future (1.10. Task Complexity and Sleep-Dependent Off-Line Motor Learning)[82]. However, no study has attempted to examine the effect of these factors on the process of sleep-dependent off-line learning in middle-aged and older adults. This work seeks to examine the role of sleep in learning a functional motor task in middle-aged and older adults and to compare these results with the results from young participants. By testing young, middle-aged, and older adults on the same functionally relevant task, we will better describe age-related changes associated with sleep-dependent off-line motor learning.

1.10. Task Complexity and Sleep-Dependent Off-Line Motor Learning

Many studies have examined the influence of task complexity on *practice-dependent motor skill learning* (for review see Wulf et al[123]). Shea et al[124] demonstrated that learning can occur for a more complex task that requires the learner to coordinate movements in accordance with an external stimulus. On the other hand, a review by Wulf and Shea[123] states that learning complex skills does not always follow the same principles as learning simple skills. In order to understand the process of motor learning, the authors suggest using complex skills (which are more typical of real-life settings) in motor-learning research.

While many studies have examined the influence of task complexity on practice-dependent motor skill learning, few studies have attempted to understand the influence of this factor on *sleep-dependent off-line motor learning* [31, 33, 34]. All these studies were conducted in young individuals. Kuriyama et al[33] have examined the potential differences in off-line learning attributed to sleep across different levels of motor skill difficulty. The researchers modified the characteristics of the finger-tapping task across two dimensions: extent of movement coordination (unimanual vs. bimanual) and memory load (five elements vs. nine elements). Kuriyama et al[33] found that overnight learning was expressed across different levels of the task complexity. However, the most complex version of the task (a bimanual 9-element sequence) showed a considerably larger improvement in performance compared with other levels of task complexity. Brawn and colleagues[34] support the findings of Kuriyama et al[33] and provide evidence that the consolidation process during sleep occurs after learning a task requiring adaptive behavior. In the later study[34] participants practiced a video game in which the participants played in a rich, multisensory simulated environment while continuously reacting to different visual and auditory stimuli. The authors found that, after a full day of wakefulness the participants' performance on the video game deteriorated significantly, however, it recovered following a night of sleep, providing evidence that sleep benefits motor learning stabilization. Moreover, in a recent study, Siengsukon and Al-Sharman[31] found that sleep enhances learning an explicit discrete task but not an explicit continuous task. Although this study[31] was not specifically designed to examine the influence of task complexity on sleep-dependent off-line learning, the authors suggest that the differences in tasks complexity support sleep-dependent off-line enhancement of the discrete task but not the continuous one.

To date, motor tasks that have been used to examine sleep-dependent off-line motor learning in young, middle-aged and older adults have been limited to relatively simple motor tasks. The motor demands of these tasks are relatively simple, and essentially consisted of key presses on a computer keyboard. Even those studies that examined the influence of task complexity on sleep-dependent off-line motor learning have utilized relatively simple tasks compared to the tasks we perform in daily-life activities. Typical daily tasks such as driving, climbing stairs, playing a sport, or walking require a high motor demand, fast reaction to environmental stimuli, and different body part coordination. Furthermore, performing these tasks usually occurs concurrently with cognitive tasks such as driving and talking.

An interesting study by Wilhelm et al[82] have found that compared with a period of wakefulness, post-learning sleep results in a significant improvement at retention testing only if the participants had been informed about the retention testing after learning a procedural motor task (finger-sequence tapping task). The authors suggest that sleep provides greater benefits for memories that are relevant to the individuals' life. Therefore, it can be hypothesized that sleep-dependent off-line motor learning can be maximized by choosing a task that is complex and relevant to the individuals' life. The work presented in this dissertation adds critical information about the impact of sleep on learning a complex functionally relevant motor task, in young, middle-aged, and older adults. It is critical to understand whether sleep enhances learning motor tasks that are functionally and clinically-relevant in order to provide suggestions for the incorporation of sleep into motor skills training in applied settings (e.g., in sports and in rehabilitation).

1.11. Significance of Proposed Study

The primary purpose of this study is to understand the role of sleep in learning a functional motor task in young, middle-aged and older adults. The proposed study is an essential enhancement of the current literature examining the role of sleep in motor learning. To date, studies examining the role of sleep in motor learning have all used simple motor tasks. As yet, no study has examined whether the findings utilizing simple tasks will generalize to functional tasks resembling those performed daily. Furthermore, the majority of sleep studies have been conducted on young adults. Few studies have attempted to examine the role of sleep in motor learning in older adults. Only one study[38] has examined whether sleep influences the learning process in middle-aged adults. This current study is the first to examine the role of sleep in learning a functional motor task in young, middle-aged, and older adults. As will be presented, young, middle-aged and older adults demonstrate sleep-dependent off-line learning of a functional motor task. The findings of this study demonstrate that sleep-dependent off-line learning is not limited to simple motor tasks, but also extends to a functional motor task that is complex and has direct implications for rehabilitation.

The findings of this work may influence the manner individuals learn a new skill such as learning a new sport, learning to play a musical instrument, and/or learning how to drive. Besides factors that are important for motor learning such as number of training sessions, and type of training, sleep may be an important factor for motor skills improvement. Thus, sleep could possibly represent a beneficial factor for those who learn a new task such as a sport or an occupation.

The findings of this current study may also have important implication for rehabilitation. In rehabilitation, physical therapists plan effective interventions that promote motor learning. Individuals who undergo rehabilitation need to learn new motor tasks or relearn old motor tasks. For example, individuals with low back pain must learn to perform a home exercise program properly, a client with a lower limb amputation learning to walk using a prosthesis, or a patient with total knee replacement learning proper walking mechanics. Improvements in motor learning are believed to be achieved through the practice and repetition of purposeful motor actions. However, we believe that incorporation of sleep into clinical interventions may improve clinical outcomes as individuals may benefit from sleep-dependent off-line motor learning. There should be practical guidelines for physical therapists to incorporate sleep as an important factor for motor learning when structuring rehabilitation interventions. Strategies should be considered to maximize the role of sleep on motor learning. Therapy sessions may need to be conducted in the evening prior to sleeping or a nap may need to be encouraged between therapy sessions. Emphasis may also be placed on adequate sleep or addressing sleep disorders and underlying conditions that limit sleep.

1.12. Specific Aims and Statement of Hypotheses

The main purpose of this presented work was to examine the role of sleep in consolidation of a functional motor skill in young, middle-aged, and older adults.

Specific Aim 1: Examine the role of sleep in learning a novel walking task in young adults. Only relatively simple tasks have been used in previous studies to examine sleep-dependent memory consolidation[2-4, 6, 7, 11, 12, 20, 65, 125]. It remains unknown if a more functional task will benefit from sleep to produce off-line motor learning. Therefore, *we hypothesize that young participants who sleep compared to those who do not sleep after practicing a novel walking task will demonstrate improved learning of the task as reflected by a decreased in time around the walking path (Hypothesis 1). We also predict that young participants who sleep compared to those who do not sleep after practicing a novel walking task will demonstrate improved learning of the task as reflected by improving the spatio-temporal gait parameters (Hypothesis 2).*

Specific Aim 2: Examine age-related differences in sleep-dependent off-line motor learning of a novel walking task.

Few studies have examined the consolidating effect of sleep in older adults[22, 28, 35-37]. Only one study has attempted to investigate whether sleep enhances motor learning in middle-aged adults[38]. *We predict that compared to the middle-aged participants, young participants will demonstrate greater sleep-dependent off-line motor learning of a novel walking task (Hypothesis 3).We also predict that compared to the older adults, young participants will demonstrate greater sleep-dependent off-line motor learning of a novel walking task (Hypothesis 4). Furthermore, we hypothesize that compared to older adult participants; middle-aged participants will demonstrate greater sleep-dependent off-line motor learning of a novel walking task (Hypothesis 5)*

Three manuscripts based on the work presented in this dissertation have been or will be submitted for publication. The first manuscript was based on data collected in this dissertation study with the aim of examining the role of sleep in learning a functional motor task in young adults (Chapter 2; submitted to *Physical Therapy*, under review). The second manuscript utilized the whole dataset of this dissertation research and examined the sleep-dependent off-line learning of a functional task in middle-aged and older adults and compared these finding with the results from young adults (Chapter 3; to be submitted to *Journal of the American Geriatrics Society*). The third manuscript assessed in particular the role of sleep in improving the cognitive aspect of the functional motor task (Chapter 4; to be submitted to *Neuroscience Letters*)

Chapter 2 Preface

Chapter 1 provided an overview of what is currently known about the role of sleep in off-line motor learning and memory consolidation. It also gives insight into the questions that remain to be answered. One of the questions that remains is the role of sleep in learning a functional motor task that is more complex and related to real-life activities. Chapter 2 sought to address the role of sleep in learning a functional motor task that is clinically-relevant in young healthy individuals.

Chapter 2

Sleep Enhances Learning a Functional Motor Task in Young Adults

This work was submitted for publication to *Physical Therapy*, 12/7/2012.

2.1 Abstract

Background. Sleep has been demonstrated to enhance simple motor skill learning “off-line” in young adults. Off-line learning refers to either the stabilization or the enhancement of a memory through the passage of time without additional practice. It remains unclear if a functional motor task will benefit from sleep to produce off-line motor skill enhancement. Physical therapists often teach clients functional motor skills; therefore, it is important to understand how sleep impacts learning of these skills.

Objective. The purpose of this study was to determine if sleep enhances the learning of a functional motor task.

Design. A prospective, cross sectional, repeated measures design.

Methods. Young, healthy participants (n=24) were randomly assigned to either the sleep or the no-sleep group. The sleep group practiced the novel walking task in the evening and underwent retention testing the following morning, while the no-sleep group practiced the task in the morning and underwent retention testing in the evening. Outcome measures included time around the walking path and the spatio-temporal gait parameters.

Results. Only participants who slept after practicing the novel walking task demonstrated a significant off-line improvement in performance. Compared to the no-sleep group, participants in the sleep group demonstrated a significant decrease in the time around the walking path, an increase in tandem velocity, an increase in tandem step length, and a decline in tandem step time.

Limitations. Time-of-day effect and inability to ensure a certain amount of sleep quantity and quality of participants.

Conclusions. This study is the first to provide evidence that sleep facilitates learning clinically-relevant functional motor tasks. Sleep is an important factor that physical therapists should consider when teaching clients motor skills.

2.2 Introduction

During rehabilitation, physical therapists are challenged to plan effective interventions which promote motor learning and relearning in individuals who undergo rehabilitation. Physical therapists frequently spend a large portion of their treatment session teaching patients how to perform skills. For example, a physical therapist will likely teach a person with low back pain how to perform a home exercise program; an athlete, following shoulder surgery, how to pitch using proper mechanics; or a client with a lower limb amputation how to walk using a prosthesis. It is critical to explore factors that could potentially enhance motor learning. Sleep is emerging as an important factor that influences motor learning.

A wide base of literature indicates that sleep is a critical brain state for motor learning and memory consolidation in young adults[1-12]. *Memory consolidation or off-line motor learning* refers to either the stabilization or the enhancement of a memory through the passage of time and without any additional practice[2, 13-20]. Young adults who sleep between practice and retention testing demonstrate improvements in task performance, as compared to participants who stay awake[1-4, 7-17, 19, 22, 26]. Sleep-dependent off-line motor learning has been demonstrated using different simple computer-based motor tasks. However, the role of sleep in learning a functional motor task remains in question.

Research has indicated that sleep enhances learning of both motor sequence[2, 3, 11, 20, 88] and motor adaptation[22, 25, 84, 126, 127] tasks, when no additional practice has taken place in young individuals. According to Schmidt and Lee[42], motor-sequence learning consists of learning a series of skilled movements that occur in a sequence or pattern and leads to "relatively permanent changes in the capability for movement". Sleep has been shown to play an important role in the consolidation of a variety of motor sequence learning, involving a finger-to-thumb opposition task[11, 12], a serial reaction time task[28, 29], and a sequential finger-tapping task[2, 3, 7, 20]. The impact of sleep on motor learning has also been demonstrated using motor adaptation paradigms in which modifying movements is required to adjust changes in either sensory input or motor output[22, 25, 84, 126, 127]. Smith et al[25] demonstrated that a group of individuals deprived of sleep the night following practice of a rotary pursuit task demonstrated impaired performance at retest compared to a group of individuals not deprived of sleep. Further support for a relationship between sleep and adaptive motor learning has been provided by Huber et al[84] who found that after learning a motor-reaching adaptation task, performance improved following a night of sleep but not after an equal period of being awake.

The findings from the above mentioned studies build strong evidence that support sleep-dependent learning across several forms of motor tasks. Interestingly, the majority of motor tasks used to date to examine sleep-dependent off-line motor learning are relatively simple, and essentially consisted of key presses on a computer keyboard or moving a joystick. In addition, the performance of these tasks requires either motor sequence components (such as sequential finger tapping task), or motor adaptation components (such as motor-reaching adaptation task). Tasks performed in daily life often consist of both motor sequence components and motor adaptation components[1]. For example, most typical daily tasks, such as walking, climbing stairs, driving a car, or playing a sport, require people to perform a sequence of hand and leg movements accurately (i.e., motor sequence learning) and also require them to adapt to sensorimotor perturbations (i.e., motor adaptation). A recent study by Debas et al[87] demonstrated that off-line consolidation process following motor sequence learning (MSL) is different when compared to the off-line consolidation process following motor adaptation (MA) learning. While MSL consolidation is supported by increased neural activity within the corticostriatal system, increased neuronal activity within the corticocerebellar system is associated with MA consolidation. Interestingly, it has been found that factors enhancing simple motor skill learning do not generalize to complex motor skill learning[35, 36]. However, the effect of sleep was not considered in these studies[35, 36].

Only a few studies have attempted to examine the influence of task complexity on the process of sleep-dependent off-line motor learning[31, 33, 34]. Kuriyama et al[33] found that the more complex a task is, the larger the degree of off-line learning. Brawn and colleagues[34] provide evidence that the consolidation process during sleep occurs after learning a task requiring "adaptive behavior". In this study[34] participants practiced playing a video game, with reactions to different visual and auditory stimuli. The authors found that, after a full day of wakefulness the participants' performance on the video game deteriorated significantly, however, it recovered and stabilized following a night of sleep. Sleep did not enhance learning of this task; however, sleep did stabilize the performance on this task. In a recent study, Siengsukon and Al-Sharman [31] demonstrated that sleep selectively enhances learning of an explicit discrete task but not an explicit continuous task due to differences in tasks complexity.

In summary, all motor tasks which have been previously used to study sleep-dependent off-line motor learning have been limited to relatively simple motor tasks. Even those studies that examined the influence of task complexity on sleep-dependent off-line learning[33, 34] have utilized relatively simple tasks compared to the tasks performed in daily life. Importantly, these simple tasks have limited implication for rehabilitation. Most of the tasks clients practice and learn during rehabilitation are more complex, need a longer time to perform, require coordination between different body parts, and also require appropriate responses to environmental stimuli. It remains unclear whether a complex functional motor task will benefit from sleep to produce off-line motor skill enhancement.

This current study aims to build upon previous work demonstrating a beneficial effect of sleep for motor-sequence and motor adaptation learning by extending these investigations to explore the influence of sleep on learning a novel walking task in young adults. Based on studies[33, 34] that examined task complexity, we hypothesize that performance on a novel walking task will improve off-line after a period of sleep compared with a similar period of wakefulness in young, healthy individuals. The potential for sleep to enhance functional motor tasks has important implications for physical therapists. Many intervention programs involve patients learning new or re-learning motor skills to improve function and participation in daily life activities. This study attempts to examine if sleep is a critical factor that might hasten motor skill learning of a functional task.

2.3 Methods

Setting and Participants

Twenty-four healthy young individuals (mean age= 25.71, SD= 2.8, 13 women) were recruited to participate in this study. This study was performed in accordance with the University of Kansas Medical Center's (KUMC) Institutional Review Board. All participants provided written informed consent prior to participation in the study. No person was excluded on the basis of sex, race, or ethnicity. Participants were recruited at the University of Kansas Medical Center and the local community.

Participants were excluded if they presented with: untreated sleep disorders including sleep apnea and restless leg syndrome, uncontrolled depression, a history of psychiatric or neurological disorders, any orthopedic problems or gait deviations that prevented them from performing the study task, or scored below a 26 on the mini-mental status exam[128]. Participants were also excluded if worked a night shift, were a regular nappers or were extreme evening or morning-type persons assessed using the Morningness-Eveningness

Questionnaire (MEQ)[129]. Individuals were instructed to avoid strenuous activity along with avoiding caffeine, alcohol, and recreational drugs for 12 hours prior to and during testing.

To assess participants sleeping habits and schedule, individuals were asked to maintain a sleep log for a week prior to testing. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI)[130]. Depression was assessed using the Beck Depression Inventory (BDI)[131]. The Timed Up and Go test (TUG)[132, 133] was performed to assess the level of functional mobility for participants prior to practice and retention testing, and the Stanford Sleepiness Scale[134] was used to assess level of sleepiness prior to practice and retention testing. Age, gender, height, weight, and medical history data were also collected from eligible participants.

Task Description

A novel walking task was used in this study to examine the role of sleep in learning a functional motor task. The task consisted of walking around an irregular elliptical pathway, 97 feet long and 1.5 feet wide, marked by yellow tape (Figure 2.1). Participants were instructed to walk safely as quickly and accurately as possible and to avoid stepping on or over the colored tape. A gait-mat (Gait-Mat II™ system E.Q., Inc) 12.7 feet long was embedded within the walking path to assess spatio-temporal gait parameters. While walking over the gait-mat, participants were instructed to walk on a marked line, tandem-like walking in which the feet advance, one after the other, in a straight line. While walking around the pathway, participants were asked to perform a cognitive task. Participants were asked to verbally count backward by 7s starting from a randomly selected number between 293 and 299. Participants were instructed to pay equal attention for both tasks. The purpose of having participants walk in tandem on the gait-mat and verbally count backwards while walking around the pathway was to approximate walking in natural settings. Daily tasks often require the individual to walk while performing cognitive functions. In addition, people usually encounter different levels of walking difficulties. Thus, backward counting and transitioning between standard walking and tandem walking serve as valid representations of walking in natural settings[135 136].

Randomization

Participants were randomly assigned to either the sleep group (n=12, 7 women) or the no-sleep group (n=12, 6 women). All participants performed the novel walking task at two sessions, one practice session and a delayed retention test to assess off-line learning. Participants in the sleep group practiced the novel walking task at 8:00 p.m. (±1h) and then returned the following morning, following a night of sleep at home, at 8:00 a.m. (± 1h) for retention testing. Participants in the no-sleep group practiced the novel walking task at 8.00 a.m. (± 1h) and then returned the same day at 8:00 p.m. (±1h) for retention testing after going about their normal daily activities. At the practice session, each participant performed the novel walking task for 6 blocks (1 baseline block and 5 practice blocks). Each block consisted of five iterations of walking around the path. In order to familiarize the participants with the path, a baseline block consisted of walking around the path without cognitive calculations. Participants were allowed to rest between blocks if needed. To assess off-line motor learning, the retention test consisted of one block of walking around the path with cognitive calculations followed by one block of single walking. In total, participants completed 8 blocks of the novel walking task.

To ensure participants in the sleep group sleep during the night between practice and retention and those in the no-sleep condition do not sleep between practice and retention, an actigraph device was used. Between the practice and the retention session, participants were instructed to wear, on their dominant wrist, an actigraph (Respironics., Inc.). Movement data were collected, summated over 15-s epoch and converted to digital activity counts at 60 Hz. The Actiware software package (version 5.57) was used for sleep scoring. The actigraph data were not available for the first 8 participants (4 participants from each group) as it was available for the study later. Actigraph data for the sleep group were analyzed to objectively assess their sleep quality and quantity, including total sleep time, sleep latency, sleep efficiency, and number of awakenings.

