SLEEP TO LEARN AFTER STROKE: THE ROLE OF SLEEP AND INSTRUCTION IN OFF-LINE MOTOR LEARNING

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Abstract

Stroke affects nearly 780,000 individuals each year in the United States and is a leading cause of adult disability. More than half of individuals following stroke experience persistent loss of function. Learning new motor skills and re-learning old motor skills is an important component of rehabilitation following stroke. Examining methods that hasten or increase the efficiency of motor skill learning following stroke is an important clinical endeavor. Sleep has been demonstrated to produce off-line improvements in motor learning in young, neurologically intact individuals. However, the role of sleep in motor learning following stroke is unclear. Addressing this question was the purpose of this body of work.

Chapter 2 utilized the discrete serial reaction time (SRT) task to examine the difference in both motor performance and learning for forty-two participants who either remained unaware of the presence of the sequence (implicit condition), were given no instruction of the sequence prior to the start of practice but gained explicit awareness during practice (acquired explicit condition), or were provided explicit instruction prior to practice (explicit condition). Results demonstrate a benefit of explicit knowledge to improve response time both during task practice and at retention regardless of whether it was acquired during or provided in advance of practice. This study highlights the frequent ability of people to acquire awareness of the regularities of the task being practice, creating a continuum of implicit motor learning from "pure" implicit learning where the participants have no awareness of the regularities being practiced to full explicit motor learning with the participants having complete awareness of the task regularities. This study led us to utilize a continuous tracking task to examine the role of sleep and type of instruction in off-line motor learning following stroke and in healthy, older control participants in order to differentiate between off-line implicit and explicit motor learning.

While mounting evidence demonstrates sleep is critical for motor skill learning in healthy, younger individuals, the importance of sleep for off-line motor learning after stroke is unknown. Therefore, Chapter 3 examined sleep-dependent off-line motor learning of an implicit continuous tracking task. Eighteen individuals following stroke in the MCA distribution practiced the tracking task and then either slept (sleep condition) or stayed awake (no-sleep condition) for a similar period of time before retention testing to assess off-line motor learning. Eighteen sex- and age-matched participants served as controls. Only the stroke participants who slept between practice and retention testing demonstrated off-line implicit motor learning at retention. The stroke participants who stayed awake between practice and retention did not demonstrate off-line motor learning nor did either of the control groups. This study provides the first evidence that individuals following stroke benefit from sleep to enhance implicit motor learning off-line.

Other learning variables, such as type of instruction, have been shown to influence the beneficial role of sleep in off-line motor skill learning in young, neurologically intact individuals. Therefore, Chapter 4 extended the findings of Chapter 3 and examined sleep-dependent off-line motor learning of both an implicit and explicit version of the continuous tracking task. Forty individuals post-stroke and

40 control participants were assigned to either the sleep group or the no-sleep group, as in Chapter 3. To examine the influence of type of instruction on off-line learning, half of the individuals in both the sleep and no-sleep condition were provided explicit instruction regarding the presence of a repeating sequence (explicit condition) while the other half were not (implicit condition). The individuals post-stroke who slept between practice and retention testing demonstrated sleep-dependent off-line motor learning of both the implicit and explicit version of the continuous tracking task. Individuals with stroke who stayed awake between practice and retention testing did not demonstrate an off-line improvement in motor performance at retention. The healthy control participants did not demonstrate off-line improvements in performance regardless of sleep of type of instruction. These results demonstrate that after stroke, individuals benefit from sleep to improve performance of a tracking task off-line regardless of type of memory system involved.

Learning a motor skill requires the integration of the spatial and temporal movement components of the task. Little is known if particular components of a motor skill task (spatial and/or temporal components) are preferentially enhanced following sleep in individuals following stroke. Chapter 5 sought to address this question by deconstructing the overall change in tracking accuracy displayed by the participants in Chapter 4 into spatial and temporal movement components. The results reveal that the individuals with stroke who demonstrated overall off-line improvements in motor learning attributable to sleep improved spatial accuracy as well as reduced the time lag of tracking off-line. Participants following stroke who

stayed awake between practice and retention testing did not demonstrate an improvement in either spatial accuracy or a reduction in time lag of tracking at retention. Likewise, the control participants did not demonstrate sleep- or time-dependent enhancement of either movement component. This study provides the first evidence that sleep enhances both spatial and temporal movement components of a motor learning task in individuals following stroke.

In summary, this body of work demonstrates that individuals following stroke benefit from sleep to enhance both implicit and explicit off-line motor learning. In addition, this sleep-dependent off-line motor learning extends to both the spatial and temporal movement components of the tracking task. This work also provides concurrent evidence that healthy, older adults fail to benefit from sleep to enhance off-line motor learning. While it remains unclear why individuals following stroke are able to benefit from sleep to promote off-line motor learning and healthy, older adults are not, we propose that alterations in sleep architecture and changes in cortical excitability following stroke likely contribute to sleep-dependent off-line motor learning. The findings of this body of work are important because evidence that sleep enhances off-line motor learning following stroke could impact the design of rehabilitation interventions; to maximize motor learning and recovery after stroke it may be critical to ensure that sleep occurs between practice sessions.