Outcome Measure

The main outcome variable of interest for this study was time to walk around the novel path. Time required to walk around the path was recorded for each block using a stopwatch. The spatio-temporal gait parameters, including tandem velocity, tandem step length, and tandem step time were also collected using the gait-mat. In standard and tandem gait, these spatio-temporal gait parameters have been used frequently to assess overall gait performance, fall risk, and capacity for community ambulation[137-139]. Further, gait velocity has been found to be a sensitive measure for assessing the effectiveness of different rehabilitation interventions[140]. Individual data were averaged by group for each of the outcome measures to represent performance for blocks 2-6 during acquisition practice and at a delayed retention test.

Statistical Analyses

Statistical analyses were performed with Statistical Package for the Social Sciences software (SPSS 20.00). One way ANOVAs were used to assess differences in participants' characteristics between groups. Acquisition performance was examined using a two factor [Group (sleep, no-sleep) X Block (2, 3, 4, 5, 6)] repeated measures ANOVAs with time around the path, tandem velocity, tandem step length, and tandem step time as dependent variables. Off-line learning was assessed using a two factor [Group (sleep, no-sleep) X Block (last practice block, retention block] repeated measures ANOVAs with time around the path, tandem velocity, tandem step length ,and tandem step time as dependent variables. Effect size (ES)[141] was calculated for the main outcome measure (by subtracting the mean saving score of the two groups and dividing this by the pooled standard deviation) to assess a real and meaningful difference between the sleep and no-sleep young participants. To assess the relationship between off-line learning and sleep quality and quantity in the sleep group, correlations were conducted between the off-line learning score of the main outcome measure and objective (actigraph data) and subjective (PSQI, sleep log) sleep measures.

Role of the Funding Source

The study was supported by a grant from the Kansas Partners in Progress grant (KPIP), Kansas, USA. Funding from the KPIP was used for participants' reimbursements.

2.4 Results

Subject Characteristics

There were no differences between the sleep and the no-sleep group in term of age, amount of sleep the week prior to practice, height, and weight. Furthermore, there were no differences between groups for PSQI, the BDI, and functional mobility level at practice or at retention testing, or the level of sleepiness at practice or at retention testing. No subjects were excluded based on the Morningness-Eveningness Questionnaire (MEQ). Table 2.1 shows the group characteristics. The actigraphic data indicated that none of the participants in the no-sleep group slept between the practice session and the retention testing. Table 2.2 summarizes actigraphic data (total sleep time, sleep latency, sleep efficiency, and awakenings number) for the sleep group.

Acquisition performance

Young adults demonstrated a practice-related improvement in performance as shown by the main effect of Block for each of the outcome measures ($F_{4,88}$=39.17, p<0.001, time around the walking path; $F_{4,88}$=45.22, p<0.001, tandem velocity; $F_{4,88}$=31.52, p<0.001; tandem step length; $F_{4,88}$=76.7, p<0.001, tandem step time, Figures 2.2.a, 2.2.b, 2.2.c, 2.2.d, respectively). The extent of improvement in performance across blocks revealed no significant difference between the sleep and the no-sleep groups as indicated by the main effect of Group for time around the walking path ($F_{1,22}$=0.56, p=0.46), tandem velocity ($F_{1,22}$=1.17, p=0.29), tandem step length ($F_{1,22}$=0.169, p=0.68), and tandem step time ($F_{1,22}$=0.54, p=0.47). The interaction of Block X Group was not significant for all of the outcome measures ($F_{4, 88}$=0.24, p=0.91, time around the walking path; $F_{4, 88}$=0. 68, p=0.60, tandem velocity; $F_{4, 88}$=1.51, p=0.21, tandem step length; $F_{4, 88}$=0.28, p=0.90, tandem step time). These results suggest that regardless of the time-of-day, performance improved similarly with practice in both groups.

Off-line learning

There was a main effect of Block for all outcome measures ($F_{1,22}$=6.7, p=0.02, time around the walking path; $F_{1,22}$=5.20, p=0.03, tandem velocity; $F_{1,22}$=33.89, p<0.001, tandem step length; $F_{1,22}$=5.35, p=0.03, tandem step time). This latter effects differed across groups as indicated by a significant Group X Block interaction for time around the walking path ($F_{1,22}$=13.51, p=0.001), tandem velocity ($F_{1,22}$=8.44, p=0.008), tandem step length ($F_{1,22}$=35.94, p<0.001), and tandem step time ($F_{1,22}$=25.54, p<0.001).

To understand these interactions, one-way ANOVAs were utilized to compare the score for each of the outcome measures after sleep with those scores after a wake interval.

Compared with the no-sleep group, participants in the sleep group demonstrated a significant decrease in the time required to walk around the path from last practice block to retention block ($F_{1,22}$=13.50, p=0.001, Figure 2.3.a); a significant increase in their tandem velocity ($F_{1,22}$=32.7, p<0.001, Figure 2.3.b), a significant increase in their tandem step length ($F_{1,22}$=35.9, p<0.001, Figure 2.3.c), and a significant decrease in step time ($F_{1,22}$=25.54, p<0.001, Figure 2.3.d). A large effect size of 1.6 suggests a real and meaningful difference between the amounts of changes in the time required to walk around the path (main outcome measure) that were associated the young individuals who slept compared to those who stayed awake.

Correlations between Sleep Measures and Off-line Learning

Sleep-dependent off-line motor learning score for time around the walking path was significantly correlated with sleep efficiency (r = 0.97, p<0.001), number of awakenings (r = -0.79, p=0.001), and PSQI (r = -0.81, p=0.008). A moderate but not significant correlations was found between off-line learning and sleep latency (r = -0.59, p=0.08) and average sleep one week prior to practice (r = 0.55, p=0.12), Table 2.3.

2.5 Discussion

This study is the first to examine the role of sleep in learning a functional motor task. Young participants who slept after practicing the novel walking task demonstrated a significant off-line improvement in performance on all walking outcome measures, while those participants who stayed awake failed to demonstrate off-line learning. The findings of this study demonstrate that sleep-dependent off-line learning is not limited to simple motor tasks, but also extends to a functional motor task that is complex and has direct implications for physical therapists.

This study appears to support Kuriyama's complexity theory (2004) which proposes that sleep enhances learning the tasks that are more complex. Also, the results from the current study are largely confirmed the results of Brown et al[34] who demonstrated consolidation during sleep for a "multimodal sensorimotor" skill (i.e., playing a video game). However, the sequential finger tapping task used by Kuriyama et al[33] and the video game used by Brown et al[34] have limited "real life" applications for learning or relearning functional skills. In the current study we found that sleep promotes learning of the novel walking task which is a functionally and clinically-relevant task, performed by most people every day. This novel walking task required an ability to control a sequence of limb movements that produce gait and an ability to walk quickly and accurately within a complex environment (i.e., the narrow pathway, transition between standard and tandem gait, and the cognitive task). Our study proved that sleep enhances learning a task that is not only complex but also clinically-relevant (i.e., has direct implication for rehabilitation).

Although the time-of-day of testing was different between groups by virtue of the study design, we believe that a time-of-day effect is not a possible explanation of our findings. Our data indicate that both the sleep and the no-sleep groups demonstrated improvements in performance across practice but did not perform significantly different from each other regardless of the time of day the practice session occurred. This suggests that the sleep and the no-sleep groups performed similarly to each other despite practicing at different times of day. In addition, the level of sleepiness and the level of functional mobility as determined by the Stanford Sleepiness Scale and Timed Up and Go test, respectively, did not reveal group differences at practice or at retention regardless of time of day testing occurred. Therefore, this study demonstrated that sleep has a significant positive impact on learning a functional motor task that is not explained by factors related to time of the day.

A sleep lab was not utilized in this study. Because of that fact, one of the study' limitations was the difficulty monitoring the amount and the quality of sleep that participants obtained during the night between practice and retention testing. Despite this limitation, we believe having participants sleep at home suggests that sleep-dependent off-line skill learning can occur in a natural environment. Our work attempted to monitor the amount and the quality of sleep by having participants maintain a sleep log for a week prior to the first session; in addition, the PSQI was used to index sleep quality of our participants. The data from this study shows no difference in average sleep one week prior to participating in the study or scores on the PSQI between groups. Furthermore, actigraph date indicate that participants in the no-sleep did not sleep between practice and retention testing and participants in the sleep group slept well during the night between practice and retention testing. Participants in the sleep group slept in average seven hours the night between practice and retention testing, with eighty-eight (87.9%) sleep efficiency, five minutes sleep latency and brief number of awakenings. These findings are comparable with those reported in previous studies that have examined sleep quality and quantity in young, healthy individuals (for review see Hirshkowitz et al[67]).

Understanding the role of sleep in learning functional tasks has important implications for physical therapists. As across settings of practice, physical therapists teach clients skills and clients have to learn how to perform these skills. It has been found that the amount and type of practice are the most important factors in motor skill training[142]. Therefore, during rehabilitation session, physical therapists focused on the need for practice and repetition of motor actions to improve the individual's participation in daily activities. Interestingly, the results of the current study suggest that sleep could be an important factor to consider when structuring rehabilitation sessions for motor skill improvement. It is possible to improve the clinical outcomes of rehabilitation by integration of sleep into clinical interventions. We believe it is important to provide physical therapists with recommendations to incorporate sleep as an important factor for motor learning. The findings of this study could impact how physical therapists design the therapy sessions. Physical therapists may need to perform therapy sessions in the evening or late day before sleeping. Instead, physical therapists may need to encourage napping following therapy session, as performance on simple motor tasks in young participants has been found to improve after a short nap of 60-90 minutes[10, 20, 78 79-81]. More future studies would be needed to confirm whether a short nap is enough to produce off-line motor learning of a functional task.

The current study demonstrates significant correlations between sleep quality (sleep efficiency, number of awakenings and the PSQI) and sleep-dependent off-line learning. These findings support the results from a recent animal study that revealed that a certain amount of sleep continuity (i.e., undisrupted sleep) is required for memory consolidation[143]. Furthermore, these findings agree with Djonlagic and colleagues[144] who demonstrated that continuous periods of sleep in human is an important factor to ensure optimal sleep-dependent consolidation and fragmented sleep by frequent arousals impairs off-line learning. These findings that sleep quality is an important factor for the process of off-line motor learning is very important as many young individuals who undergo rehabilitation are frequently presented with poor sleep quality and sleep disorders which might interfere with the process of sleep-dependent motor learning[145-148]. For example, sleep disturbance are frequently recognized in people with chronic low back pain[148], shoulder pain[146], and after lower limb amputation[145]. Furthermore, in many medical disorders such as sleep apnea and alcoholism sleep continuity is disrupted[143] leading to off-line consolidation impairment. As a result therapists should be educated to recognize and address sleep issues in individuals undergoing therapy and should consider encouraging adequate sleep. Sleep quality assessment should be considered as an essential part in the routine exam. More importantly, physical therapists need to be educated about normal sleep cycle, sleep disorders, and sleep assessment methods. The ability of therapists to recognize sleep disorders in clients would enable those clients to be referred to the appropriate medical personnel for treatment.

In summary, this study provides the first evidence that sleep enhances learning a complex functional motor skill that has direct applications for rehabilitation. The findings from this work suggest that during rehabilitation sleep should be considered as an important factor that enhances motor learning. Different strategies need to be considered by therapists to ensure the beneficial role of sleep on the rehabilitation sessions. Emphasis should be placed on addressing sleep disorders and on ensuring adequate sleep for individuals who go through rehabilitation. Future research is needed to investigate the role of sleep in learning functional tasks in older adults and following neurological disorders.

2.6 Tables

Groups	Age	MMSE	SSS1	SSS2	Avg. Sleep	PSQI	Weight	Height	TUG1	TUG2	BDI
Sleep	**25.6 (3.2)**	**29.8 (0.6)**	**1.5 (0.5)**	**1.6 (0.7)**	**7.20 (0.8)**	**2.5 (1.6)**	**70.3 (10.3)**	**171.6 (9.3)**	**7.71 (0.7)**	**7.8 (0.6)**	**2.00 (1.04)**
No-Sleep	**25.8 (2.6)**	**29.8 (0.4)**	**1.4 (0.7)**	**1.58 (0.7)**	**7.31 (0.6)**	**2.7 (1.7)**	**71.2 (8.5)**	**173.1 (9.7)**	**7.76 (0.5)**	**7.9 (0.7)**	**2.7 (1.3)**
p -value	**0.83**	**0.69**	**0.74**	**0.76**	**0.70**	**0.70**	**0.84**	**0.72**	**0.80**	**0.62**	**0.18**

Table 2.1. Descriptive information. Data are mean (standard deviation). MMSE= Mini Mental Status Examination; SSS1= Stanford Sleepiness Scale taken at practice session; SSS2= Stanford Sleepiness Scale taken at retention testing; PSQI= Pittsburgh Sleep Quality Index; Ave. Sleep= Average amount of sleep participants had the week prior to testing demonstrated by sleep log. TUG1= Timed Up and Go taken at practice session; TUG2= Timed Up and Go taken at retention session; BDI= Beck Depression Inventory.

Sleep Measures (Actigraph data)	Total Sleep Time (hours)	Sleep Latency (minutes)	Sleep Efficiency (percent)	Number of Awakenings
	7.1(0.5)	**5.4 (1.4)**	**87.9 (1.1)**	**18.3 (3.8)**

Table 2.2. Actigraphic data of sleep measures for 8 participants in the sleep group. Data are mean (standard deviation). Total Sleep Time= Time between sleep onset and final awake time; Sleep Latency= Time between bed time and sleep onset; Sleep Efficiency= Time of sleep/total time in bed*100; Number of Awakenings = Number of awakes during a night of sleep between practice and retention testing.

		Sleep Efficiency	Number of Awakenings	PSQI	Sleep Latency	Avg. Sleep	Total Sleep Time
Off-line Learning	Pearson r	0.97	-0.79	-0.81	-0.59	0.55	0.43
	p-Value	<0.001	0.001	0.008	0.08	0.12	0.29

Table 2.3. Correlations between off-line learning score and sleep measures for the sleep group.

2.7 Figure Legends

<u>Figure 2.1.</u>The walking pathway. The functional motor task consisted of walking around an irregular elliptical pathway. A gait-mat (Gait-mat II™ system E.Q., Inc) 12.7 feet long was embedded within the walking path to assess spatio-temporal gait parameters. Participants were instructed to walk safely as quickly and accurately as possible while performing a cognitive task. While walking over the gait-mat, participants were instructed to walk on a marked line in tandem.

<u>Figure 2.2.a.</u> Performance changes across the training blocks (block 2-6) demonstrated by time around the walking path. Error bars are SEM.

<u>Figure 2.2.b.</u> Performance changes across the training blocks (block 2-6) demonstrated by tandem velocity across gait-mat. Error bars are SEM.

<u>Figure 2.2.c.</u> Performance changes across the training blocks (block 2-6) demonstrated by tandem step length across gait-mat. Error bars are SEM.

<u>Figure 2.2.d.</u> Performance changes across the training blocks (block 2-6) demonstrated by tandem step time across gait-mat. Error bars are SEM.

Figure 2.3.a. Off-line learning scores or change on performance on the novel walking task between the last practice block and the retention testing for the sleep and no-sleep groups, demonstrated by time around the walking path. Negative values indicate better performance. Error bars are SEM. ****p <0.001**

Figure 2.3.b. Off-line learning scores or change on performance on the novel walking task between the last practice block and the retention testing for the sleep and no-sleep groups, demonstrated by tandem velocity across gait-mat. Error bars are SEM. ****p <0.001**

Figure 2.3.c. Off-line learning scores or change on performance on the novel walking task between the last practice block and the retention testing for the sleep and no-sleep groups, demonstrated by tandem step length across gait-mat. Error bars are SEM. ****p <0.001**

Figure 2.3.d. Off-line learning scores or change on performance on the novel walking task between the last practice block and the retention testing for the sleep and no-sleep groups, demonstrated by tandem step time across gait-mat. Error bars are SEM. ****p <0.001**