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Chapter 1

Introduction

1.1 Overview

Mounting evidence has demonstrated that sleep has an important role in motor learning and memory consolidation in young, healthy individuals (review articles[1-7]). Memory consolidation refers to a slow process in which memory traces are transformed through the passage of time and without further practice from a labile state into a more permanent form[8]. Although some disagreement remains[9-11], sleep has been shown to enhance motor performance on a task "off-line" when no further practice has taken place[12-16]. Furthermore, sleep may interact with other learning variables such as type of instruction (explicit instruction vs. no explicit instruction or implicit learning; 1.8. Type of Instruction). The difference between implicit and explicit off-line motor learning is based on the participant's awareness of the regularities contained in the skill being practiced; explicit learning refers to knowledge of the regularities of the skill to be learned, whereas implicit learning occurs without this awareness [17]. Sleep appears to preferentially benefit off-line motor skill learning in young, healthy individuals who are given explicit instruction prior to acquisition; where as implicit off-line motor learning is time dependent (i.e. the performance of people given no instruction prior to acquisition improves both following a period of sleep and a period of being awake)[18]. This finding is consistent with work that demonstrates a preferential enhancement of explicit awareness and recognition following a period of sleep[19, 20].

The role of sleep in off-line motor skill memory consolidation may also depend on other factors including which stage of memory formation is considered

(1.2. Memory Processing), the type of memory being consolidated (1.3 Types of Memory), as well as the task utilized for practice (1.5.Type of Task). Furthermore, a different stage or stages of sleep may be critical for different types of memory consolidation (1.7 Learning and Stage of Sleep). The manner in which sleep-dependent off-line motor learning reconfigures neural circuits (1.9. Neuroimagaing, Learning and Sleep) as well as the mechanisms underpinning the need for sleep to consolidation memories (1.10 Neural Mechanisms of Sleep-dependent Memory Consolidation) are questions currently under consideration. While many questions regarding sleep-dependent off-line memory consolidation have been and are currently being addressed, many more questions lie in wait.

While sleep has been demonstrated to have an important role in off-line motor learning and memory consolidation in young, healthy individuals, it is less clear if sleep is important for off-line learning in older, healthy individuals. Two studies that examined the role of sleep in off-line learning and memory consolidation in healthy, older adults demonstrate that older individuals are not reliant on sleep for either motor[21] or declarative memory consolidation[22]. Older adults demonstrate changes in sleep architecture[23, 24, 25, 26] which may limit the potential benefits of sleep.

Importantly, the significance of sleep for off-line motor learning in neuropathological populations is poorly characterized. It is well known that individuals with stroke are able to learn new motor skills[27-31]. However, because many individuals post-stroke experience sleep disturbances[32,33] and alterations in sleep architecture following stroke[34-36,34,37], the potentially confounding role of sleep on motor learning is a critical clinical issue. *This study seeks to define the impact of sleep and type of instruction on off-line motor skill learning in people with stroke in the MCA distribution*. This work has implications for the manner in which rehabilitation is conducted following stroke.

1.2. Memory Processing

The role of sleep in motor learning likely depends on which stage of memory processing is being considered. Motor memory develops over time in at least four distinct stages[38]. The first step is encoding or acquisition when the memory is initially formed into a representation in the brain. This is followed by consolidation, where the memory is taken from a labile form and made more permanent. Walker et al.[39,15] further divides consolidation into two different categories: stabilization and enhancement. Stabilization refers to the maintenance of motor skill performance, occurs simply through the passage of time and is not dependent on sleep, whereas enhancement refers to an improvement in performance of a skill and is thought to be dependent on the activity of sleep. The third step in motor memory processing is storage, when the memory is maintained in the brain over time. The final step is recall when the motor memory is able to be brought out of storage for further use.

Sleep may differentially affect each stage of motor memory processing, although consolidation is the most often studied to date and appears to be the stage most impacted by sleep. The permissive environment created during sleep (discussed in 1.10 Neural Mechanisms of Sleep-dependent Memory Consolidation) allows the memory trace initially encoded during practice to be consolidated into a more permanent form. This consolidated memory trace is thought to be fairly stable across time until recalled from memory during subsequent task practice. Following recollection, the motor memory is capable of being modified and is believed to undergo another period of consolidation (called reconsolidation) for that memory to again be placed into more permanent storage. Reconsolidation may also be a sleep-dependent process, but more research is needed on this topic[7, 40, 41].

1.3 Types of Memory

The role of sleep in memory consolidation is thought to depend on the type of memory being considered. Types of memory are typically classified into two broad categories: declarative memory and nondeclarative memory. Declarative memory is able to be brought to conscious recollection and includes memories of facts and events[42, 43]. Nondeclarative memory is unable to be brought to conscious recollection and is assessed indirectly through performance of the skill in which the memory is contained[42, 43]. Procedural memory is one type of nondeclarative memory and can be assessed through testing of motor skills. Although procedural memory is often thought to be synonymous with implicit learning and declarative memory with explicit learning, these terms are not always interchangeable. The implicit-explicit distinction is based on the participant’s awareness of the regularities being practiced; explicit learning refers to having an awareness of the regularities of the environment to be learned where as implicit learning occurs without this awareness[17]. While procedural skill learning is generally implicit in nature, there are exceptions, such as if explicit instruction is provided prior to the start of practice or if explicit awareness is acquired through practice[18, 44].

Declarative and procedural memory has been demonstrated to be neuroanatomically separate. The medial temporal lobe has been confirmed to be important for declarative learning and memory formation[45, 46]. The neural circuit supporting procedural learning is more widely distributed and includes the sensorimotor cortex, the cerebellum, and the basal ganglia[47-49]. Therefore, completely abolishing procedural learning via brain damage is much more unlikely. There are inconsistencies in the findings of neuroimaging studies that have examined the neural components of procedural learning[50-61]. This disparity is likely explained by those studies using different experimental designs and tasks, varying levels of explicit instruction, as well as the different degrees of explicit awareness obtained during implicit learning. Furthermore, limitations due to neuroimaging technique and analysis methods also contribute to the varying results[53]. Nonetheless, of interest for the present work, imaging studies support the role of the sensorimotor cortex[50, 51, 54] (particularly M1[62, 63]), premotor cortex[52, 57], SMA[50, 51], and basal ganglia[50-53, 57, 60, 61] in procedural learning. All of these brain areas receive their blood supply from the MCA, which is the most often occluded artery during stroke[38].

Although neuroanatomically and functionally separate, declarative and procedural memory can develop in parallel. Evidence to support this has been demonstrated in participants who are given explicit instruction on the presence of a sequence prior to learning the sequence implicitly and both explicit and implicit memories of the sequence are formed[64]. Participants also can gain a degree of explicit awareness following practice of an implicit sequence, often depending on the length of the sequence and type of sequence to be learned. For example, neurologically intact participants often gain explicit awareness of a short sequence using the Serial Reaction Time (SRT) task, but have much difficulty, if any ability at all, to detect a pattern in a continuous tracking task. This demonstrates that while neuroanatomically separate, implicit and explicit learning can occur simultaneously depending on the type of task.

1.4 Procedural Learning and Sleep

Performance on procedural memory tasks has been well documented to benefit from sleep in that performance on the task is enhanced off-line following a period of sleep. Participants who practice the task and then sleep perform better on the task following a period of sleep versus a similar period of being awake. This has been shown to be true using both a visual discrimination perceptual task [65-68] and a variety of simple motor[12-16] skill tasks. Fischer et al[16] found that participants demonstrated improved performance on a finger-to-thumb opposition motor task following sleep both at night as well as during the day suggesting sleep rather than circadian rhythm resulted in the skill enhancement. Even a short nap of 60-90 minutes can produce an improved performance on both motor[69, 70] and perceptual[71] memory tasks in young, neurologically intact participants.

While the majority of studies to date examined off-line sleep-dependent performance enhancement in young, neurologically intact individuals, little work has examined sleep-dependent memory consolidation in older individuals. Hornung, Danker-Hopfe, and Heuser[72] suggest that because older adults experience both sleep and memory changes with advancing age, the relationship between sleep and memory in older individuals should be addressed. The two studies that have examined the role of sleep in learning in older individuals found that older adults demonstrate a lack of off-line sleep-dependent enhancement on both an explicit and implicit version of a procedural sequence learning task[21] and a declarative memory word-pair associations task[22]. Based on this prior work, it does not appear that older individuals benefit from sleep to enhance off-line learning. However, it is possible that the changes in sleep architecture often demonstrated by older individuals limits the potential benefits of sleep (sleep architecture of older adults discussed in1.6. Stages of Sleep). Another study found improvement in REM sleep parameters through the use of sleep-aid medication was correlated with enhanced performance of older adults on a word recall task[73]. No apparent attempts were made to correlate other sleep stages or characteristics such as non-REM stage 2 or sleep spindle activity with performance improvement, therefore, the impact of other sleep characteristics cannot be ruled out. Nonetheless, the findings of this study suggest that older individuals may in fact benefit from sleep to enhance off-line learning if underlying changes in sleep architecture are addressed.

It remains unclear as to whether sleep impacts off-line skill learning and memory consolidation after stroke. Individuals following stroke are able to learn new motor skills[27-31]. However, none of these studies considered the influence of sleep on off-line motor learning. This current work sought to add to the understanding of the role of sleep in off motor skill learning in older, healthy adults and after stroke.

1.5. Type of Task

The beneficial effect of sleep on learning and memory consolidation may depend on the type of procedural task being considered. Two important task classifications for motor skills are discrete versus continuous. Discrete skills are movements with an obvious beginning and end, such as kicking or throwing a ball, whereas continuous skills have no obvious beginning or end, such as walking, swimming or jogging[74]. Studies to date examining the beneficial role of sleep in off-line motor performance enhancement have used several different discrete tasks: a finger-to-thumb opposition task[13-16, 19, 75], a sequential finger-tapping task[18, 74, 76, 77], and the SRT task[78-82]. One study[76] used a pursuit task but 18 seconds of practice was interspersed with 18 seconds of rest thus making the task more discrete in nature. Recent evidence demonstrates that while sleep enhances performance on a number of simple discrete tasks, sleep may not in fact benefit all kinds of discrete tasks; a probabilistic discrete task was not enhanced off-line by a night of sleep[83]. Therefore, it appears not all discrete tasks experience sleep-dependent off-line memory consolidation.

Questions remain regarding whether the overall findings that discrete tasks are enhanced off-line by sleep will generalize to a continuous task. Due to the often rapid nature of discrete tasks, these types of skills are thought to rely on a motor program to produce the rapid movement whereas continuous tasks are thought to rely on the ability to use feedback to correct movements while the movement is being produced[74]. Therefore, these differences in motor control may result in a differential effect of sleep on learning these skills.