Figure 2.1

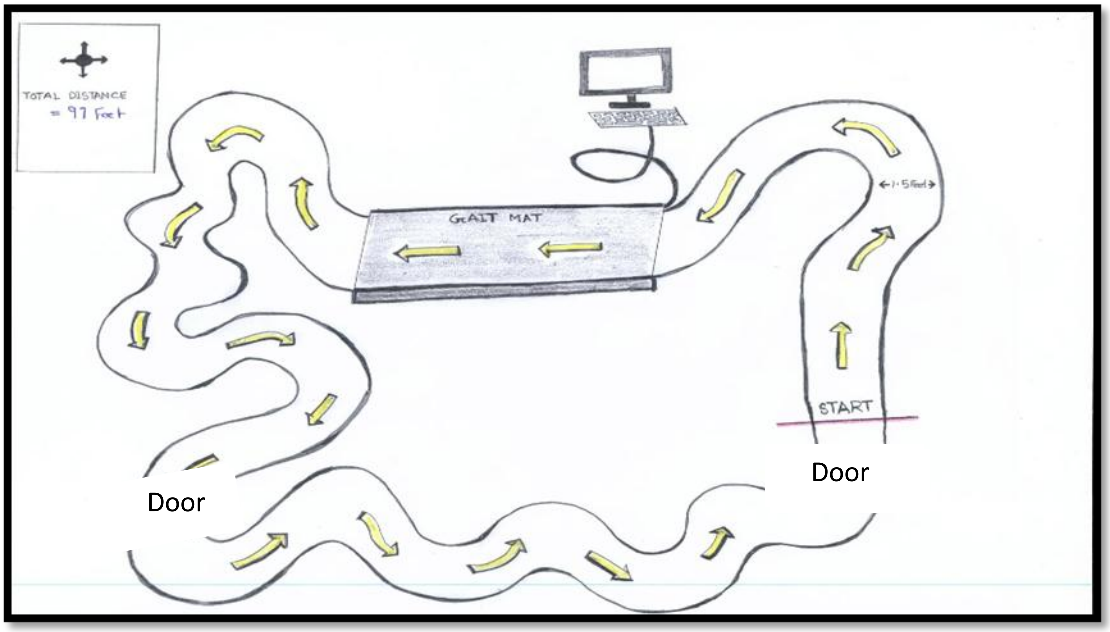


Figure 2.2.a

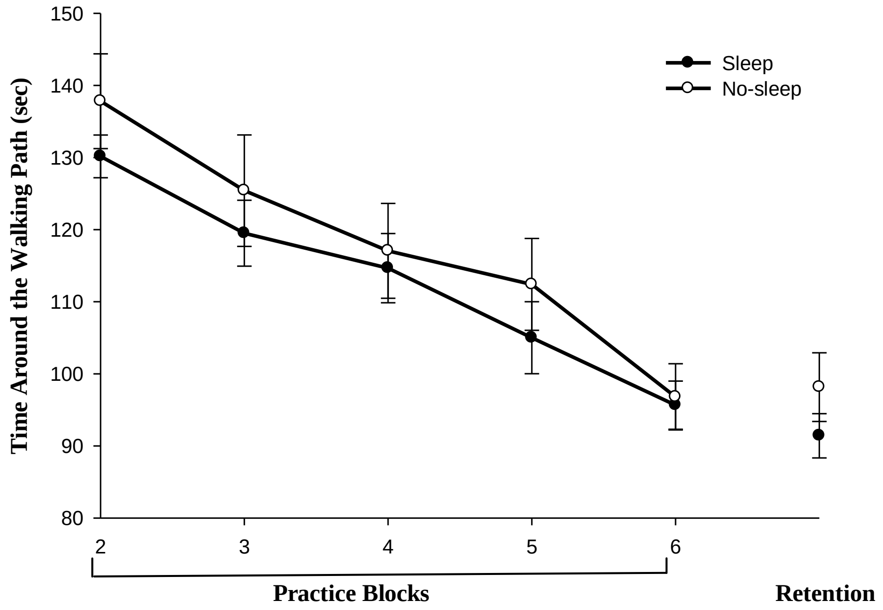


Figure 2.2.b

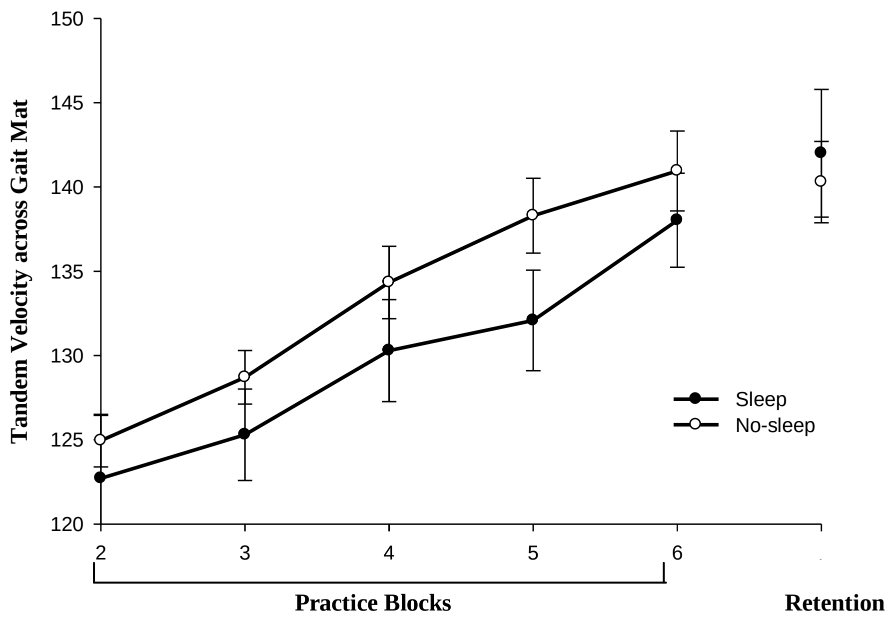
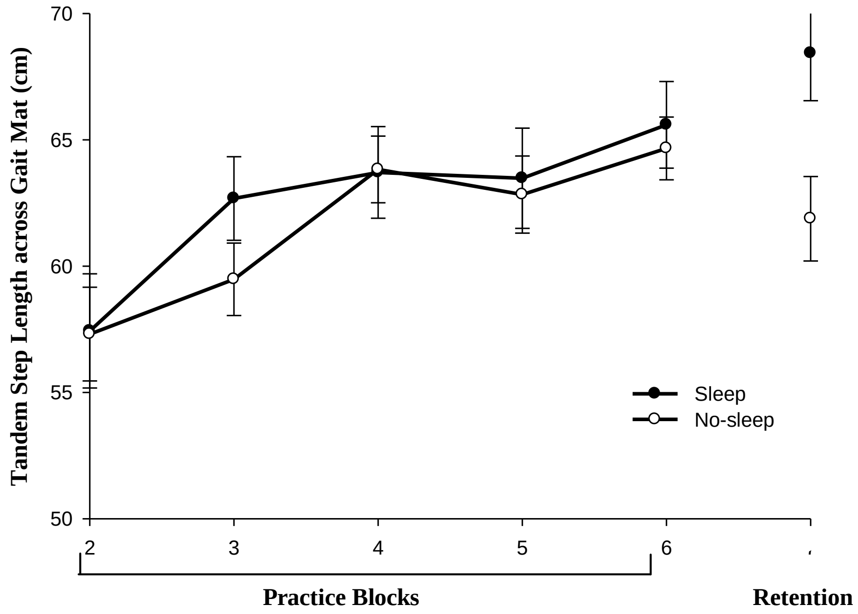


Figure 2.2.c



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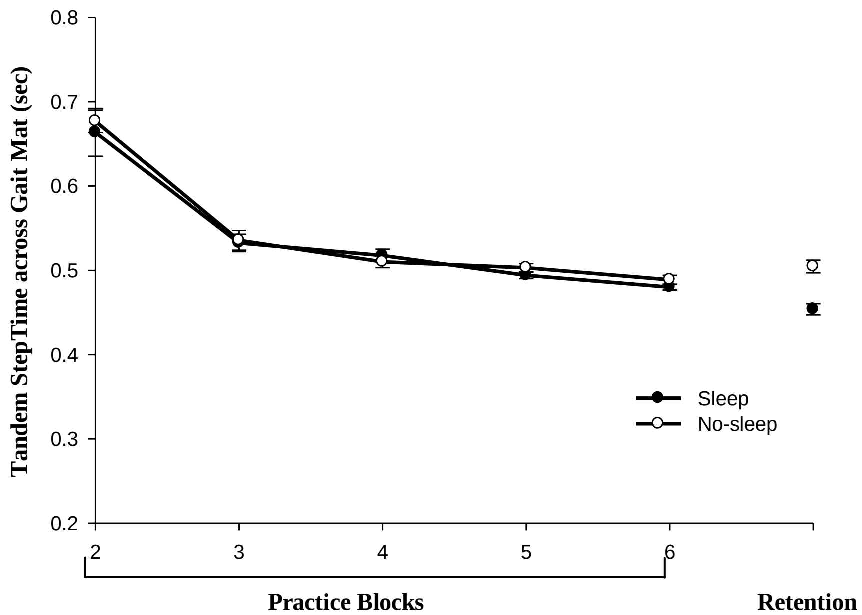


Figure 2.3.a

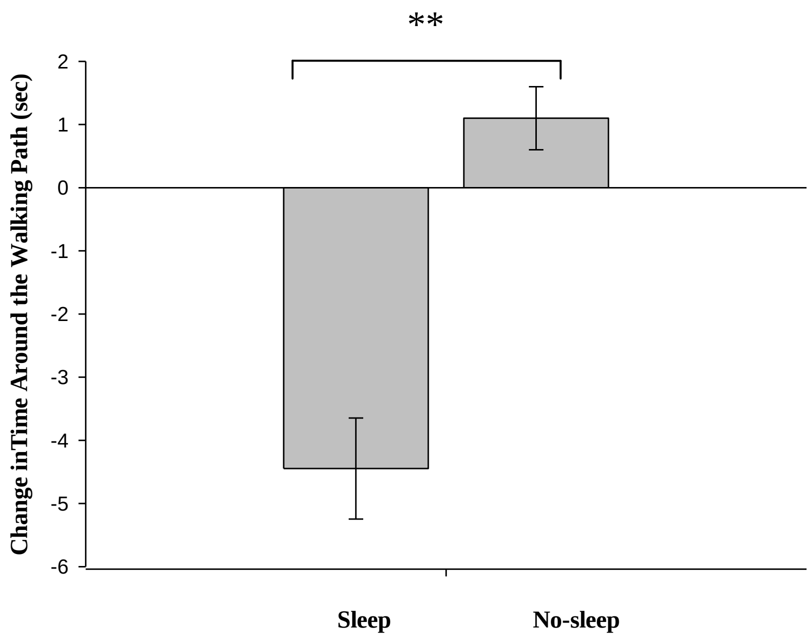


Figure 2.3.b

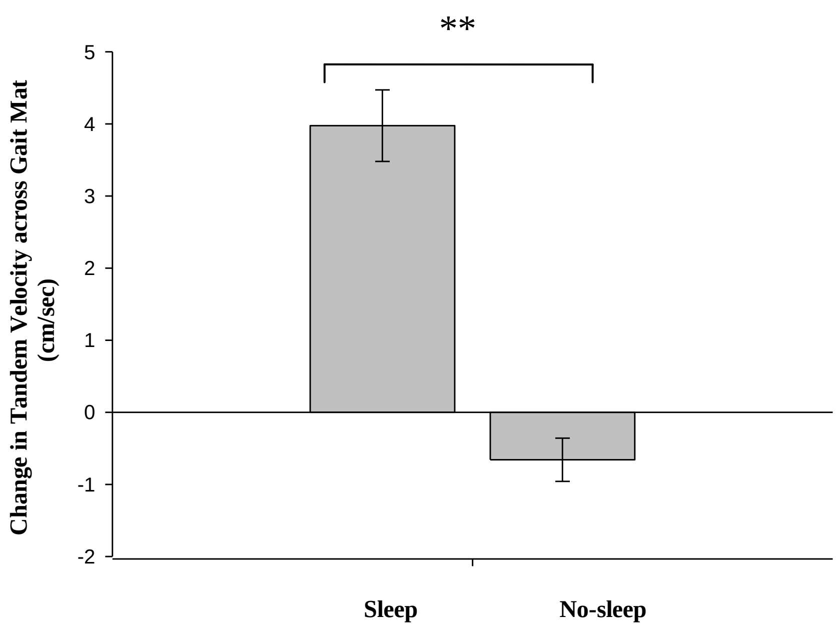


Figure 2.3.c

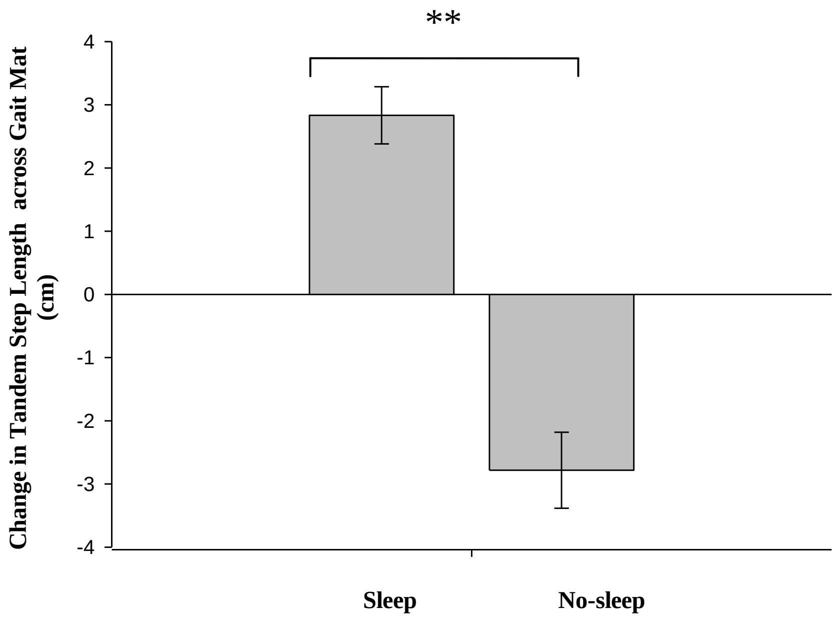
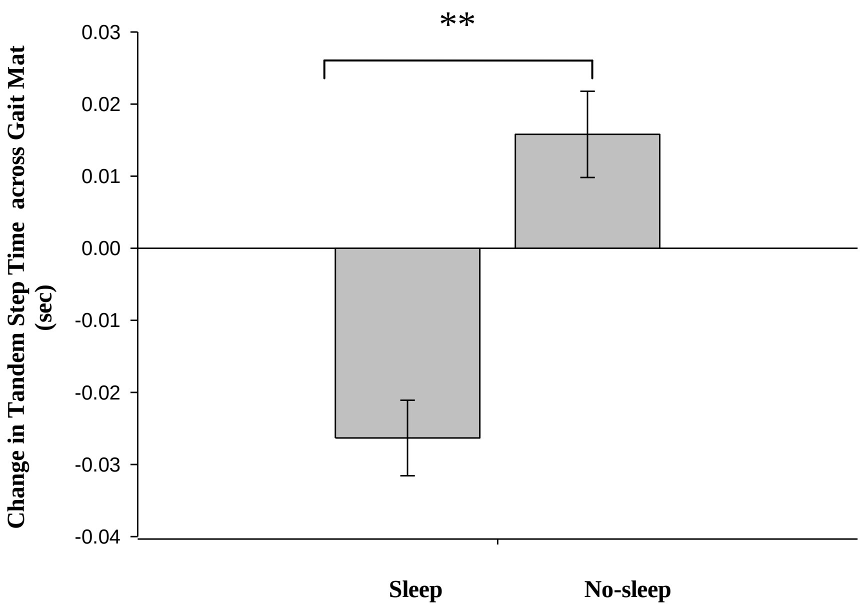


Figure 2.3.d



Chapter 3 Preface

Chapter 2 provides evidence that sleep enhances learning a functional motor task in young, healthy individuals. Chapter 3 extends our work and assessed sleep-dependent off-line learning on the same functionally task in middle-aged and older adults. Furthermore, in Chapter 3 the whole set of data (i.e., young, middle-aged, and older adults) was utilized to assess aged-related changes in sleep-dependent off-line learning of a functional motor task.

Chapter 3

Performance on a Functional Motor Task is Enhanced by Sleep in Middle-Aged and Older Adults

This work will be submitted for publication to *Journal of the American Geriatrics Society.*

3.1 Abstract

Background/Objective. Mounting evidence demonstrates that sleep enhances the learning of simple motor skills in young adults. Only a few recent studies have investigated sleep-dependent off-line motor learning in older adults. These studies all used simple computer-based motor tasks and offered mixed conclusions. It remains unknown whether sleep enhances learning a functional motor task in middle-aged and older individuals. The purpose of this study was to examine whether, after practicing a functional motor task, sleep will enhance motor performance in middle-aged and older adults.

Design. A prospective, cross-sectional, repeated-measure design.

Setting. The study was conducted at the University of Kansas Medical Center.

Participants: Twenty middle-aged and 20 older individuals participated in this study.

Method/Measurements. Participants in each age group were randomly assigned to either the sleep condition or the no-sleep condition. Participants in the sleep condition practiced a functional motor task in the evening and returned the following morning for a retest. Participants in the no-sleep condition practiced the functional task in the morning and returned the same day in the evening for a retest. Outcome measures included time around the walking path and spatiotemporal gait parameters.

Results. Only the middle-aged and older adults in the sleep condition demonstrated significant off-line improvement in performance on the novel walking task. For both age groups, post-training sleep resulted in a significant decrease in the time around the walking path, an increase in tandem velocity, an increase in tandem step length, and a decrease in tandem step time. No significant difference in sleep-dependent off-line learning was found between middle-aged and older adults. The middle-aged and older adults in the no-sleep condition failed to demonstrate off-line motor learning of the functional task.

Conclusions. This is the first study that provides evidence that sleep facilitates learning a clinically-relevant functional motor task in middle-aged and older adults. Since the bulk of the world's productivity is in the hands of the middle-aged, memory and learning need to be optimized in this age group. Further, the proportion of older adults is increasing in the United States as well as all over the world, investigating factors that enhance learning and memory consolidation, such as sleep, in older individuals is critical.

Key words: sleep, off-learning, functional task, rehabilitation

3.2 Introduction

Sleep changes with advancing age[66, 67, 77, 94]. Aging is associated with changes in sleep quality, pattern, and distribution[22, 36, 77, 95-102]. In a large epidemiological study of more than 9,000 older adults aged 65 years and older, more than 80% reported at least one sleep problem, such as waking during the night and waking without feeling rested in the morning[115]. Only 12% of the sample reported no sleep complaints[115]. Studies have found that sleep efficiency continues to decrease in older adults after age 65[116]. The average sleep duration is significantly shorter in middle-aged and older adults when compared to young individuals[149]. Moreover, evidence suggests that sleep becomes more fragmented with age; that is, older individuals experience more frequent arousal from sleep[66, 77, 95, 96, 103].

Studies also report changes in sleep architecture with aging[66, 67, 77, 103-105]. Total sleep time, time spent in rapid eye movement (REM) sleep, and time spent in slow wave sleep (SWS) declined with age[150-152]. Time spent in SWS decreases 2 percent per decade up to 65 years of age and then becomes constant. The mean percentage of SWS decreases from 18.9% in young adults to 3.4% in middle adulthood (ages 36-50 years)[153]. REM sleep decreases significantly in middle-aged adults (ages 40-59 years) after which only small further reductions are noted[67]. On the other hand, time spent in stage 2 non-REM appears to increase across an adult's life span[150]. Studies also report a reduction in the number, density, and duration of sleep spindles, which are the prominent electrophysiological event in Stage 2 non-REM sleep, with advancing age[107, 154]. Overall, many changes in the quality, quantity and architecture of sleep are seen with advancing age.

Sleep has an important role in motor learning and memory consolidation in young, healthy individuals[5, 15, 16, 64, 91, 155]. Memory consolidation refers to a process in which motor skill performance is either stabilized or enhanced "*off-line*" without further practice[20, 28, 51]. While sleep has been demonstrated to have an important role in motor learning and memory consolidation in young individuals[1-3, 11, 156], research examining sleep-dependent off-line motor learning in older adults offers mixed conclusions[22, 28, 35-39]. Older adults fail to benefit from sleep to enhance their performance on a continuous tracking task[36, 37], or on explicit and implicit versions of a serial reaction time task (SRTT)[35]. Spencer et al[35] suggest that the process of sleep-dependent off-line learning is impaired with advancing age.

Studies[35-38] suggest that changes in sleep architecture typically experienced by older individuals limit the beneficial role of sleep to produce off-line motor learning. Evidence suggests that stage 2 non-REM[3], REM sleep[11], or a combination of the two stages are important for the consolidation of simple motor tasks in young, healthy individuals. Specifically, studies found that sleep spindles play an important role in sleep-dependent off-line memory consolidation[81, 89, 90]. Therefore, a reduction in the time spent in REM sleep and a reduction in the number of sleep spindles are possible reasons to explain why older adults fail to demonstrate sleep-dependent off-line motor learning.

While few studies find that older adults fail to demonstrate sleep-dependent off-line improvement[35-37], other studies suggest the opposite[22, 39]. Peter et al[22] compared sleep-dependent off-line learning in young and older participants after practicing a pursuit rotor task. Both the young and older groups showed significant off-line improvement in performance on the pursuit task after a 1-week delay; however, compared to the older group, young individuals demonstrated a larger improvement in performance at retest. Stage 2 sleep spindles density increased from baseline to retention testing in both the young and the older groups, though these results failed to reach significant levels in the older group[22].

In another study that demonstrates older adults benefit from sleep to promote motor skill learning, Tucker et al[39] assessed the off-line improvement in performance of older and young adults on a sequential finger tapping task. Older participants who slept after practicing the task demonstrated a stabilization of their performance at the beginning of the retest session ("immediate off-line improvement") and demonstrated a significant improvement in performance by the end of the retest session ("plateau off-line improvement"). Conversely, participants who stayed awake showed a 22% decline in performance at the beginning of the retest session and showed a small, non-significant improvement at the end of the retest session. Therefore, studies assessing sleep-dependent off-line motor learning in older adults have provided mixed results, and the role of sleep in off-line motor learning in older adults remains an active topic of debate. Due to multiple tasks and methodological differences, it is very difficult to elucidate the reasons behind such conflicting results.

In addition to the mixed conclusions about the role of sleep in off-line motor skill learning in older adults, only one study by Wilson et al[38] has assessed sleep-dependent off-line motor learning in middle-aged individuals. In this later study[38] middle-aged adults demonstrated sleep-dependent off-line motor learning on a SRTT. However, the magnitude of sleep-dependent improvement in performance in middle-aged adults was less, compared to young individuals. Considering that sleep architecture begins to change during midlife, it is important to study how these changes affect the process of sleep-dependent off-line learning in this age group. Therefore, more studies are needed to examine the role of sleep in motor learning in middle-aged adults.

A common feature of the previous studies that assessed sleep-dependent off-line motor learning in middle-age and older adults is that all these studies utilized simple fine motor tasks conducted on a computer. Most of the tasks performed in everyday life such as walking, driving, dancing, and playing sports are more complex and require coordination between different body parts to be performed successfully. It is currently unknown if the findings from these fine motor tasks will generalize to a functionally relevant gross motor task that has important implications for everyday activities and for rehabilitation.