A continuous tracking task was originally developed by Pew[77] and has since been used by others[78-82] to examine continuous motor sequence learning. In a series of experiments, Boyd and Winstein[80, 82] found that providing explicit information while learning a continuous tracking task aided learning of the task for neurologically intact participants but inhibited learning in participants with basal ganglia or sensorimotor cortical lesions. Shea et al.[79] found that providing explicit awareness of the presence of a sequence to neurologically intact participants inhibited learning of the sequence, but a more complex task of balancing on a stabilometer was used in this study. The difference found in the Shea et al. study is not surprising given a review by Wulf and Shea[84] which concluded that the factors influencing learning of simple motor skills do not automatically apply to complex motor skill learning. Importantly, the effect of sleep or the participants' quality of sleep was not considered in any of these studies. Interestingly, one study found that the more complex the motor task was, the greater the off-line improvements following sleep[85]. This suggests that "real-life" complex motor tasks may benefit from off-line sleep-dependent enhancement. We tested this hypothesis by using a continuous tracking task which more closely mimics a continuous “real-life” task, such as walking.

1.6. Stages of Sleep

According to Rechtschaffen and Siegel[86], sleep is “defined behaviorally by four criteria: (1) reduced motor activity, (2) decreased response to stimulation, (3) stereotypic postures (in human, for example, lying down with eyes closed), and (4) relatively easy reversibility (distinguishing it from coma, hibernation, and estivation).” Sleep is generally classified into two different stages: non-rapid eye movement sleep (NREM) or rapid eye movement (REM) sleep (Table 1.1). NREM sleep is divided into four characteristic substages corresponding to increasing depth of sleep as shown using EEG: stage 1 involves the transition from wakefulness to the onset of sleep and is characterized by sinusoidal alpha wave activity (10Hz); stage 2 is characterized by bursts of sleep spindles (12-14 Hz) and K complexes; stage 3 and 4 are grouped into slow-wave sleep (SWS) and are characterized by high-amplitude slow delta waves (0.5-2hz)[86]. REM sleep, also known as paradoxical sleep because the EEG pattern is similar to the normal awake pattern with a low-voltage, mixed-frequency pattern, is characterized by rapid eye movements, ponto-geniculo-occipital spikes (PGO spikes), and muscle atonia[86].

Humans fall asleep by entering NREM sleep first followed with REM sleep, and the phases then alternate cyclically every 90-110 minutes through four to six cycles a night[86, 87]. The ratio of NREM to REM sleep changes as the night progresses, with stages 3 and 4 of NREM (SWS) being prevalent in the first half of the night and stage 2 NREM and REM sleep dominating in the latter half of the night[87].

Stage of Sleep	**Characteristic Activity**	**Characteristic Wave Form**	**Time Spent (Young Adults)**
REM	muscle atonia; rapid eye movements	low-voltage, mixed-frequency pattern; PGO spikes	20-25%
NREM Stage 1	Slow rolling of eyes	sinusoidal alpha wave activity (10Hz)	about 5%
Stage 2		sleep spindles (12-14 Hz) and K complexes	50-60%
SWS (Stages 3 & 4)		high-amplitude slow delta waves (0.5-2hz)	15-20%

Table 1.1 Summary of sleep stages

Young adults spend the largest amount of sleep in stage 2 non-REM sleep (50-60%), followed by REM sleep (20-25%), SWS (15-20%), and stage 1 non-REM sleep (about 5%)[86]. With advancing age, total sleep time decreases as does the percentage of time spent in REM and slow wave sleep (SWS)[23, 24]. While the amount of time spent in Stage-2 non-REM sleep remains fairly stable[23], there is a reduction in the number of sleep spindles that occur with age[25, 26]. Sleep spindles, a defining characteristic of Stage-2 non-REM sleep, are a burst of brain activity of 12-14 Hz[88, 89]. Furthermore, sleep spindles have been demonstrated to play an important role in off-line sleep-dependent motor memory improvement[69, 90, 91].

Alterations in sleep patterns are a common experience for many people after stroke. A review by Bassetti[32] estimates that between 20 and 40% of people with stroke have sleep-wake disorders (SWD), including insomnia, excessive daytime sleepiness/fatigue, or hypersomnia. Another study found 56.7% of people 3-4 months following stroke suffered from insomnia[33]. These SWD's can be attributed to a number of factors including depression, sleep-disordered breathing, complications due to stroke itself, and medications[32]. Furthermore, sleep architecture changes following stroke, including decreased total sleep time and sleep efficiency and increased waking after sleep onset following acute stroke[34-36]. A reduction in REM sleep[92] and NREM sleep stages 2-4[34] has also been reported following acute stroke. Sleep patterns do not appear to normalize with time; 53% chronic stroke participants (5-24 months post-stroke) showed differing sleep EEG characteristics compared to published norms[37]. Considering the large number of people after stroke who experience sleep alterations in combination with evidence supporting the role of sleep in off-line motor memory consolidation, examining the effect of sleep on off-line motor learning following stroke is a critical issue which this current work sought to address.