In young adults it has been found that complex motor tasks undergo more sleep-dependent off-line performance enhancement when compare to simple motor tasks[31, 33, 34]. For example, Kuriyama et al[33] assessed the role of sleep in off-line motor learning for different complexity levels of a finger tapping task and found that sleep provides the greatest improvement in performance for the most difficult version of this task. However, this complex task is still a computer-based motor task that has limited implication in daily life. Interestingly, a study by Wilhelm et al[82] found that when the young participants expected to be retested at the retention session, sleep resulted in the largest degree of performance improvement on a finger-sequence tapping task. Accordingly, the authors[82] suggest that sleep provides more benefits for memories that are relevant for an "individual's future". Therefore, it can be proposed that sleep-dependent off-line motor learning in middle-aged and older adults can be maximized by choosing a task that is more complex and relevant to an individual's life.

Recently we found that sleep enhances learning a functional motor task in young adults[157]. This current study seeks to examine the role of sleep in learning the same functional motor task in middle-aged and older adults. We hypothesized that performance on the functional motor task will improve off-line after a period of sleep compared with performance after a similar period of wakefulness in middle-aged and older individuals.

Since the responsibility of leadership and productivity is largely in the hands of the middle-aged[158], memory and learning need to be optimized in this age group. Furthermore, the proportion of older adults is increasing faster in the United States and all over the world than other age groups[158]. It has been estimated that the older population will increase from 35 million to 71 million between 2000 and 2030. Importantly, older adults require more medical services than young adults; thus, their impact on the health system is highly significant. Approximately 500,000 Medicare patients are treated in inpatient rehabilitation facilities

(IRF) across the United States annually[122]. During rehabilitation, middle-aged and older adults need to learn new or relearn old skills such as learning how to perform correct exercise programs for given disabilities. It is critical to understand whether sleep enhances learning motor tasks that are functionally and clinically-relevant in middle-aged and older adults.

3.3 Methods

Participants

Twenty middle-aged (48±3.66 years of age) and 20 older (70.4±3.8 years of age) adults participated in this study. Individuals who presented with untreated sleep disorders including sleep apnea and restless leg syndrome, uncontrolled depression, a history of psychiatric or neurological disorders, any orthopedic problems or gait deviations that made performing the study task difficult, or scored below a 26 on the mini-mental status exam[128] were excluded. We also excluded participants who worked a night shift, were regular nappers, or individuals who were identified as extreme evening or morning-type persons by the Morningness-Eveningness Questionnaire (MEQ)[129]. This study was approved by the Institutional Review Board at the University of Kansas Medical Center's (KUMC). Written informed consent was obtained from all participants prior to participation in the study. Participants were recruited from the University of Kansas Medical Center and the local community. For 12 hours prior to and during the study, participants were instructed not to engage in strenuous activities or consume caffeine, alcohol, or recreational drugs.

To assess sleep quality, participants were asked to complete the Pittsburgh Sleep Quality Index (PSQI)[130] and to maintain a daily sleep log for a week prior to testing. To assess participants' level of sleepiness prior to practice and retention testing, participants completed the Stanford Sleepiness Scale[134]. Depression was assessed using the Beck

Depression Inventory (BDI)[131]. To assess the level of functional mobility prior to practice and retention testing, the Timed Up and Go test (TUG)[132, 133] was performed. Other demographic information including age, gender, height, weight, and medical history was collected from participants.

Functional Motor Task

The task utilized in this study to assess sleep-dependent off-line motor skill learning consisted of a novel walking task. This task is identical to the task we used in our previous work demonstrating the role of sleep in learning a functional motor task in young adults[157]. The pathway for the walking task was an irregular elliptical pathway, 97 feet long and 1.5 feet wide, marked by yellow tape. Each participant was instructed to walk safely around the walking path as quickly and accurately as possible and to avoid stepping on or over the colored tape. To assess spatio-temporal gait parameters, a gait-mat (Gait-Mat II™ system E.Q., Inc.) 12.7 feet long was embedded within the walking path. A single, straight line was marked on the gait-mat and participants were instructed to do tandem-like walking in which the feet advance, one after the other. Participants were also instructed to perform a mental cognitive task (count backward by 7s starting from a randomly selected number between 293 and 299) while walking around the pathway. Counting backwards serves as a valid representation of walking in natural settings[135 136].

Procedure

Participants in the middle-aged and older age groups were randomized into 2 conditions: the sleep condition and the no-sleep condition. Participants in the sleep condition practiced the novel walking task in the evening (between 7 and 8 pm) and underwent retention testing the next morning (between 7 and 8 am), while participants in the no-sleep condition practiced the walking task in the morning (between 7 and 8am) and underwent retention testing in the evening of the same day (between 7 and 8pm). During the practice session, participants completed 6 blocks of walking around the path (one baseline block and 5 practice blocks). In the baseline block participants were instructed to walk without performing the cognitive calculation in order to become familiar with the path. Rests between practice blocks were allowed if needed. The retention test consisted of one block of walking around the path with cognitive calculations followed by another block of walking without performing the cognitive calculation. Each block in practice and retention consisted of five iterations of walking around the path. In total, participants completed 8 blocks (40 times around the path) of the novel walking task.

Between practice and retention testing, a subgroup of participants in each age group were asked to wear an actigraph (Respironics., Inc.) on their dominant wrist. Actigraph data was collected for 12 participants in the older age group (6 participants in each condition) and 16 participants in the middle-aged group (8 participants in each condition). Movement data were collected summated over 15-s epoch and converted to digital activity counts at 60 Hz. Sleep measures were assessed using Actiware Software Package (version 5.57)

Outcome Measures

The time required to walk around the path was the main outcome measure of interest and was recorded for each block using a stopwatch. Tandem velocity, tandem step length, and tandem step time were also collected using the gait-mat software. These spatiotemporal gait parameters have been used to assess gait performance as well as risk of fall, fear of falling, and community ambulation ability[137, 138]. For each of the outcome measures, individual data were averaged by condition to represent performance for blocks 2-6 during acquisition practice and a delayed retention test. Sleep measures including total sleep time, sleep latency (i.e., time between lights off and sleep onset), sleep efficiency (i.e., total sleep time/time in bed (from lights off to lights on)*100), and number of awakenings were objectively assessed for the sleep conditions in each age group, using the actigraph data.

Statistical Analyses

For each of the age groups, one way ANOVAs were used to assess differences between characteristics of the sleep and no-sleep conditions. A two-factor [Condition (sleep, no-sleep) X Block (2, 3, 4, 5, 6)] repeated-measures ANOVA was used to assess performance acquisition during practice in older and middle-aged group. Time around the path, tandem velocity, tandem step length, and tandem step time were used as dependent variables.

Off-line learning was assessed using a two-factor [Condition (sleep, no-sleep) X Block [last practice block, first retention block] repeated-measures ANOVA with time around the path, tandem velocity, tandem step length, and tandem step time as dependent variables for each age group. Effect sizes (ES) were calculated for the main outcome measure in both age groups to examine if the differences between the sleep and the no-sleep conditions were clinically meaningful[141].

3.5 Results

Subject Characteristics

For the middle and older age groups, there were no differences between the sleep and no-sleep conditions in any of the following measures: age, amount of sleep the week prior to practice, height, and weight. Furthermore, there were no differences between the sleep and the no-sleep conditions in term of sleep quality, depression, and functional mobility level at practice or at retention testing, or the level of sleepiness at practice or at retention testing.

Table 3.1 shows the sleep and the no-sleep characteristics for both middle-aged and older adults.

The actigraphic data indicated that for both age groups, none of the participants monitored in the no-sleep condition slept between the practice session and retention testing. The actigraphic data for middle-aged adults indicated that participants in the sleep condition had 7.1hours total sleep time, a sleep latency of 5.44 minutes, 87.93% sleep efficiency, and 18.25 awakenings. The actigraphic data for older adults showed that participants in the sleep condition demonstrated 7.57 hours total sleep time, a sleep latency of 6.47 minutes, 86.3 % sleep efficiency, and 24.8 awakenings.

Acquisition Performance

Middle-aged participants

Middle-aged participants in the sleep and the no-sleep conditions showed improvement in performance during the practice session as demonstrated by a significant main effect of Block for all of the outcome measures ($F_{4,72}$=9.17, p<0.001, time around the walking path; $F_{4,72}$=16.42, p<0.001, tandem velocity; $F_{4,72}$=8.30, p<0.001; tandem step length; $F_{4,72}$=4.30, p=0.003, tandem step time, Figures 3.1.a, 3.1.b, 3.1.c, 3.1.d, respectively). The main effect of Condition for all outcome measures indicated no significant difference between the sleep and no-sleep conditions in the extent of improvement across the practice session ($F_{1,18}$=0.64, p=0.44, time around the walking path; $F_{1,18}$=0.02, p=0.88, tandem velocity; $F_{1,18}$=0.03, p=0. 80, tandem step length ; $F_{1,18}$=2.20, p=0.15, tandem step time). Thus, the sleep and no-sleep conditions performed similarly at the practice session. The interactions between Block X Condition were not significant for all of the outcome measures ($F_{4, 72}$=0.78, p=0.53, time around the walking path; $F_{4, 72}$=0. 93, p=0.45, tandem velocity; $F_{4, 72}$=0.92, p=0.46, tandem step length; $F_{4, 72}$=0.52, p=0.72, tandem step time).

Older Adult Participants

Training on the novel walking task resulted in performance improvement in both the sleep and the no-sleep older adults as indicated by the main effect of Block for each outcome variables ($F_{4,72}$=13.04, p<0.001, time around the walking path; $F_{4,72}$=35.27, p<0.001, tandem velocity; $F_{4,72}$=20.88, p<0.001; tandem step length; $F_{4,72}$=2.50, p=0.047, tandem step time, Figures 3.2.a, 3.2.b, 3.2.c, 3.2.d, respectively). The extent of improvement in performance revealed no differences between the sleep and the no-sleep conditions at the practice session, demonstrated by a lack of Condition main effect for time around the walking path ($F_{1,18}$=0.37, p=0.54), tandem velocity ($F_{1,18}$=1.02, p=0.33), tandem step length ($F_{1,18}$=0.52, p=0.48), and tandem step time ($F_{1,18}$=2.11, p=0.16). No interactions were found between Block and Condition for any of the outcome measures ($F_{4, 72}$=1.6, p=0.18, time around the walking path; $F_{4, 72}$=1. 02, p=0.33, tandem velocity; $F_{4, 72}$=.051, p=0.48, tandem step length; $F_{4, 72}$=0.46, p=0.76, tandem step time).

Off-line learning

Middle-aged participants

Interactions between Condition X Block were significant for all of the outcome measures. To explore these interactions one-way ANOVAs were utilized. Off-line learning scores for each of the outcome measures were used as dependent variables. Off-line learning scores were calculated by subtracting first retention block scores from last practice scores for each of the outcome measures for both the sleep and no-sleep conditions.

The results indicated that compared to participants in the no-sleep condition who failed to demonstrate off-line improvement in performance, participants in the sleep condition demonstrated a significant decrease in the time required to walk around the path from the last practice block to the retention block ($F_{1,18}$=54.06, p<0.001, Figure 3.3.a); a significant increase in tandem velocity ($F_{1,18}$=10.43, p<0.005, Figure 3.3.b), a significant increase in tandem step length ($F_{1,18}$=8.9, p=0.008, Figure 3.3.c), and a significant decrease in step time ($F_{1,18}$=44.77, p<0.001, Figure 3.3.d).

A large effect size of 3.4 suggests a real and meaningful difference between the amounts of change in the time required to walk around the path (main outcome measure) for middle-aged individuals who slept compared to those who stayed awake.

Older Participants

Similar results for middle-aged adults were found in older adults. Significant Condition by Block interactions were found for all outcome measures. Compared to the no-sleep condition, one-way ANOVAs result indicated that participants in the sleep condition demonstrated a significant decrease in time required to walk around the path at retention block compared to time needed at the last practice block ($F_{1,18}$=17.10, p=0.001, Figure 3.4.a); a significant increase in tandem velocity ($F_{1,18}$=17.90, p<0.001, Figure 3.4.b), a significant increase in tandem step length ($F_{1,18}$=7.50, p=0.013, Figure 3.4.c), and a significant decrease in step time ($F_{1,18}$=4.6, p<0.046, Figure 3.4.d).

These differences between the sleep and no-sleep conditions are real and meaningful as a large effect size of 1.9 was found for the amount of change in the time required to walk around the path for the older individuals who slept compared to those who stayed awake.

Age-Related Change in Sleep-Dependent Off-Line Learning

To determine the effect of age on sleep-dependent off-line learning, data for young adults previously gathered and reported in a recent study by Al-Sharman and Siengsukon[157] was included in post-hoc data analysis. An off-line learning score for the main outcome measure was calculated (by subtracting the first retention block score from the last practice block score) for the sleep and no-sleep conditions for each age group. A between-subject analysis of variance (ANOVA) was conducted with the off-line learning score of the main outcome measure as the dependent variable. Age (young, middle-aged, and older adults) and condition (sleep, no-sleep) were used as between-subject factors. Post hoc Fischer's least significant difference (LSD) was used to test specific differences between age groups.

Although the three age groups demonstrated significant sleep-dependent off-line learning of a functional motor task, the results indicated a significant difference in off-line motor learning between the three age groups as demonstrated by the main effect of age ($F_{2,58}$=3.39, p=0.04). Post hoc LSD testing demonstrated that this finding was significant between the young and older adults groups (p=0.02) and near significant between young and middle-aged groups (p=0.058). Middle-aged and older adults groups did not differ (p=0.63), Figure 3.5. A post hoc Pearson's correlation was conducted between off-line learning score for the time around the path and age. A negative significant correlation was found between age and off-line learning (r = -0.54, p=0.002), indicating that off-line learning decline with advancing age. Figure 3.6 shows correlation between off-line learning and age.

Then we examined whether reduced sleep-dependent off-line learning in middle-aged and older adults resulted from differences in sleep quality and quantity among the three age groups. To examine this, one way ANOVAs were used to compare both subjective sleep measures (PSQI and average sleep one week before testing) and actigraphic data (total sleep time, sleep latency, sleep efficiency, and number of awakenings) among the three age groups. The results indicated no significant differences among the three age groups in PSQI (p=0.50), average sleep one week before testing (p=0.18), total sleep time (p=0.20), sleep latency (p=0.09), and sleep efficiency (p=0.41). Despite the older adults waking up 7 times more than the middle-aged or young adults, this difference was also not significant (p=0.26). Table 3.2 summarizes these results.

Pearson's correlations were conducted between off-line learning score for the time around the path and each of the sleep measures (total sleep time, sleep latency, sleep efficiency, awakening numbers, PSQI, and average sleep one week before testing). The off-line motor learning score for time around the walking path was significantly correlated with sleep efficiency (r = 0.60, p=0.007) and PSQI (r = -0.62, p=0.002) across the age groups. Weak non-significant correlations were found between off-line learning and sleep latency (r= -0.36, p=0.09), number of awakenings (r= -0.24, p=0.28), and average sleep one week prior to practice (r =0.38, p=0.08).

We considered whether diminished age-related sleep-dependent off-line learning resulted from differences in performance at the practice session between older groups and young adults. A three factor [Age (young, middle-aged, older) X Condition (sleep, no-sleep) X Block (2, 3, 4, 5, 6)] repeated-measures ANOVA was used to assess performance acquisition during practice with time around the path as a dependent variable. Block X Age interaction was significant ($F_{8,232}$=15. 50, p<0.001). Post hoc LSD testing demonstrated that this finding was significant between the young and older adults groups (p=0.005), between young and middle-aged groups (p<0.001), but no significant difference between middle-aged and older adults (p=0.40). Despite the fact that all age groups had the same amount of practice, slower performance was observed with advancing age (i.e., more time is required to walk around the walking path in older groups compared to young adults)

3.5 Discussion

This study demonstrates that middle-aged and older adults improved performance on a functional motor task after a night of sleep but not after a period of wakefulness. In both age groups, only participants who slept after practicing the novel walking task demonstrated a significant decrease in the time around the walking path, an increase in tandem velocity, an increase in tandem step length, and a decrease in tandem step time. However, when compared with the magnitude of off-line learning in young adults[157], the results indicate that the magnitude of off-line improvement was less for the middle-aged and older adults groups. These findings suggest that middle-aged and older adults are able to benefit from sleep to enhance motor skill learning of a functional task, but this ability diminishes with aging.

Our results provide further evidence that older adults are able to benefit from sleep to enhance learning of motor tasks. This study supports the findings of Tuker et al[39] and Peter et al[22] in showing sleep-dependent enhancement in older adults. Furthermore, the results from this current study support the findings from Wilson et al[38] that sleep enhances motor performance in middle-aged individuals. Our work expands on these previous studies that have examined the role of sleep in motor learning using fine motor tasks to assess the role of sleep in learning a functional gross motor task in middle-aged and older adults.

Emerging evidence suggests that the role of sleep in off-line learning is dependent task on task characteristics[20, 31]. This may explain the lack of consistency between our findings and the results from earlier studies by Siengsukon et al[36, 37], Spencer et al[35], and Wilson et al[38] who found older adults failed to demonstrate sleep-dependent motor skill learning. Compared with motor tasks which were used in previous studies, the functional walking task utilized in the current study is more complex. This task requires a whole body to perform, coordination between different body parts, and response to environmental stimuli (narrow path way and transition from standard gait to tandem gait). Furthermore, performing a mental task while walking is considered a very demanding task[159].

Our finding that sleep enhances learning of a novel walking task supports the theory that proposes sleep selectively enhances the learning of tasks that are more complex. Kuriyama et al[33] and Siengsukon et al[31] both found that, in young adults, sleep enhanced the learning of tasks that are more complex. Our study is the first to confirm these results in middle- aged and older adults. Furthermore, our findings agree with the conclusion drawn from a study by Wilhelm et al[82] who found that, in young adults, sleep benefits learning tasks that are significant to the individual's future behavior. Therefore, we believe that sleep enhances learning the functional motor task presented in this study because it is more complex and relates to an individual's behavior as compared to motor tasks previously used.

One limitation of this study is that we cannot completely rule out the influence of time-of -day effect. Although we believe this limitation does not have a large effect on the results of this study. In both age groups, participants in the sleep and the no-sleep conditions practiced this novel task and reached a similar level of performance at the end of the training session, regardless of whether the practice took place in the evening (i.e., sleep condition) or in the morning (i.e., no-sleep condition). Further, in both the middle-aged and older adults the level of sleepiness and the level of functional mobility revealed no differences between the sleep and the no-sleep at practice or at retention testing regardless of time of day the testing occurred. This suggests that in both age groups, delayed off-line improvement in performance observed in the sleep but not in the no-sleep conditions was a result of the consolidation process that occurs during sleep and not the circadian rhythm or time-of-day effect.

The findings from the current study indicate that the sleep-dependent off-line learning process declines with advancing age. Middle-aged and older adults demonstrated sleep-dependent off-line improvement in performance on a functional motor task; however, the degree of off-line improvement was less than that reported in young participants[157]. These results largely confirm results by Peter et al[22] who detected a decline in off-line improvement in older adults on a simple motor task compared to young adults. There are several possible explanations for age-related decline in the process of sleep-dependent off-line consolidation. First, because so few studies have assessed off-line motor skill learning in middle-aged and older adults, it is difficult to know the amount of practice required to achieve optimal memory consolidation in middle-aged and older adults. With advanced age older adults experience changes in their sensory and neuro-muscular system[160, 161]. Furthermore, older adults' ability to walk and perform a cognitively-demanding task declines with age[159, 162]. Perhaps with advancing age more practice is needed for sleep to produce off-line improvements. Interestingly, Walker et al[2] found no correlation between the amount of practice-dependent learning and the amount of sleep-dependent learning. Furthermore, doubling the practice did not result in additional off-line improvement of the task in young individuals[2]. As yet, no studies have examined if more practice will increase off-line learning in middle-aged and older adults. Future studies are needed to explore this issue.