1.7 Learning and Stage of Sleep

There is some agreement among researchers concerning which stage of sleep is important for the consolidation of a certain type of memory, but discrepancies persist. There are two different theories to explain the role of the various sleep stages on the consolidation of different memory traces, with more recent studies showing increased support for the latter. According to the "*dual-process theory*", a single sleep stage (i.e. REM or SWS sleep) acts on a memory trace (i.e. procedural or declarative) depending on which memory system that trace is from[3]. According to the "*sequential hypothesis*", memories are consolidated through the ordered sequence of NREM followed with REM sleep, so that both stages of sleep are necessary for consolidation[93]. However, both of these theories may be true in that both NREM and REM sleep stages are important for memory consolidation, but some memory traces may require more SWS sleep (i.e. declarative memory) and other memory traces may require more stage-2 NREM or REM sleep (i.e. procedural memory).[3]

Though some conflict remains, current consensus indicates that SWS is important for declarative memory consolidation. For example, declarative memory of word list recall[94, 95] was facilitated by periods of early nocturnal sleep, which corresponds to SWS. Participants who are sleep deprived of the first half of sleep, a period that is rich in SWS, did more poorly on recall of word list compared to participants deprived of sleep for the second half of the night, rich in REM sleep[96]. In addition, stimulating cortical neurons during SWS was found to enhance recall of a word list[97] which provides concurrent evidence that SWS is important for the consolidation of declarative memories.

Other research has demonstrated that REM sleep is important for consolidating declarative memories. REM sleep has been demonstrated to be important for the learning of a foreign language[98] or Morse code[99], and recalling lists of words and prose passages[100]. However, Chernik[101] found no significant difference in the ability to recall word pairs between a REM-deprived group and the control group who was deprived of a similar amount of non-REM sleep. The discrepancy to which stage of sleep is important for the consolidation of declarative memory may be because episodic (memory of events) and semantic (memory of facts) memory, which are both types of declarative memory, require a different stage(s) of sleep for consolidation; semantic memory may require REM sleep to consolidate, whereas episodic memory may require anywhere from one to all stages of sleep[3]. Wagner et al.[102] suggest that REM sleep is important for the consolidation of declarative memory that has an emotional content, but emotionally neutral declarative memory does not benefit significantly from sleep.

Consensus is building that procedural memory for perceptual-motor tasks requires stage-2 and/or REM sleep for consolidation. Procedural memory of mirror-tracing[94, 95] was facilitated by periods of late nocturnal sleep, which corresponds to Stage-2 NREM and REM sleep. Research has demonstrated that procedural tasks are impaired by either REM[67] or stage-2 sleep deprivation[103,104]. Overnight improvement in the performance of a finger-tapping task was found to correlate with the amount of stage-2 NREM sleep[13], whereas overnight improvement in a similar finger-to-thumb opposition task correlated with the amount of REM sleep[16]. Smith et al. [105] suggest that an increase in the number of rapid eye movements and density of REM (number of REMs per minute of REM sleep) during sleep are important for procedural task consolidation, rather than time spent in REM sleep. Another factor to consider is the cognitive requirement of the skill being learned with less cognitively taxing procedural skills benefiting from stage-2 sleep while more cognitively involved procedural tasks benefiting from REM sleep for consolidation[90]. Another interesting caveat in trying to determine which stage of sleep is important for procedural memory consolidation is the initial skill level of the learner; REM sleep was shown to be important when the skill to be learned was novel where as Stage 2 sleep was beneficial for learning if the skill only needed refinement[106].

The need for an ordered sleep cycle to consolidate memories may be the reason for the discrepancies mentioned regarding which sleep cycle is important for a particular type of memory. Stickgold et al[65] and Gais et al[68] both demonstrated using a visual discrimination task that performance was enhanced following the ordered sequence of SWS followed with REM sleep. Ribeiro and Nicolelis[107] demonstrated in rats that neuronal circuits involved in a novel tactile stimulation are replayed during SWS while increase in gene expression occurred during REM sleep. This evidence from neurophysiological recordings conducted in rodents provides additional support for the sequential hypothesis that purports it is the ordered cycle of NREM sleep followed with REM sleep that is important for memory consolidation.

In summary, memories are likely consolidated through the repeated pattern of NREM followed with REM sleep throughout the course of sleep with SWS being the stage more important for declarative memory consolidation and stage-2 and REM sleep being more important for procedural memory consolidation. However, many other variables such as the emotional content of the memory, the cognitive load of the task, or the initial skill level of the learner appear to impact which stage of sleep is critical for declarative and procedural memory consolidation. While assessing the influence of various sleep stages on off-line motor skill learning was outside the scope of the presented work, future studies will undoubtedly seek to answer these questions and clarify the role of the various sleep stages in procedural and declarative memory consolidation.

1.8. Type of Instruction

Another factor to consider when examining the role of sleep in off-line motor learning and memory consolidation is the type of instruction a participant receives prior to practicing a skill. Explicit instruction may either aid[64, 82, 108] or inhibit[79, 109, 110] procedural learning in neurologically intact people. This discrepancy likely depends on the type, timing, and quality of explicit knowledge given. In a study by Robertson et al.[18], healthy, young participants who had no awareness (implicit condition) of the sequence to be learned demonstrated an improvement in performance at retention both following a period of being a sleep and a similar period of being awake. Participants who were given explicit instruction on the presence of the sequence to be learned only demonstrated improvement in performance of the skill following a period of being a sleep, but not following a period of being awake. Robertson et al.[18] concluded that motor memory consolidation using implicit instruction is time dependent, whereas motor memory consolidation using explicit instruction is sleep dependent. In examining prior studies[13-16] that also demonstrated off-line enhancement in skill ability following a period of sleep, the similarity between these studies, although not outright stated, is that the participants in these studies all had explicit awareness of the skill being learning and, thus, lends support that off-line motor memory consolidation using explicit knowledge is sleep dependent.

Other studies have also demonstrated that explicit knowledge and memory may preferentially benefit from sleep compared to implicit memory. Fischer et al[19] found that participants who slept after practicing the SRT task demonstrated enhanced explicit awareness of the presence of the sequence compared to participants who did not sleep between practice and retention. Furthermore, participants who slept in a study by Drosopoulus et al[20] demonstrated improved explicit recollection memory on a word-list discrimination task but did not demonstrate improved implicit familiarity memory. Using 3 different versions of the SRT task, Spencer et al[111] demonstrated that participants who slept had improved performance on an explicit version as well as an implicit contextual version but not on the implicit non-contextual version. Because contextual association formation is hippocampus-dependent as is explicit memory formation, the authors concluded that sleep-dependent enhancement in performance is dependent on the hippocampus. Interestingly, Schendan et al.[59] found medial temporal lobe activation in both an implicit and explicit version of the SRT task. Furthermore, the amount of medial temporal lobe activation was not related to the amount of explicit awareness obtained by the participants in the implicit condition. This evidence appears to refute the theory that the medial temporal lobe (which includes the hippocampus) is critical solely for explicit memory formation.

It is possible that the implicit and explicit memory systems interact or compete with one another during learning and memory consolidation. In a study by Wagner et al[112], participants who slept between practicing a sequence and retention testing demonstrated an improved ability to detect a hidden rule compared to participants who did not sleep during the intervening interval. However, sleep only resulted in a significant decrease in reaction time in those participants who did not discover the hidden rule. This suggests that declarative memory is enhanced at the expense of procedural memory for this particular task[113], which would support the theory that different memory systems interact during formation[114]. Further evidence that memory systems interact is a recent study that demonstrated off-line implicit procedural learning was impaired by learning an explicit declarative word-list task if participants did not sleep between practicing the procedural task and retention testing but was not impaired if the participants slept between practice and retention testing[115]. Conversely, learning the explicit declarative word-list task was likewise impaired by learning an implicit procedural task if the participants did not sleep between practicing the word-list task and re-testing but was not impaired if the participants slept between practice and retention testing. The authors of the study propose that sleep may disconnect the neural circuits of the two memory systems, thus permitting them to function in an isolated manner to allow consolidation of their respective memory traces[115].

Sleep may also preferentially enhance certain parameters of an implicit motor task (motor parameters vs. spatial parameters). Robertson et al[18] demonstrated that implicit motor learning does not benefit from sleep for off-line motor memory consolidation, but is simply time dependent (enhanced performance both following a period of sleep and a period of being awake). However, Cohen et al[116] suggest that different aspects of an implicit motor learning are preferentially enhanced off-line by sleep. Using the serial reaction time (SRT) task and having the participants switch to the untrained hand at retention testing, these authors found that only the goal or spatial regularities of the task was enhanced by sleep following practice whereas the mirror finger movement sequence or motor pattern was enhanced over the day without sleep. This suggests that distinct aspects of an implicit motor memory are supported by different mechanisms of off-line learning, thus providing a potential explanation for the variety of findings in the learning literature[17]. The presented work sought to extend these findings by determining if different movement components (spatial and temporal components) of a continuous tracking task are preferentially enhanced off-line by sleep in individuals after stroke and healthy, older adults.

In summary, while explicit learning and memory appear to be preferentially enhanced by sleep, the lack of apparent sleep-dependent off-line learning of implicit motor tasks maybe due to only certain components of an implicit motor skill are enhanced by sleep. However, the work summarized in this section examined the interaction of sleep and type of instruction only for young, healthy individuals. Therefore, the presented work sought to add to the body of literature by examining if type of instruction (explicit instruction vs. no instruction or implicit learning) interacts with sleep to influence off-line motor learning as well as examined if different movement components of a tracking task are enhanced off-line by sleep in healthy, older adults and following stroke.

1.9. Neuroimagaing, Learning and Sleep

Neuroimaging techniques have been used to determine if areas of the brain activated during acquisition of a motor skill are re-activated during sleep. Reactivation during sleep may lead to the modification of synaptic connections that were established during acquisition of the motor skill. Maquet et al.[117] were the first to show using PET scan that areas of the brain activated during acquisition of a probabilistic SRT task were reactivation during REM sleep after training. The areas that were re-activated included the cuneus and adjacent striate cortex bilaterally, the left premotor cortex, and the mesencephalon. Peigneux et al.[118] expanded on this first study and also found re-activation during post-training REM sleep in the bilateral cuneus using the same probabilistic SRT task. Furthermore, they found that the functional coupling between the cuneus and striatum was increased during post-training REM sleep. They proposed that this indicates the role of the basal ganglia in sleep-dependent consolidation of implicitly learned information. Laureys et al.[119] further show an increased functional connectivity between the left dorsal premotor cortex and the left posterior parietal cortex and left pre-supplementary motor area (SMA) during post-training REM sleep in trained participants compared to untrained participants. These authors concluded that cerebral areas re-activated during post-training sleep do not act in segregation, but, rather, act as a part of an integrated neuronal network. None of these studies examined if re-activation occurred during non-REM sleep, so a role of non-REM sleep cannot be excluded.