Age-related decline in sleep-dependent off-line learning might be explained by changes in sleep quality and quantity with advancing age. However, our data indicated that the sleep quantity and quality did not differ between young, middle-aged, and older individuals. There were no differences between the three age groups in the average amount of sleep prior to testing or in their sleep quality as assessed using the PSQI. Furthermore, objective sleep measures including total sleep time, sleep latency, sleep efficiency, and number of awakenings in the current study were not significantly different between the three age groups. Indeed, it is important to mention that the middle-aged and older participants in this study were all healthy individuals as none of the participants reported any health problems that would affect their sleep quality and quantity. This supports the hypothesis that changes in sleep quality and quantity are not part of the normal aging process but are secondary to other co-morbidities that arise with advanced age such as arthritis and depression.[118, 119] Ohayon et al[118] found that age-related complaints of insomnia are reduced when health status and life satisfaction are improved in older adults. Therefore, in this study changes in sleep quality and quantity are not a likely reason for the reduced degree of sleep-dependent off-line learning of middle-aged and older adults compared to young adults.

The decline in sleep-dependent off-line motor skill learning in middle-aged and older adults might be explained by changes in sleep architecture with advancing age. However, the design of this study did not allow us to examine this possibility. Emerging evidence suggests that reduced number of sleep spindles and the decreased time spent in REM sleep in older adults may explain the decline in sleep-dependent off-line learning in middle-aged and older adults. Interestingly, Peter et al [22] found that older adults demonstrated an increase in time spent in SWS after practicing the task but the younger group did not. The authors[22] speculate that increased time spent in SWS represents a "compensatory response" the brain uses following task encoding to enhance learning as mechanisms required for simple motor tasks consolidation are impaired in older adults. According to the "synaptic homeostatic hypothesis"[163] SWS function is to downscale synaptic strength that build during wakefulness leading to more efficient connections that are effective for memory and learning. Thus, mechanisms explaining sleep-dependent off-line learning in middle-aged and older adults are still unclear. Future studies are needed to explore these mechanisms.

The enhancement of performance of a functional motor task in healthy middle-aged and older adults by the action of sleep is a very important finding and has significant implications for rehabilitation. Middle-aged and older adults during rehabilitation sessions learn functional skills such as how to ambulate using proper mechanics with an assistive device following total knee replacement or following lower limb fractures. We believe that clinical outcomes could be improved if the process of sleep-dependent consolidation is intact. In this study improved walking ability even, for seconds, could increase older adults' ability to walk safely and function normally in their home and in the community. For example, older adults' ability to walk across the street safely before light changes or their ability to get to bathroom quickly could improve, and that could affect their quality of life which is essential for continuing good health and longevity. Our results demonstrated that sleep quality is an important factor for the sleep-dependent off-line motor learning process. Middle-aged should consider taking care of their sleep quality for maximum learning and productivity. Further, as many of the co-morbidities presented with advanced age affect sleep quality and could consequently impair the sleep-dependent learning process, clinicians should assess sleep quality and educate middle-aged and older adults on methods to achieve best quality sleep. Also, referral to a sleep specialist may be recommended.

Furthermore, studies found that some medications affect sleep architecture and either enhance[164] or inhibit[165] sleep-dependent off-line learning. For example, it has been found that donepezil, an acetylcholinesterase inhibitor, increased time spent in as well as density of REM sleep[164]. Administration of an acetylcholinesterase inhibitor after practicing a mirror tracing task resulted in a significant overnight improvement in older adults' performance[166]. Therefore, clinicians should be aware of the medications their patients are taking. Moreover, pharmacological approaches that alter sleep architecture could be considered as a possible way to increase sleep-dependent learning.

In summary, this study provides the first evidence that sleep enhances learning of a complex functional motor skill that has direct application to rehabilitation for middle-aged and older adults. There was, however, an age-related decline in sleep-dependent off-line learning. Effective plans need to be considered by clinicians to maximize the role of sleep on motor learning in this population. Emphasis should be placed on addressing sleep disorders and on ensuring adequate sleep for individuals who go through rehabilitation.

3.6 Acknowledgments

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Author Contributions: Siengsukon and Al-Sharman: study conception, study design, data analysis, interpretation of results, and manuscript preparation.

Sponsor's Role: None

3.7 Tables

Groups	Age	MMSE	SSS1	SSS2	Avg. Sleep	PSQI	Weight	Height	TUG1	TUG2	BDI
Middle-aged adults											
Sleep	49.6 (3.6)	29.8 (0.4)	2.0 (0.8)	2.2 (0.4)	7.5 (0.7)	3.2 (1.9)	168.0 (37.8)	171.1 (10.4)	8.8 (0.4)	8.7 (0.5)	3.3 (2.9)
No-sleep	47.0 (3.4)	29.7 (0.5)	2.2 (1.03)	2.5 (0.8)	7.6 (0.8)	2.5 (1.4)	178.5 (20.3)	172.5 (10.1)	8.4 (0.7)	8.6 (0.8)	2.3 (1.6)
p-value	0.11	0.63	0.63	0.50	0.80	0.37	0.45	0.78	0.27	0.57	0.23
Older adults											
Sleep	69.1 (1.9)	29.8 (0.4)	1.7 (0.8)	1.5 (0.7)	7.30 (0.5)	3.3 (1.5)	170.2 (37.9)	171.3 (11.8)	9.3 (0.7)	9.2 (0.6)	2.00 (1.7)
No-sleep	71.6 (1.9)	29.6 (0.7)	1.6 (0.8)	1.6 (0.6)	7.49 (0.4)	4.1 (2.0)	157.6 (35.4)	167.2 (11.8)	9.1 (0.9)	9.1 (0.8)	4.00 (3.4)
p-value	0.12	0.44	0.80	0.75	0.68	0.30	0.40	0.42	0.69	0.70	0.14

Table 3.1. Descriptive information for middle-aged and older participants. Data are mean (standard deviation). MMSE= Mini Mental Status Examination; SSS1= Stanford Sleepiness Scale taken at practice session; SSS2= Stanford Sleepiness Scale taken at retention testing; PSQI= Pittsburgh Sleep Quality Index; Ave. Sleep= Average amount of sleep participants had the week prior to testing demonstrated by sleep log. TUG1= Timed Up and Go taken at practice session; TUG2= Timed Up and Go taken at retention session; BDI= Beck Depression Inventory.

Sleep Measures (Actigraph data)	Total Sleep Time (hours)	Sleep Latency (minutes)	Sleep Efficiency (percent)	Awakenings Number
Young adults* **(8 participants)**	**7.1(0.5)**	**5.44 (1.4)**	**87.93 (1.1)**	**18.25 (3.77)**
Middle-aged (8 participants)	**7.46 (0.78)**	**10.65 (7.52)**	**87.42 (3.5)**	**18.62 (4.5)**
Older adults (6 participants)	**7.57 (0.6)**	**6.47 (1.3)**	**86.3 (3.4)**	**24.8 (13.8)**
P- *value*	**0.20**	**0.09**	**0.41**	**0.26**

Table 3.2. Acigraph data for young, middle aged and older adults. Data are mean (standard deviation). Total Sleep Time= Time between sleep onset and final awake time; Sleep Latency= Time between bed time and sleep onset; Sleep Efficiency= Time of sleep/total time in bed*100; Awakenings Number= Number of awakes during the night of sleep between practice and retention testing for the sleep group. **Young adults*: These data from a previous study that assessed the role of sleep in learning a functional task in young individuals[157].**

3.8 Figure Legend

Figure 3.1.a. Performance changes across the training blocks (block 2-6) for middle-aged group demonstrated by time around the walking path. Error bars are SEM.

Figure 3.1.b. Performance changes across the training blocks (block 2-6) for middle-aged group demonstrated by tandem velocity across gait-mat. Error bars are SEM.

Figure 3.1.c. Performance changes across the training blocks (block 2-6) for middle-aged group demonstrated by tandem step length across gait-mat. Error bars are SEM.

Figure 3.1.d. Performance changes across the training blocks (block 2-6) for middle-aged group demonstrated by tandem step time across gait-mat. Error bars are SEM.

Figure 3.2.a. Performance changes across the training blocks (block 2-6) for older adults demonstrated by time around the walking path. Error bars are SEM.

Figure 3.2.b. Performance changes across the training blocks (block 2-6) for older adults demonstrated by tandem velocity across gait-mat. Error bars are SEM.

Figure 3.2.c. Performance changes across the training blocks (block 2-6) for older adults demonstrated by tandem step length across gait-mat. Error bars are SEM.

Figure 3.2.d. Performance changes across the training blocks (block 2-6) for older adults demonstrated by tandem step time across gait-mat. Error bars are SEM.

Figure 3.3.a. Off-line learning scores or change on performance on the novel walking task between the last practice block and the retention testing for the sleep and no-sleep groups in the middle-aged adults demonstrated by time around the walking path. Negative values indicate better performance. Error bars are SEM. ****p <0.001**

Figure 3.3.b. Off-line learning scores or change on performance on the novel walking task between the last practice block and the retention testing for the sleep and no-sleep groups in the middle-aged adults demonstrated by tandem velocity across gait-mat. Error bars are SEM. ***p <0.05**

Figure 3.3.c. Off-line learning scores or change on performance on the novel walking task between the last practice block and the retention testing for the sleep and no-sleep groups in the middle-aged adults demonstrated by tandem step length across gait-mat. Error bars are SEM. ***p <0.05**

Figure 3.3.d. Off-line learning scores or change on performance on the novel walking task between the last practice block and the retention testing for the sleep and no-sleep groups in the middle-aged adults demonstrated by tandem step time across gait-mat. Error bars are SEM. ****p <0.001**

<u>Figure 3.4.a.</u> Off-line learning scores or change on performance on the novel walking task between the last practice block and the retention testing for the sleep and no-sleep groups in the older adults demonstrated by time around the walking path. Negative values indicate better performance. Error bars are SEM. ****p <0.001**

<u>Figure 3.4.b.</u> Off-line learning scores or change on performance on the novel walking task between the last practice block and the retention testing for the sleep and no-sleep groups in the older adults demonstrated by tandem velocity across gait-mat. Error bars are SEM. ***p <0.05**

<u>Figure 3.4.c.</u> Off-line learning scores or change on performance on the novel walking task between the last practice block and the retention testing for the sleep and no-sleep groups in the older adults demonstrated by tandem step length across gait-mat. Error bars are SEM. ***p <0.05**

<u>Figure 3.4.d.</u> Off-line learning scores or change on performance on the novel walking task between the last practice block and the retention testing for the sleep and no-sleep groups in the older adults demonstrated by tandem step time across gait-mat. Error bars are SEM. ***p <0.05**

<u>Figure 3.5.</u> Age-related change in sleep-dependent off-line learning of a functional motor task. Error bars are SEM. ***p <0.05**

<u>Figure 3.6.</u> Correlation between offline learning for time around the walking path (primary outcome measure) and age

Figure 3.1.a

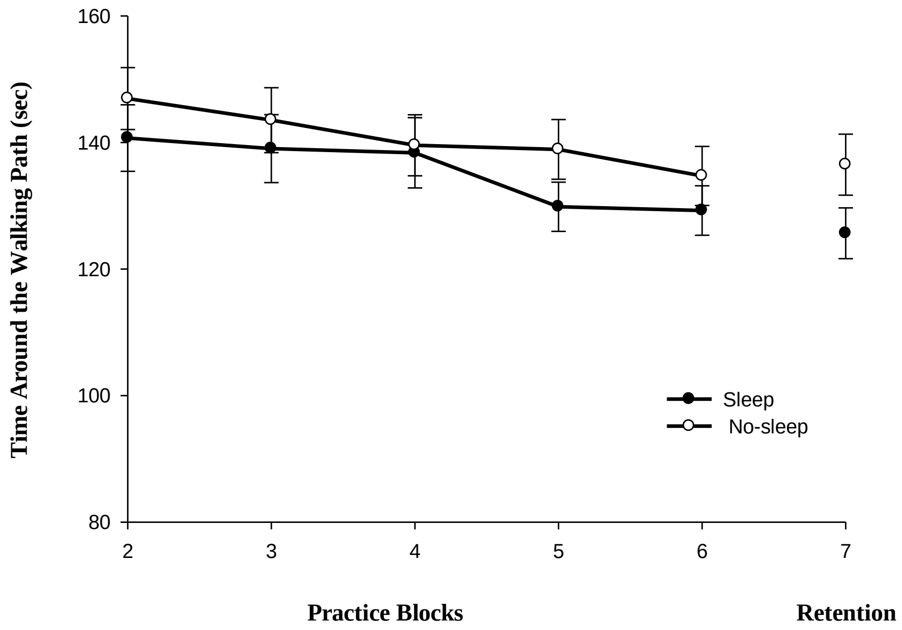


Figure 3.1.b

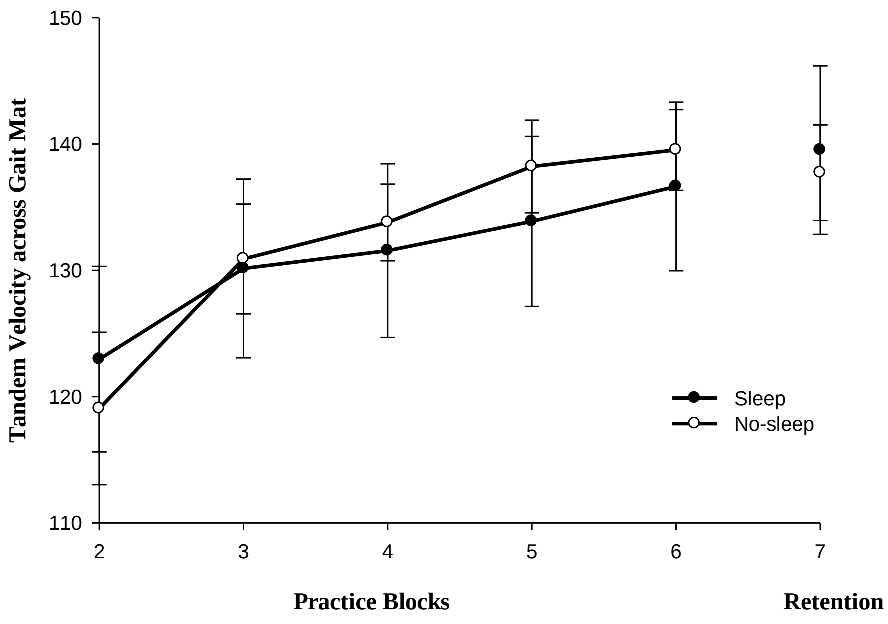


Figure 3.1.c

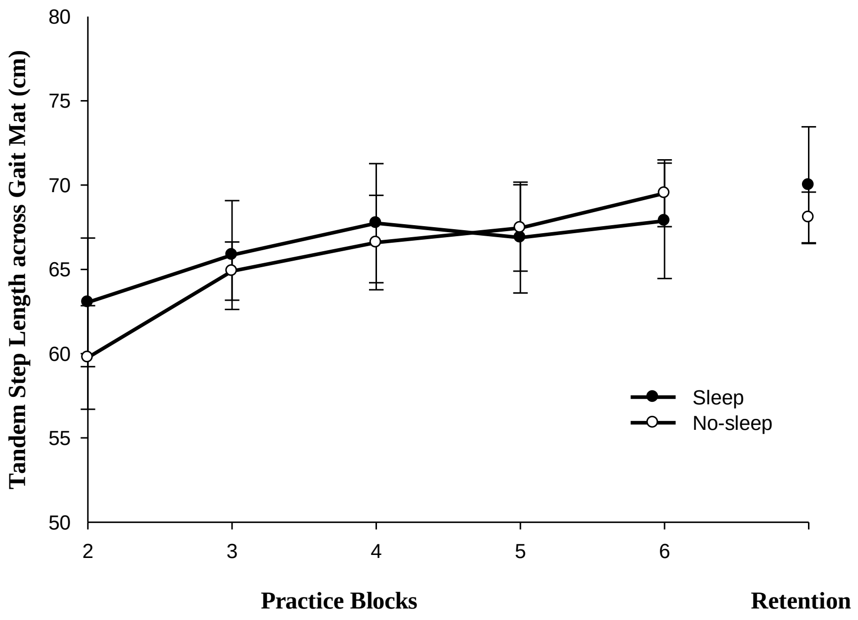


Figure 3.1.d

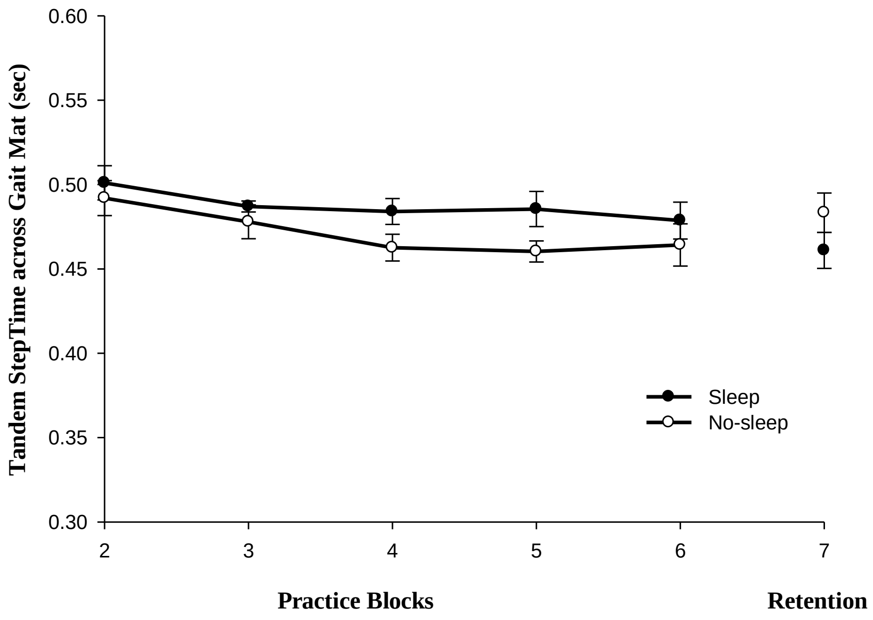
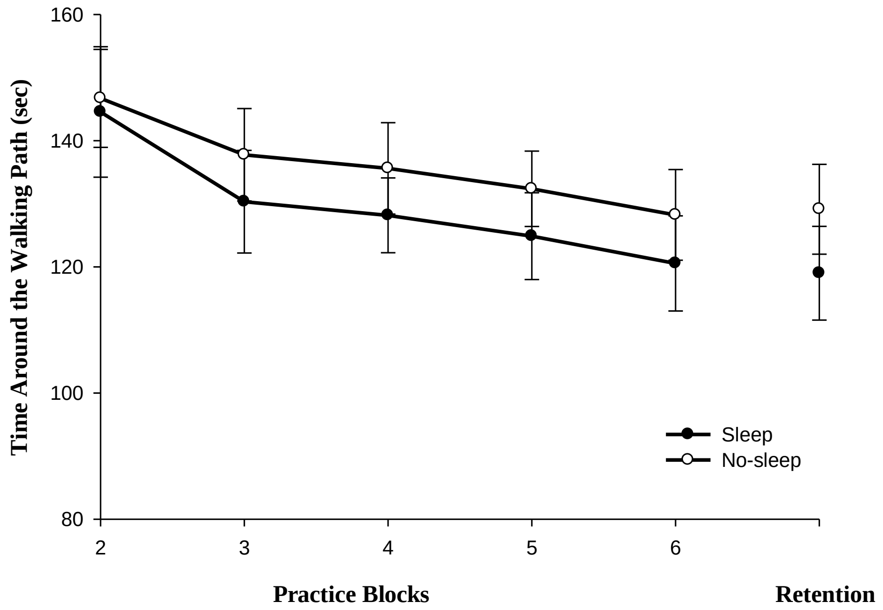


Figure 3.2.a



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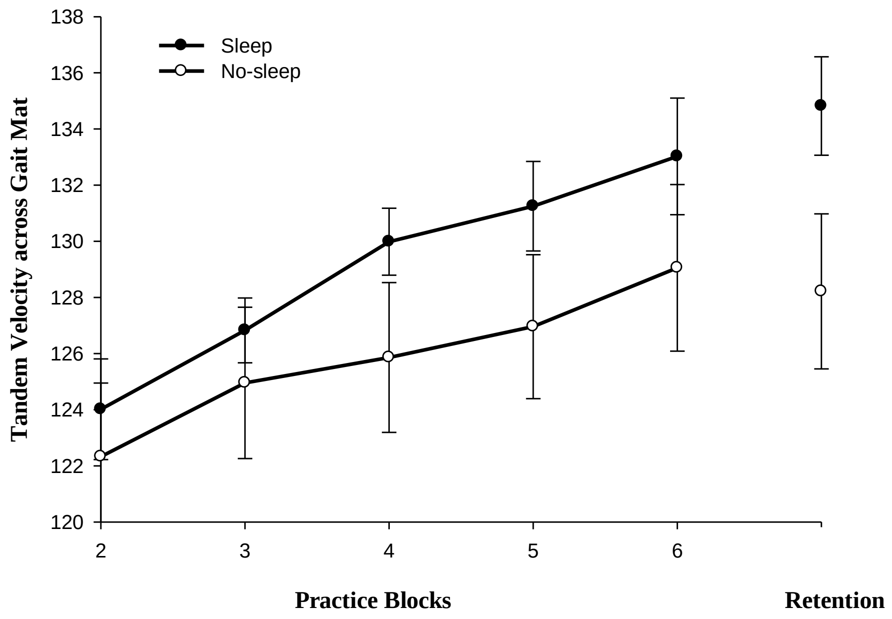
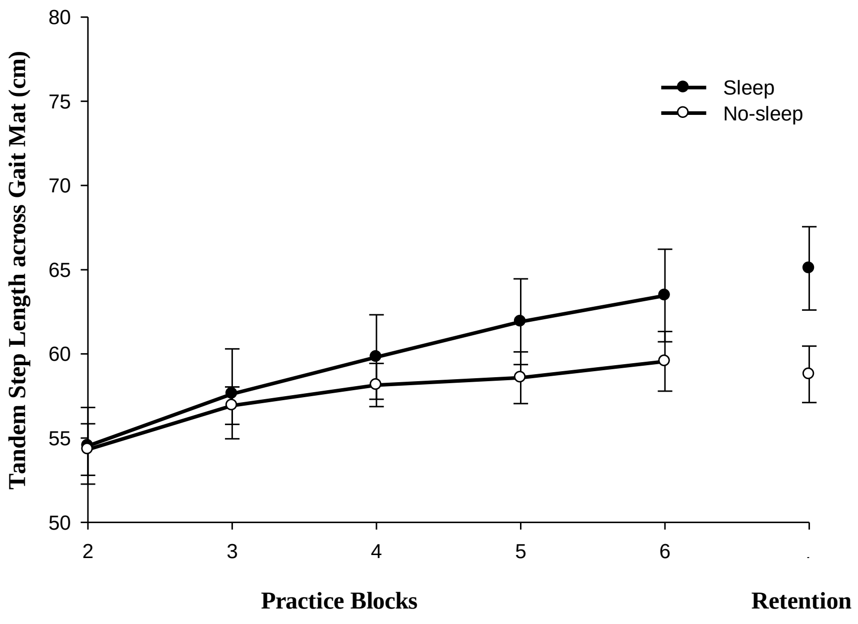


Figure 3.2.c



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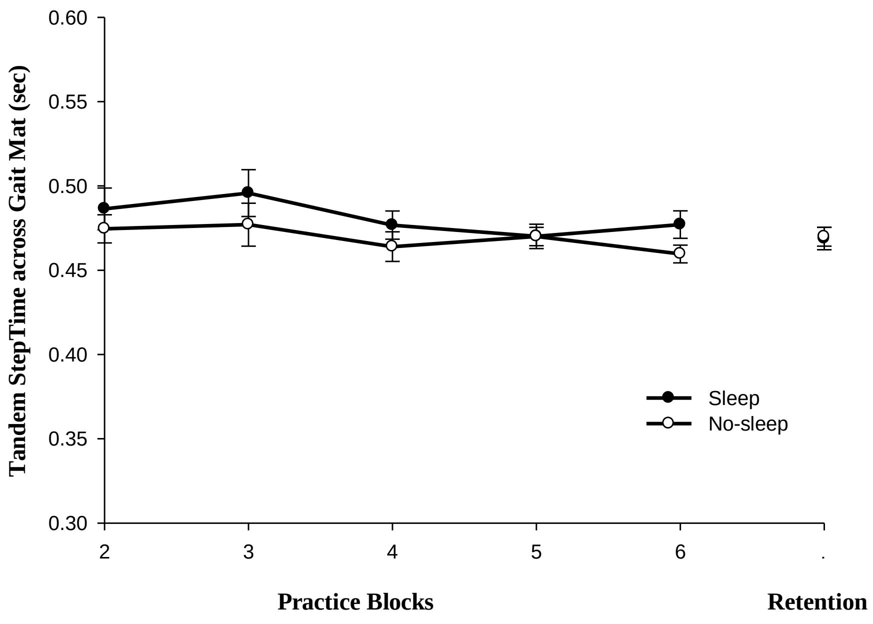

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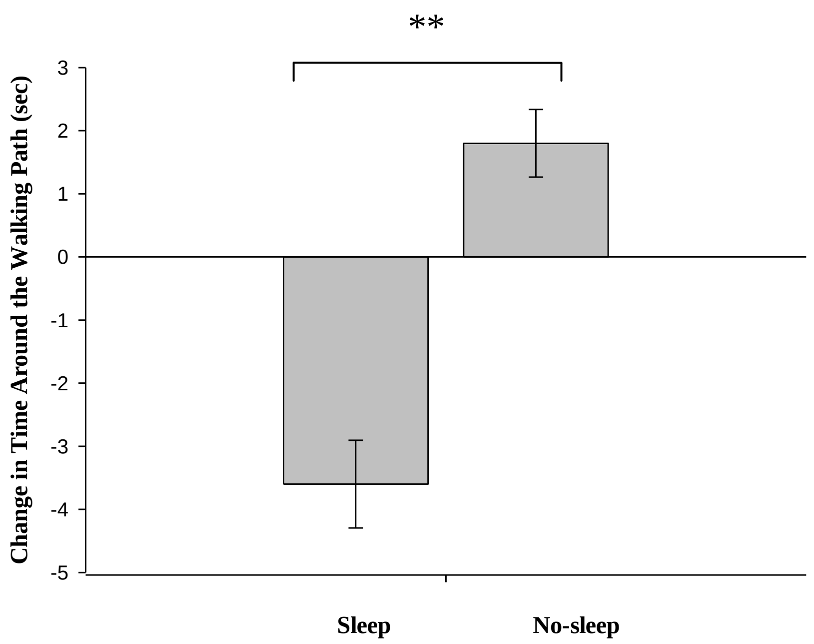

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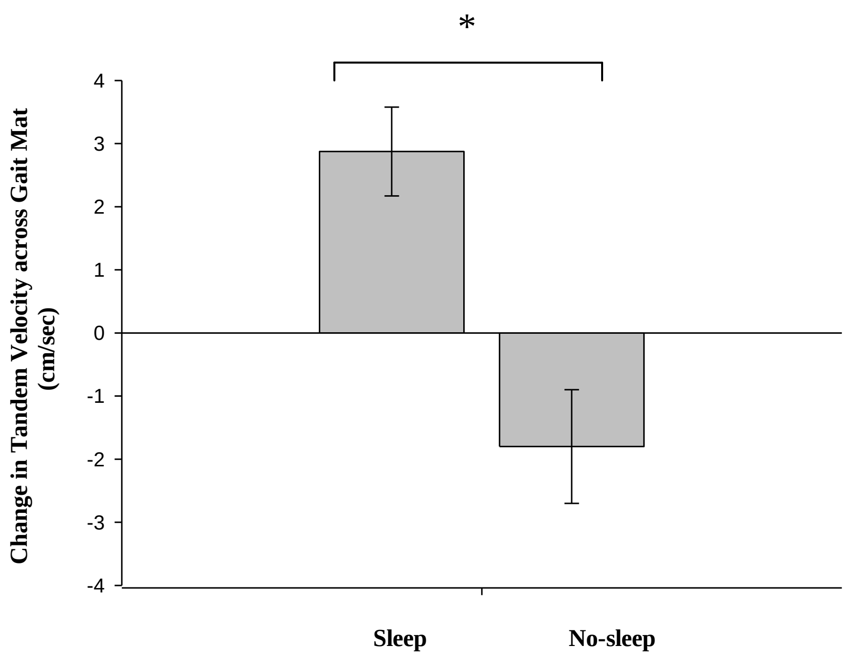

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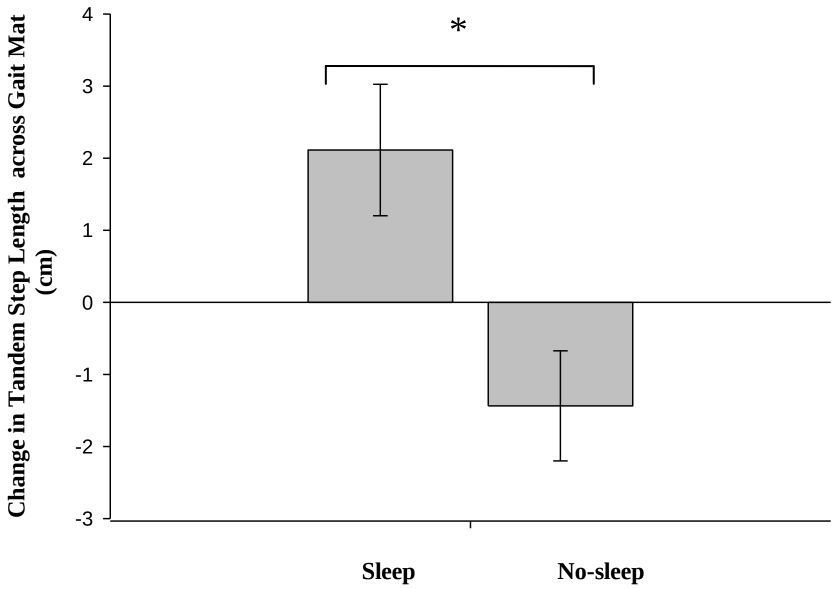

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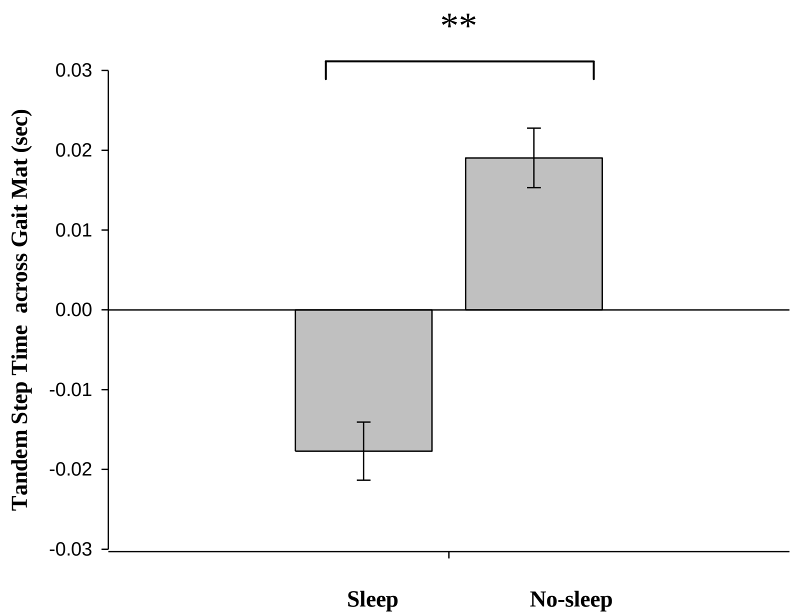

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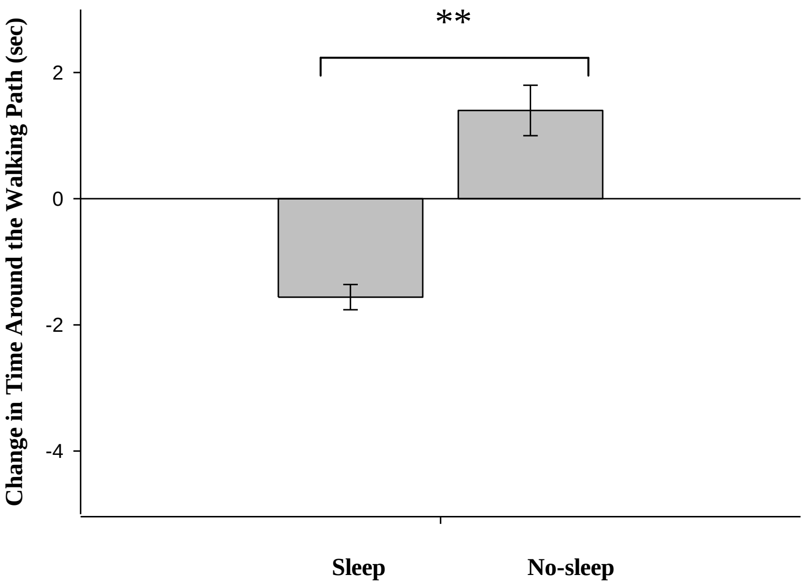

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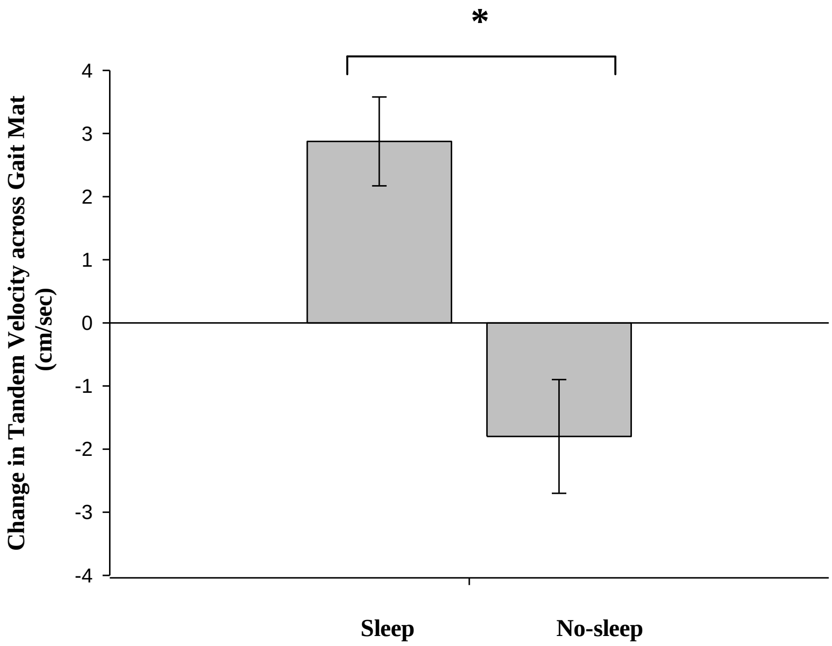

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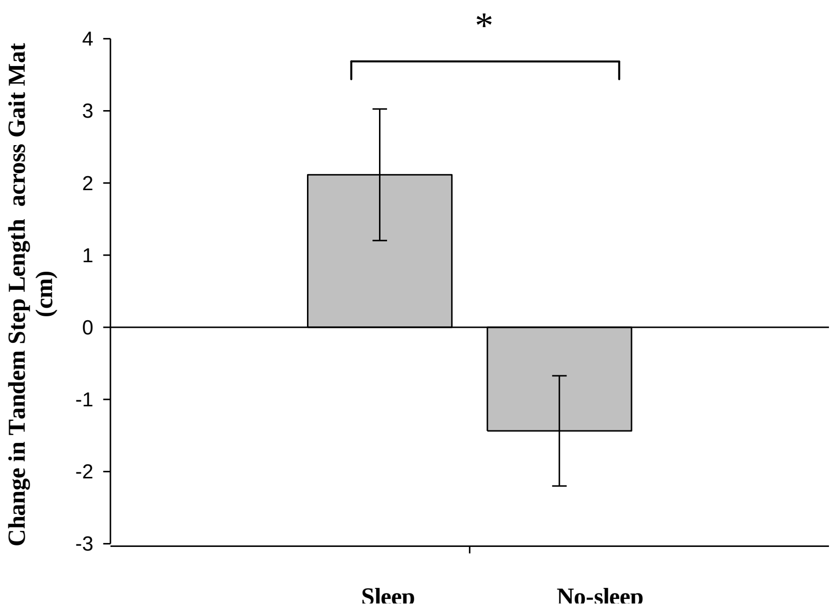

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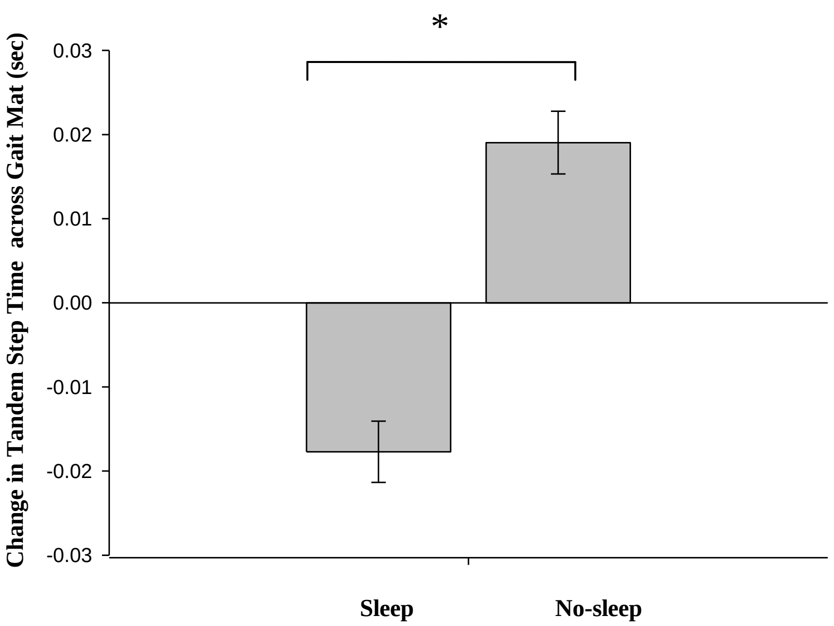