Neuroimaging techniques have also been used to elucidate changes in the representation of motor memory following sleep. Fischer et al.[120] used fMRI to determine brain areas active during practice of a finger-to-thumb opposition task using the left hand were re-activated during retention testing 48 hours later. As expected, they found improved performance at retention in the sleep-group compared to the sleep-deprived group. Interestingly, they found a *reduction* in brain activation in the left prefrontal cortex and the right lateral premotor cortex in the sleep group from training to retention. The authors suggest that this indicates a decreased need to consciously regulate and monitor continued finger movements. The area of *increased* activity was found in the left superior parietal lobe, which they concluded indicates that this area is involved in automated performance. The decrease in brain activation following sleep supports the "synaptic homeostasis hypothesis" by Tononi and Cirelli[121] which proposes that the role of sleep (slow wave sleep in particular) is to globally downscale the synaptic strength of brain circuits that were increased during learning back to baseline to save energy and gray matter space.

In a similar study using fMRI, Walker et al.[75] found different activation patterns but arrived at a similar conclusion. These researchers determined that participants who practiced a sequential finger-tapping task using the left hand and slept following training exhibited at retention an *increased* activation in the right primary motor cortex, right prefrontal lobe, right hippocampus, right ventral striatum, and left cerebellum compared to participants who stayed awake following training. They suggest that increases in activation support faster, more efficient output and optimize transitions. The increase in hippocampal activation is likely due to the explicit nature of this task due to the hippocampus having a role in explicit memory formation[45]. Walker et al.[75] found a *decrease* in bilateral parietal cortices, the left insular cortex, the left temporal pole, and the left inferior front-polar cortex. They attribute this decrease in activation to a reduction in need to monitor performance and a decrease in emotional burden. The discrepancy between the findings these two studies may be due to Walker et al.[75] used a paced task versus an un-paced task in the Fischer et al.[120] study as well as due to the slightly different task used. However, these two studies provide the first glimpse into the consolidation of motor memory following sleep.

1.10 Neural Mechanisms of Sleep-dependent Memory Consolidation

Sleep is thought to provide a permissive environment promoting various cellular and molecular mechanisms enabling the consolidation of memories. The various mechanisms include activity of neuroendocrine molecules, gene transcription, and protein synthesis[40, 122, 123]. During non-REM sleep, there is a reduction in norepinephrine, serotonin, and acetylcholine compared to awake levels; REM sleep is characterized by a further reduction in serotonin and norepinephrine levels, but acetylcholine levels return to levels similar to those seen during waking or higher[39, 124]. An increase in acetylcholine and a decrease in serotonin during REM sleep in rodents has been shown to facilitate protein synthesis and long-term potentiation (LTP) in the hippocampus[125]. The increase in acetylcholine during REM sleep is thought to activate postsynaptic receptors leading to a cascade of cellular events resulting in protein synthesis needed for LTP[39].

The unique electrophysiolgical events of both REM (i.e. PGO waves) and non-REM (i.e. sleep spindles) are thought to play a role in long-term synaptic potentiation[2, 123]. In particular, sleep spindles which are characteristic of stage-2 non-REM sleep have been demonstrated to play an important role in sleep-dependent memory improvement[69, 90, 91]. Sleep spindles, in theory, act similarly to spike trains which result in synaptic potentiation; sleep spindles are hypothesized to depolarize the postsynaptic membrane resulting in a large influx of calcium ions leading to a cascade of cellular events which results in gene expression and protein synthesis necessary for LTP of the postsynaptic membrane[123,39].

The above section (1.9. Neuroimagaing, Learning and Sleep) provided evidence that memories are “replayed” during sleep with a reactivation of the neural circuits associated with learning the task. This “replaying” of the memory during sleep is thought to result in a functional coupling of the synapses leading to LTP of the neural circuit responsible for that memory trace. Ribeiro and Nicolelis[107] propose that the reactivation of the neural circuits associated with a memory trace (“neuronal reverberation”) occurs during slow wave sleep while the expression of genes necessary for remodeling of the circuit and thus memory storage occurs during REM sleep. These authors further postulate that the cycling between slow wave sleep and REM sleep during the course of the night results in the movement of memory traces from the hippocampus into storage in the cortex[107].

As mentioned above, the "synaptic homeostasis hypothesis"[121] proposes a very different role for slow wave sleep (SWS). This hypothesis suggests the purpose of SWS is to downscale the synaptic connections formed during awake learning making neural connections more efficient. The low frequency waves characteristic of SWS result in the entry of calcium into the postsynaptic membrane at much slower rate than seen during sleep spindles[39]. This slow entry of calcium triggers a cascade of cellular events that ultimately result in long-term depression (LTD)[39], which would provide support for Tononi and Cirelli's "synaptic homeostasis hypothesis".

The studies performing *in vivo* recordings of neural activity are frequently conducted in animals for obvious limitations in the ability to conduct these studies in humans. Furthermore, many of the animal studies examining the role of sleep in learning or sleep deprivation in learning utilize "hippocampus-dependent" learning paradigms in rats which may be very different from procedural learning in humans which is not thought to rely on the integrity of the hippocampus. Therefore, while the animal studies provide very important insight into the cellular and molecular underpinnings of sleep-dependent memory consolidation, there is currently a void between the physiological findings from the animal studies and the behavioral findings in humans[126].