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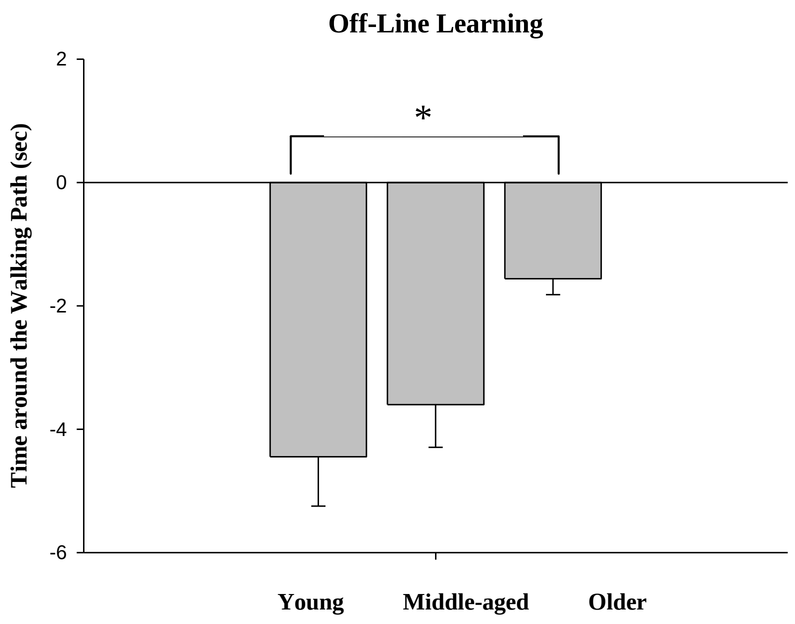
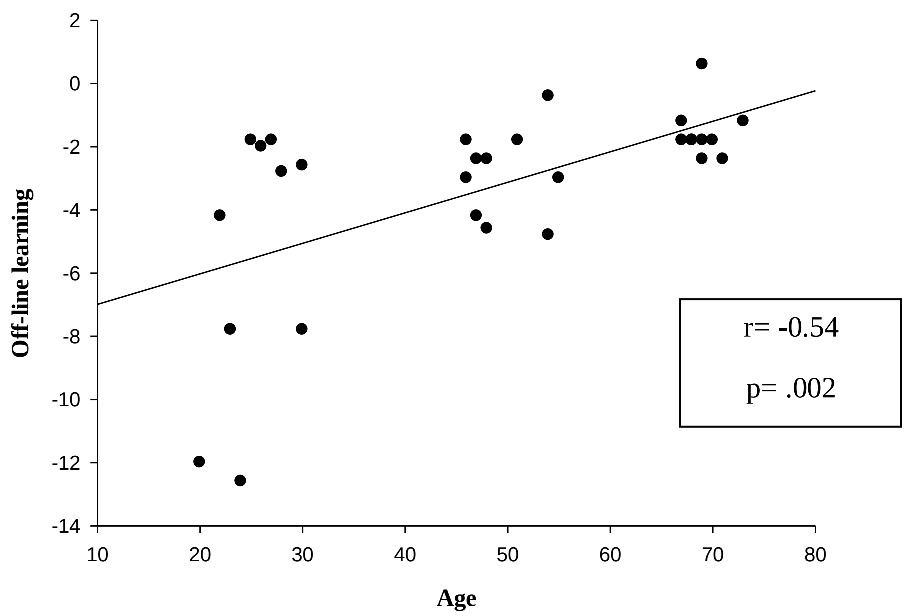


Figure 3.6



Chapter 4 Preface

Chapter 2 and Chapter 3 demonstrated that sleep enhances learning a functional task in young, middle-aged and older adults. We have found that, in all age groups, walking performance improved following a period of sleep compared to an equivalent period of wakefulness. These findings suggest that sleep enhances learning the motor aspect of the functional walking task. However, it is unclear if motor performance was improved as a result of declined performance on the cognitive component of the functional task or if sleep also enhanced the cognitive component of the functional task. Therefore, the work presented here sought to extend the findings from Chapter 2 and Chapter 3 by examining the impact of sleep on the cognitive component of a functional task in young, middle-aged, and older adults.

Chapter 4

Sleep Enhances the Cognitive Component of a Functional Task

This work will be submitted for publication to *Neuroscience Letters*.

4.1 Abstract

Sleep has a critical role in memory consolidation of motor tasks. In everyday functions, however, people often carry out more than one task at a time. It is important to understand the role of sleep in learning functional tasks that include both cognitive and motor components. Recently, we examined the role of sleep in learning a functional motor task that requires walking while performing a cognitive task (Al-Sharman and Siengsukon, 2012). We found that sleep enhances the walking performance of this task. The current study examined whether sleep enhances the cognitive performance of the same functional task. Twenty-four young (25.71 ± 2.8 years of age), 20 middle-aged (48 ± 3.66 years of age) and 20 older (70.4 ± 3.8 years of age) adults participated in this study. Participants in each age group practiced a novel walking task while performing a cognitive task (counting backwards by 7s) and then either slept (sleep condition) or stayed awake (no-sleep condition) between practice and retention testing. Primary measures of interest included the correct responses rate on the cognitive task and the percent change in performance between the last practice block and the retention testing. The results indicated that, in all age groups improvement in cognitive performance is facilitated by sleep but not by an equal period of wakefulness. After 12 hours of wakefulness, cognitive performance reduced by 3.4% in young, 6.02% in middle-aged, and 11.7% in older adults. However, after a night of sleep, cognitive performance improved by 17.5%, 13.04 %, and 11.0% in young, middle-aged, and older adults, respectively. These findings provide compelling evidence that sleep enhances cognitive performance even when performed concurrently with a motor task.

Keywords: sleep, off-line learning, cognitive skill, dual-task

4.2 Introduction

Many activities in everyday life require people to perform more than one task at a time such as walking while talking on the phone or walking while remembering a shopping list[167, 168]. Multitasking plays an integral role in our life functions. In research, a dual-task paradigm is frequently used to understand age-related changes in the ability to multitask[159, 169, 170].Studies have found that, compared to young individuals, an older adult's ability to perform dual-tasks in everyday settings declines[159, 167, 170]. Walking while performing a concurrent cognitive task has been found to disrupt performance on one or both tasks in older adults[159, 162]. Impaired balance and increased risk of falling have been repeatedly reported in older adults under dual-task paradigms[162, 171, 172]. Appropriate strategies (i.e., prioritization) are essential to meet the challenge of performing two tasks concurrently[173, 174].

Both cognitive and motor deficits may affect the ability to perform two tasks simultaneously[159, 175]. In a recent study by Hall et al[159] both motor and cognitive variables were associated with older adults' ability to walk under dual-task conditions. Motor factors such as gait speed and balance significantly contributed to walking ability while simultaneously performing a cognitive task. Furthermore, participant's cognitive abilities, specifically working memory, sustained attention, and divided attention were also associated with ability to multitask[159]. Many studies have also confirmed that specific cognitive abilities are required to achieve successful functional walking (i.e., walking while performing a cognitive task)[176, 177]. Executive function frequently has been found to play an important role in walking while performing activities of daily living (ADL) [159, 176, 178]. Therefore, factors that may improve motor and cognitive factors contributing to successful performance of a functional task should be explored.

Emerging evidence has demonstrated that sleep is a critical brain state for motor learning and memory consolidation in young [2, 3, 7, 18, 19, 179] and older [22, 39] healthy adults.

Memory consolidation refers to the transformation of the memory of a learned task into a more stable and enduring form[10]. Studies have shown that delayed gains in performance on a variety of simple motor tasks are enhanced after a period of sleep, but not after an equivalent period of day-time wakefulness[2, 3, 11]. However, sleep studies have, almost exclusively, examined the role of sleep in motor learning using a single motor task such as, a finger-to-thumb opposition task[11, 12], a serial reaction time task[29], a sequential finger-tapping task[7, 26], or a continuous tracking task[31]. Furthermore, only one study has examined the impact of sleep on learning a cognitive task[167]. Kuriyama et al[167] examined whether sleep enhances performance on the *n-back* task which is a cognitive task that has been frequently used to assess the characteristics of working memory after a period of sleep and wakefulness. Accuracy on the *n-back* task improved only if participants slept post-training but not if they stayed awake. This study by Kuriyama et al[167] provided the first evidence that sleep enhances cognitive performance. Considering that most daily life tasks require the simultaneous performance of motor activities and cognitive functions, it is critical to understand the impact of sleep on such tasks.

Recently, we found that sleep enhances learning a functional task in young[157], middle-aged and older adults[180]. Participants practiced a functional walking task in which they were instructed to walk as fast and as accurately as possible between a narrow, irregular pathway, while performing a cognitive task (counting backward by 7s). We have found that, in all age groups, walking performance improved following a period of sleep compared to an equivalent period of wakefulness[157, 180]. These findings suggest that sleep enhances learning the motor component of the functional task. However, it is unclear whether performance on the motor component was improved as a result of declined performance on the cognitive component of the functional task or whether sleep also enhanced the cognitive component of the functional task. Therefore, the purpose of this current study was to examine the impact of sleep on the cognitive component of a functional task in young, middle-aged, and older adults. The data presented here are part of a larger study examining the role of sleep in learning a functional motor task in young, middle-aged, and older adults.

4.3 Materials and Methods

Participants

Twenty-four young (25.71 ± 2.8 years of age), 20 middle-aged (48 ± 3.66 years of age) and 20 older (70.4±3.8 years of age) adults participated in the study. Participants were recruited from the University of Kansas Medical Center (KUMC) as well as local communities. This study was approved by the institutional human research review board at KUMC, and all participants signed an approved consent form to participate in the study.

The inclusion and exclusion criteria as well as baseline assessments have been described previously[157, 180]. Briefly, individuals with untreated sleep disorders, uncontrolled depression, neurological disorders, psychiatric history, or orthopedic problems were excluded from this study. We also excluded participants who scored below a 26 on the mini-mental status exam (MMSE) [128], worked a night shift, were regular nappers, or who were found to be extreme evening or morning-type persons by the Morningness-Eveningness Questionnaire (MEQ)[129]. Twelve hours prior to and during the course of the study, all participants were instructed not to participate in strenuous activities or to ingest caffeine, alcohol, or recreational drugs.

Both the Pittsburgh Sleep Quality Index (PSQI)[130] and Beck Depression Inventory (BDI)[131] were completed by all participants to assess their sleep quality and depression, respectively. A week prior to testing, participants were instructed to maintain a daily sleep log. Level of sleepiness was assessed prior to practice and retention testing by asking participants to complete the Stanford Sleepiness Scale[134]. To assess the level of functional mobility prior to practice and retention testing, the Timed Up and Go test (TUG)[132, 133] was performed by all participants. Demographics including age, gender, years of education, height, weight, and medical history were collected from all participants.

Procedure

The functional walking task used has been described previously[157, 180]. Briefly, walking was performed on a 97 feet long and 1.5 feet wide, irregular, elliptical pathway which was marked by colored tape. Within the walking path, a gait mat 12.7 feet long (Gait-Mat II™ system E.Q., Inc.) was embedded for spatiotemporal gait assessment. Participants were instructed to walk safely as fast as they could, to avoid stepping on or over the tape, and to keep walking until told to stop. On the gait mat participants were instructed to do tandem-like walking in which the feet advance, one after the other on a single, straight line. While walking around the pathway participants were instructed to perform a mental cognitive task, counting backward by 7s starting from a randomly selected number between 293 and 299. Participants were asked to pay equal attention to walking and the cognitive task.

Participants in each age group (young, middle-aged, and older adults) were randomly assigned into either the sleep or the no-sleep conditions. The sleep condition participants practiced the functional walking task in the evening and underwent retention testing the following morning. Conversely, the no-sleep condition participants practiced the functional walking task in the morning and underwent retention testing in the evening of the same day. Participants in the no-sleep condition were instructed not to nap between practice and retention testing. The same amount of time (~12 hours) transpired between the practice session and the retention session for both the sleep and no-sleep groups.

During the practice session, all participants completed 5 blocks of the functional walking task. A baseline block on performing the walking component of the task without simultaneously performing the cognitive component was performed by all participants; they were instructed to walk without performing the cognitive calculation in order to familiarize them with the walking path. Rests between practice blocks were allowed if needed. The retention testing consisted of one block of performing the functional walking task followed by another block of walking without performing the cognitive calculation. Each block in the practice session and the retention testing consisted of five iterations around the walking path.

To examine the impact of sleep on the cognitive performance of the functional task, the correct response rate on the cognitive task was calculated for blocks 2-6 during acquisition practice and for the delayed retention testing. Individuals' data were averaged by condition for each age group to represent performance. To assess off-line learning in both the sleep and the no-sleep conditions for all age groups, the retention scores (i.e., correct response rate at retention testing) were subtracted from block number 6 scores (i.e., correct response rate at the last practice block). Percent changes in performance between the last practice block and the retention block were also calculated for the sleep and the no-sleep conditions for all age groups.

Data analysis

A three-factor [Age (young, middle-aged, older) X Condition (sleep, no-sleep) X Block (2, 3, 4, 5, 6)] repeated-measures ANOVA was used to assess performance acquisition of the cognitive component of the functional task during the practice session for all age groups. Correct response rate was used as dependent variable. Off-line learning was assessed using a three-factor [Age (young, middle-aged, older) X Condition (sleep, no-sleep) X Block [last practice block, first retention block] repeated-measures ANOVA with correct response rate as the dependent variable. Effect sizes (ES) were calculated for each age group to examine if the differences between the sleep and the no-sleep conditions were clinically meaningful[141].

4.4 Results

Subject Characteristics

Data for demographic and base line assessments are presented in our previous studies [157, 180] and summarized in Table 4.1.

Acquisition performance

Young, middle-aged, and older adults demonstrated a practice-related improvement on the cognitive component of the functional task as shown by the main effect of Block ($F_{4,232}$=95.70, p<0.001). The extent of improvement in performance across blocks revealed no significant difference between the sleep and the no-sleep conditions in any of the age groups as indicated by the lack of interaction between Block X Condition ($F_{4,232}$=0.33, p=0.85). These results suggest that, regardless of the time of day, cognitive performance improved with practice in all age groups. The interaction of Block X Age and Age X Condition were also not significant ($F_{8, 232}$=0.96, p=0.46; $F_{2, 58}$=0.26, p=0.77, respectively), suggesting that the cognitive performance on the functional task improved with practice in the sleep and the no-sleep condition to the same extent in all age groups. An overall block X age X condition interaction was not significant ($F_{4,232}$ =1.08, p=0.37). Figure 4.1 illustrates acquisition performance on the cognitive component for young, middle-aged, and older adults.

Off-line learning

Interaction between Condition X Block was significant ($F_{1,58}$ =42.6, p < 0.001). To explore this interaction post hoc analyses were performed. Analysis of variance (ANOVA) was conducted with the off-line learning score of the correct response rate as a dependent variable. Age group (young, middle-aged, and older adults) and condition (sleep, no-sleep) were used as between-subject factors. The results indicated that all age groups benefited from sleep to enhance their cognitive performance as demonstrated by main effect of condition ($F_{1,58}$ =8.5, $p < 0.001$). The main effect of age was not significant ($F_{1,58}$ =2.18, $p < 0.12$), suggesting no significant differences in off-line motor learning between the three age groups.

Compared to the no-sleep participants whose cognitive performance declined by 3.4% for the young, 6.02% for the middle-aged, and 11.7% for older adults from last practice block to retention, cognitive performance for the sleep condition improved by 17.5%, 13.04%, and 11.0% in young (Figure 4.2.a), middle-aged (Figure 4.2.b), and older adults (Figure 4.2.c). Effect size[141] calculations indicate that the difference between the amounts of change in the correct responses rate associated with individuals who slept compared to those who stayed awake are real and meaningful for each age group. Moderate to large effect sizes of 0.51, 0.65, and 1.6 were found for young, middle-aged, and older adults, respectively.

4.5 Discussion

This study is the first to examine the role of sleep in learning a functional task that required walking while performing a cognitive task. In this study we examined whether sleep specifically enhances the cognitive aspect of the functional task. Our data indicate that in young, middle-aged, and older adults, cognitive performance improved only after a night of post-learning sleep and not after a similar period of wakefulness. This study adds to our previous findings that sleep enhances the walking component of a functional task in young, middle-age and older adults[157, 180].

The results of this work support the findings of Kuriyama et al[167] demonstrating that sleep enhances cognitive performance. However, in this current study we extended these findings by Kuriyama et al[167] to show that sleep also enhances the cognitive performance even if it is concurrently performed with a motor task. Improved performance on the motor component reported previously in young [157], middle-aged and older adults [180] was not due to decrement or at a “cost” to the cognitive component. Both the motor and cognitive components of the functional task improved off-line by the action of sleep. The results from this current study along with findings from our previous studies [157, 180] provide the first evidence that practicing two tasks at the same time does not interfere with the process of sleep-dependent off-line motor learning. Sleep may play an important role in individuals’ ability to walk effectively in a complex environment as well as to adequately allocate the attentional resources for successful completion of the functional task. More future studies are needed to confirm these results and investigate sleep stage(s) and neural mechanisms are responsible for sleep-dependent off-line learning of functional tasks.

One limitation of this study is the time-of the day-effect. However, the possibility that time-of-day effect explains our findings is unlikely. The training session was similar for participants who trained in the morning (no-sleep condition) or in the evening (sleep condition) for all age groups. The same case was found for level of sleepiness and functional mobility at the practice or at the retention testing in all age groups. We consider sleep to be the most likely reason behind the improvement on the cognitive performance observed in this study. Another important limitation is that we cannot completely separate the cognitive improvements from the motor improvement as both tasks were conducted simultaneously. The functional task we utilized in this study was not a true dual-task paradigm; neither a single cognitive task nor a single walking task was performed at the end of the practice session. Further, a single cognitive task was not performed at retention testing. A study that addresses this limitation is needed to better understand the role of sleep in learning a dual-task.

The enhancement of cognitive performance of a functional task by sleep has very important clinical implications. Older adults often have difficulty maintaining balance while simultaneously walking and performing a cognitive task[159, 169-172, 176]. The risk of falling is also increased[159, 169, 170]. In addition to exercise programs that focus on improving gait and balance abilities to improve dual-task performance, cognitive training can also provide additional benefit and enhance walking under dual-task conditions. Practicing these tasks increases older adults' ability to multitask in natural environments. The current study provides the first evidence that besides training, sleep might be an important factor to maximize the cognitive performance under dual-task intervention.

4.6 Conclusion

This study is the first to investigate that sleep enhances the cognitive component of a functional task. Clinicians should be aware of sleep problems in individuals who undergo rehabilitation. In order to maximize the effectiveness of rehabilitation interventions, sleep assessment should be performed to exclude any disorders that might interfere with the process of sleep-dependent off-line learning.

4.7 Acknowledgment

The study was supported by a grant from the Kansas Partners in Progress grant (KPIP), Kansas, USA.

4.8 Tables

Groups	Age	MMSE	SSS1	SSS2	Avg. Sleep	PSQI	Weight	Height	TUG1	TUG2	BDI	Years of education
Young adult												
Sleep	25.6 (3.2)	29.8 (0.6)	1.5 (0.5)	1.6 (0.7)	7.20 (0.8)	2.3 (1.2)	154.9 (22.7)	171.6 (9.3)	7.71 (0.7)	7.8 (0.6)	2.00 (1.04)	15.7 (0.96)
No-Sleep	25.8 (2.6)	29.8 (0.4)	1.4 (0.7)	1.58 (0.7)	7.31 (0.6)	2.7 (1.7)	157 (18.7)	173.1 (9.7)	7.76 (0.5)	7.9 (0.7)	2.7 (1.3)	15.5 (1.5)
Middle-aged adults												
Sleep	49.6 (3.6)	29.8 (0.4)	2.0 (0.8)	2.2 (0.4)	7.5 (0.7)	3.2 (1.9)	168.0 (37.8)	171.1 (10.4)	8.8 (0.4)	8.7 (0.5)	3.3 (2.9)	15.8 (2.2)
No-sleep	47.0 (3.4)	29.7 (0.5)	2.2 (1.03)	2.5 (0.8)	7.6 (0.8)	2.5 (1.4)	178.5 (20.3)	172.5 (10.1)	8.4 (0.7)	8.6 (0.8)	2.3 (1.6)	15.9 (1.7)
Older adults												
Sleep	69.1 (1.9)	29.8 (0.4)	1.7 (0.8)	1.5 (0.7)	7.30 (0.5)	3.3 (1.5)	170.2 (37.9)	171.3 (11.8)	9.3 (0.7)	9.2 (0.6)	2.00 (1.7)	16.2 (1.8)
No-sleep	71.6 (1.9)	29.6 (0.7)	1.6 (0.8)	1.6 (0.6)	7.49 (0.4)	4.1 (2.0)	157.6 (35.4)	167.2 (11.8)	9.1 (0.9)	9.1 (0.8)	4.00 (3.4)	15.5 (1.7)

Table 4.1. Descriptive information for young, middle-aged, and older adults. Data are mean (standard deviation). MMSE= Mini Mental Status Examination; SSS1= Stanford Sleepiness Scale taken at practice session; SSS2= Stanford Sleepiness Scale taken at retention testing; PSQI= Pittsburgh Sleep Quality Index; Ave. Sleep= Average amount of sleep participants had the week prior to testing demonstrated by sleep log. TUG1= Timed Up and Go taken at practice session; TUG2= Timed Up and Go taken at retention session; BDI= Beck Depression Inventory.

4.9 Figure Legend

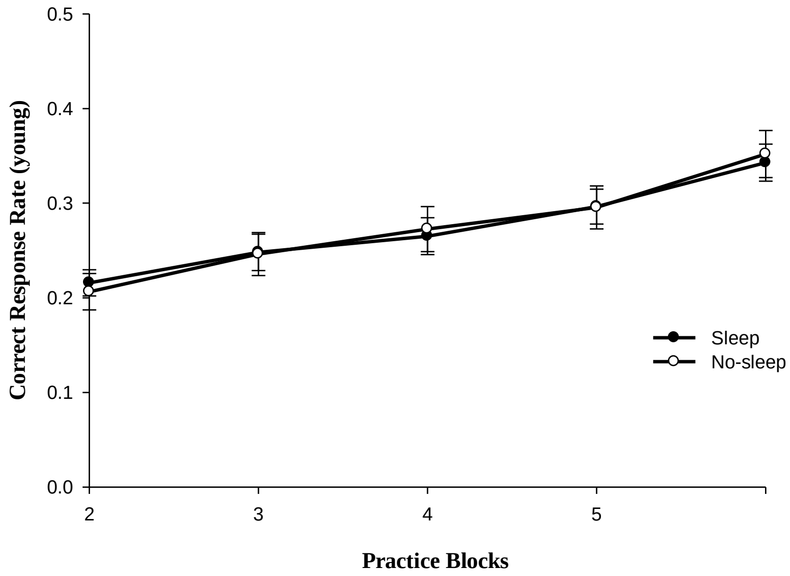
Figure 4.1. Performance changes across the training blocks (block 2-6) on cognitive performance in young, middle-aged, and older groups demonstrated by correct response rate. Error bars are SEM.

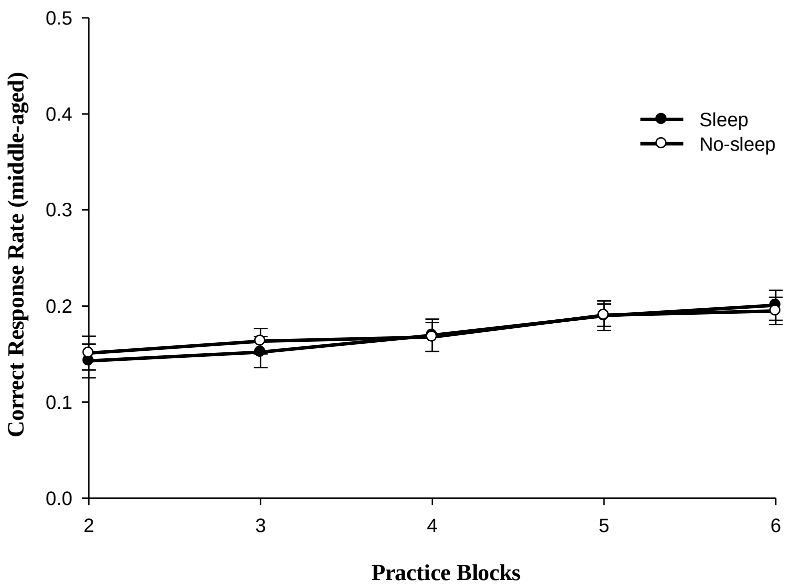
Figure 4.2.a. Off-line learning scores or change on performance on the cognitive component of the functional task between the last practice block and the retention testing for the sleep and no-sleep conditions, for the young adults. Error bars are SEM. *$p < 0.001$

Figure 4.2.b. Off-line learning scores or change on performance on the cognitive component of the functional task between the last practice block and the retention testing for the sleep and no-sleep conditions, for the middle-aged. Error bars are SEM. **$p < 0.05$

Figure 4.2.c. Off-line learning scores or change on performance on the cognitive component of the functional task between the last practice block and the retention testing for the sleep and no-sleep conditions, for the older adults. Error bars are SEM. **$p < 0.05$

Figure 4.1


Correct Response Rate (young)
0.5
0.4
0.3
0.2
0.1
0.0
2
3
4
5
Practice Blocks
Sleep
No-sleep


Correct Response Rate (middle-aged)
0.5
0.4
0.3
0.2
0.1
0.0
2
3
4
5
6
Practice Blocks
Sleep
No-sleep

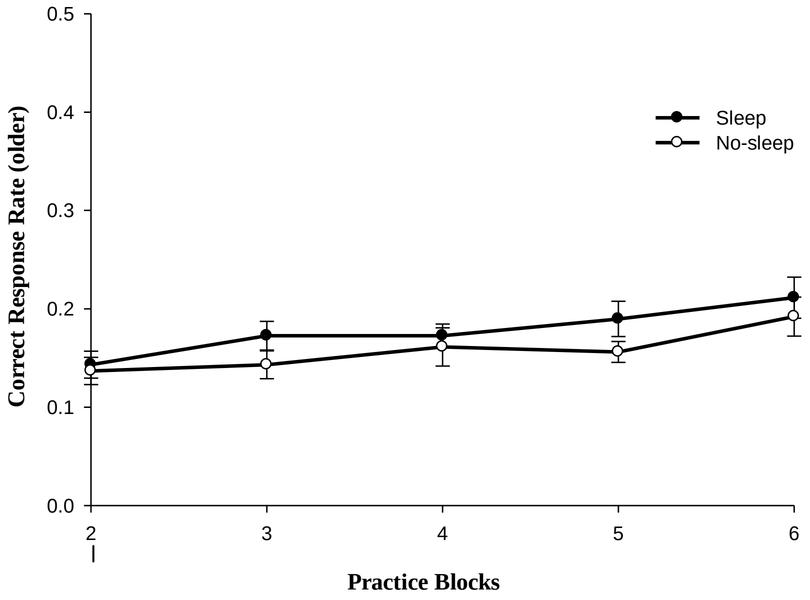

0.5
0.4
0.3
0.2
0.1
0.0
Correct Response Rate (older)
Sleep
No-sleep
2
3
4
5
6
Practice Blocks

Figure 4.2.a

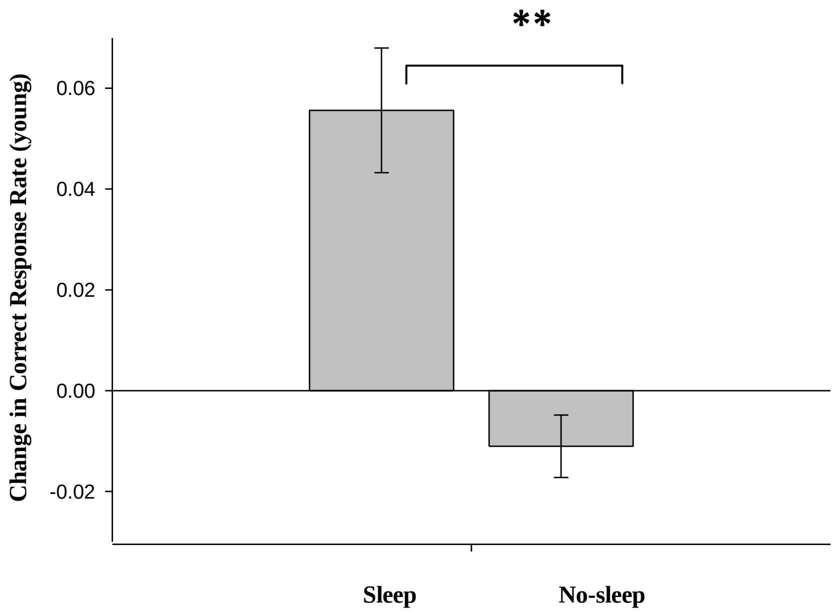


Figure 4.2.b

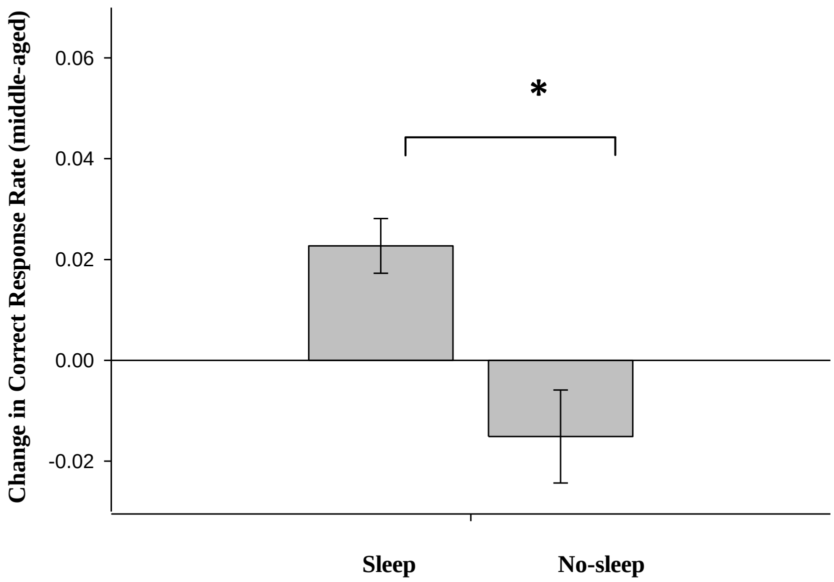


Figure 4.2.c

Change in Correct Response Rate (older)
0.06
0.04
0.02
0.00
-0.02
*
Sleep
No-sleep

Chapter 5

Discussion and Conclusion

5.1 Summary of Findings

The body of work presented here was conducted to investigate the role of sleep in learning a functional motor task. This research extends the literature examining the role of sleep in learning simple motor tasks that have limited real-life implications to examine the role of sleep in learning a functional motor task that is clinically-relevant. This research is the first to examine the role of sleep in learning a functional motor task in young, middle-aged, and older adults. Overall findings of this work demonstrate that sleep enhances learning a functional motor task in young, middle-aged, and older adults. However, young individuals demonstrated greater off-line improvement in performance compared to middle-aged and older adults, suggesting an age-related decline in sleep-dependent off-line motor learning. The findings of this research have very important implications for rehabilitation for young, middle-aged and older adults.

Chapter 2. Sleep Enhances Learning a Functional Motor Task in Young Adults

To date, all studies that examined the role of sleep in motor learning used simple fine motor tasks, conducted on a computer. These tasks also have very limited implications for real-life activities and for rehabilitation. It is still unclear if sleep enhances learning a functional motor task. Therefore, the purpose of Chapter 2 was to examine the role of sleep in learning a functional motor task that is clinically-relevant and has important implications for rehabilitation. Chapter 2 provides the first evidence that sleep is critical for learning a functional motor task in young adults.

Chapter 3. Performance on a Functional Motor Task is Enhanced by Sleep in Middle-Aged and Older Adults

While sleep has been demonstrated to have an important role in off-line motor learning and memory consolidation in young individuals, a few studies examined sleep-dependent off-line motor learning in older adults and offered mixed conclusions. All of these studies also used simple fine motor tasks. In young adults, it has been found that sleep enhances tasks that are more complex and are relevant to the individual's behavior; however, no studies have examined if these factors will maximize off-line learning in older adults. Further, only one study has attempted to examine role of sleep in motor learning in the middle-aged. The purpose of Chapter 3, therefore, was to examine if sleep enhances learning a task that is complex and relevant to the middle-aged and older adult's life. Also, we assess age-related changes in sleep-dependent off-line learning of a functional motor task. Middle-aged and older adults demonstrated a clear benefit from sleep. In both age groups, participants who slept after practicing the novel walking task demonstrated a significant off-line improvement in performance on all walking outcome measures, while those participants who stayed awake failed to demonstrate off-line learning. However, the magnitudes of off-line improvements were reduced compared to those observed in young individuals.

Chapter 4. Sleep Enhances the Cognitive Performance of a Functional Task

Many functions in everyday life require people to perform more than one task at a time such as walking while remembering a shopping list (multitask). Studies to date examined the role of sleep in motor learning using a single motor task. No study has attempted to examine the role of sleep in learning a task that requires both cognitive and motor performance. In Chapters 2 and 3 we found that sleep enhances performance of the walking (i.e., motor) aspect of the functional task. In Chapter 4 we assessed whether sleep also enhances the cognitive performance of the functional task. This study is the first to provide evidence that sleep does enhance the cognitive performance of the functional task.

5.2 Clinical Implications

During rehabilitation, physical therapists frequently spend a large portion of their treatment session teaching patients how to perform skills to improve a given disability and to increase independence in daily live activities. Exploring factors that may enhance motor learning is critical. The findings from this work indicate that sleep promotes learning a clinically-relevant task in young, middle-aged, and older adults.

We believe it is important to provide physical therapists with recommendations to incorporate sleep as an important factor for motor learning. It is possible to improve clinical outcomes of rehabilitation by integration of sleep into clinical interventions. The findings of this study could impact how physical therapists design the therapy sessions. Physical therapists may need to perform therapy sessions in the evening or late day before sleeping. Alternatively, napping following therapy session might be encouraged. Performance on simple motor tasks has been found to improve after a short nap of 60-90 minutes[10, 20, 78 79-81].

The findings from the current study that sleep-dependent consolidation process declines with advancing age should encourage clinicians and researchers to explore methods to improve sleep architecture. For example, pharmacological approaches that can improve sleep architecture could be considered as a possible way to increase sleep-dependent learning.

Sleep quality is very important factor for sleep-dependent off-line learning. Many individuals who undergo rehabilitation frequently present with poor sleep quality and sleep disorders which might interfere with the process of sleep-dependent motor learning[145-148]. As a result therapists should consider encouraging adequate sleep. Therapist should also address sleep issues in individuals undergoing therapy. Thus, sleep quality assessment should be considered an essential part of the routine exam. Physical therapists need to be educated about normal sleep cycle, sleep disorders, and sleep assessment methods.

5.3 Limitations

Time-of-Day Testing

A factor that might influence the results of the current study is time-of-day testing. However, our data indicate that both the sleep and no-sleep groups for all age groups demonstrated improvements in performance across practice blocks. Regardless of the time of day the practice session occurred, the participant's performance was not significantly different from each other. This suggests that the sleep and no-sleep groups performed similarly to each other despite practicing at different times of day. If time-of- day of testing had influenced the findings of the presented study, we would have expected to have seen better performance in in the no-sleep group who practiced in the morning compared to the sleep group who practiced in the evening. This was not the case. In addition, in all age groups, the level of sleepiness and functional mobility as determined by the Stanford Sleepiness Scale and Timed Up and Go test, respectively, did not reveal differences between the sleep and the no-sleep at practice or retention testing regardless of the time of day testing occurred. This study demonstrated that sleep has a significant positive impact on learning a functional motor task that is not explained by factors related to the time of the day.

Monitoring Sleep Quality and Quantity

As this study was not conducted in a sleep lab, one of the study's limitations was the difficulty in monitoring the amount and the quality of sleep participants obtained the night between practice and the retention testing. Despite this limitation, we believe having participants sleep at home provides evidence that sleep-dependent off-line skill enhancement occurs in a natural environment. Furthermore, sleep structure has been found to be adversely affected by polysomnographic recording in a sleep laboratory. Delayed sleep onset, sleep disruption, and decreases in REM sleep and SWS occurred when individuals slept in a sleep laboratory[67]. Our work attempted to monitor the amount and the quality of sleep by having participants maintain a sleep log for a week prior to the first session. In addition, the PSQI was used to index the sleep quality of our participants. In all age groups, no significant differences were found between the sleep and the no-sleep groups with respect to the amount of sleep reported for the week prior to the study as well as the PSQI scores. Furthermore, available actigraph data indicate that, for all age groups, participants in the no-sleep did not sleep between practice and retention testing. Participants in the sleep group had good sleep quality during the night between practice and retention testing.

5.4 Future Directions

Investigating Sleep Parameters Associated with Off-Line Learning of a Functional Motor Task

A longstanding line of research indicates that the sleep stages REM and Stage 2 non-REM sleep are associated with the neural processes underling the consolidation of newly encoded simple procedural memories in young adults. However, the particular sleep stage (s) that is/are important for sleep-dependent off-line learning in middle-aged and older, healthy individuals remains to be explored. Studies also indicated that factors such as cognitive load and an initial skill level of the learner seem to affect which stage is important for a given procedural memory. In this work we used a functional motor task to assess sleep-dependent off-line learning in young, middle-aged, and older adults. This task is very different compared with simple motor tasks previously used. Therefore, future studies are needed to be conducted in the sleep laboratory following practice of a functional motor task to investigate which sleep stage (s) might be associated with sleep-dependent off-line learning of a functional motor task in young, middle-aged and older adults.

Understanding Neural Activity Associated with Off-Line Learning of a Functional Motor Task

Neuroimaging studies demonstrate changes in brain activity that relate to procedural motor task consolidation in young adults. No studies have examined the changes in neural activity associated with sleep-dependent off-learning in middle-aged and older adults. Furthermore, all studies that have been conducted in young adults assessed brain activity related to simple motor task consolidation. Therefore, neuroimaging studies are needed to assess changes in neural activity following learning a functional motor task in young, middle-aged, and older adults.

Examining whether Sleep Enhances Learning a Functional Motor task in Neurological Population

This body of work demonstrates that young, middle-aged, and older healthy adults benefit from sleep to enhance off-line learning on a functional motor task. This task was chosen to assess if sleep enhances learning complex tasks that are clinically-relevant (i.e., have important implications for rehabilitation). During rehabilitation, learning new motor skills and relearning old motor tasks is very important for neurologically impaired individuals such as those with stroke or multiple sclerosis. Few studies have found that sleep enhances off-line motor learning in neurologically impaired individuals (i.e., stroke) [36, 37]. However, these studies have used simple motor tasks that have limited implications for rehabilitation (such as continuous tracking task). Therefore, future studies are needed to determine whether neurologically impaired individuals will benefit from sleep to enhance learning functional motor tasks they usually need to learn or relearn during rehabilitation.

5.5 Conclusions

The work presented in this dissertation extends the current sleep literature and investigates the role of sleep in learning a functional motor task that is more clinically-relevant. The findings of this work demonstrate that sleep enhances learning a functional motor task in young, middle-aged, and older adults. Furthermore, the presented work provides the first evidence that sleep enhances learning both the motor and the cognitive aspects of the functional walking task. Also, the present work provides additional support that sleep-dependent off-line learning decline with advanced age. Clinically, these findings suggest that clinicians should consider sleep as an important factor when structuring rehabilitation interventions. Different strategies need to be considered by clinicians to ensure the beneficial role of sleep on rehabilitation sessions. Emphasis should be placed on addressing sleep disorders and ensuring adequate sleep for individuals who undergo rehabilitation. Furthermore, the routine exam should include sleep quality assessment. Normal sleep cycle, sleep disorders, and sleep assessment methods need to be incorporated in the educational plans for physical therapists.

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