1.11. Motor Learning Following MCA Lesion

Although many studies support the role of sleep in off-line motor skill learning in neurologically, intact people, no study to date has examined the role of sleep in off-line motor learning in neurologically impaired individuals. Despite literature that suggests implicit learning is impaired in participants following a stroke[127], a larger body of research supports that after stroke, individuals are able to learn new skills[27-31]. People were able to learn implicitly following lesions in the MCA distribution affecting the sensorimotor cortex, but providing these participants with explicit instruction disrupted implicit learning[108]. However, in this study, participants in the explicit instruction group were not told there was a sequence to be learned until the second day of practice and did not receive more significant instruction on the sequence until the third and last day of practice. Perhaps the lack of explicit instruction prior to the start of practice influenced the ability to adequately utilize the explicit information to learn the implicit task. Furthermore, the role of sleep in off-line motor learning or the sleep characteristics of the participants was not examined in this study.

Evidence suggests that different neural circuits are involved in over-the-day vs. over-night off-line motor skill learning. Robertson et al.[128] found that disrupting the primary motor cortex using transcranial magnetic stimulation following implicit learning of a sequence resulted in disruption of implicit off-line skill learning over the day but overnight off-line improvements persisted. The authors propose that the primary motor cortex is important for over-the-day implicit off-line skill learning but not important for overnight implicit off-line skill learning. This suggests that the SMC plays a role in implicit skill learning, but that sleep may differentially benefit skill learning if the SMC (particularly the primary motor cortex) is impaired. This also provides evidence that different neuronal circuits support off-line learning during sleep versus periods of being awake.

Studies testing participants with focal basal ganglia lesions have had conflicting results regarding the role of the basal ganglia in procedural skill learning. Neuroimaging studies have demonstrated activity in the basal ganglia during skill learning[50-53, 57, 60, 61], but behavioral data has been conflicting. Some behavioral studies indicate a basal ganglia lesion does impair procedural learning[129, 130] where as others have demonstrated a basal ganglia lesion does not impair procedural learning [82, 131-133]. However, few of these studies used retention or transfer tests to differentiate learning versus performance improvements[82, 129, 130] and none of the studies considered the role of sleep in off-line motor learning. One study has demonstrated that providing explicit knowledge impairs implicit learning in participants with a basal ganglia infarct[82]. However, in this study, explicit instruction was progressively provided over three days of practice which may have interfered with the ability to adequately incorporate an explicit learning strategy. The presented work sought to clarify the influence of type of instruction as well as the effect of sleep on off-line motor skill learning following a lesion in the MCA distribution, which includes both the SMC and the basal ganglia.

1.12. Significance of Present Work

As stroke is a leading cause of adult disability in the United States, it is imperative that any factor that could potentially improve recovery and enhance function for this group of people be explored. In addition, due to the large number of people with stroke suffering from sleep alterations, understanding the role of sleep in off-line motor learning and memory consolidation in the damaged brain has tremendous implications for rehabilitation. As will be presented, individuals following stroke demonstrate sleep-dependent off-line motor learning of both an implicit and explicit version of a continuous sequencing task. Furthermore, sleep enhances both spatial and temporal movement components of the continuous tracking task after stroke. The age- and sex-matched healthy control participants did not experience sleep- or time-dependent off-line motor learning on either version of the tracking task and did not show off-line learning of the spatial or temporal movement components of the task.

The findings of this current study may change the way therapists teach motor skills to patients who have suffered from a stroke and may lead to emphasizing the need for sleep between therapy sessions. Therapy may need to be conducted in the evening prior to sleeping for the night or a nap may become a standard part of therapy. A new added emphasis may also be placed on ensuring adequate sleep following stroke by altering environments (i.e. ensuring quiet environment to sleep in hospital or reducing disturbances while asleep) or addressing underlying conditions limiting sleep.

The findings of this work may also influence the manner other researchers perform their studies. For example, sleep may be the reason motor skills improve between sessions when sleep is permitted (i.e., when overnight delays are built into research designs between practice and retention test days) rather than the number of practice sessions, the amount of practice in a session, or the type of practice. Thus, sleep could potentially represent either a confounding or beneficial variable in the experimental designs of those who study learning. The current work helps disentangle the influence of sleep and instruction on off-line motor skill learning, thereby contributing to our understanding of the previous literature.

Furthermore, the literature to date examining the role of sleep in off-line motor learning have all used discrete tasks. No study prior to the current one has yet examined whether the findings from these discrete tasks would generalize to a continuous task. This has important implications considering many of the movements performed during daily life include movements that are continuous in nature, such as walking. In addition, using a continuous tracking task rather than a discrete task such as the serial reaction time task reduces the confounding variable of explicit awareness obtained by the implicit condition group[78, 79, 82] and allows the examination of more "pure" implicit off-line learning.

1.13 Specific Aims and Statement of Hypotheses

The main purpose of this presented work was to examine the role of sleep in off-line motor skill learning following stroke. It is proposed that neurological injury, namely stroke, affecting areas of the brain that participate in motor skill learning may alter the role of sleep in off-line motor memory consolidation. In addition, the type of instruction provided to participants prior to practice (i.e. explicit instruction vs. no explicit instruction) may also influence the effect of sleep on off-line motor learning following stroke.

Specific Aim 1: Determine the role of sleep and instruction in off-line motor skill learning of a continuous task.

Because sleep-dependent off-line skill enhancement has previously only been demonstrated with discrete tasks, we hypothesized that a similar sleep-dependent off-line enhancement would be shown on a continuous task by healthy control participants. Motor skill performance of discrete sequences when explicit instruction is provided is preferentially enhanced by sleep compared to performance involving purely implicit knowledge or awareness. Therefore, we hypothesized that healthy control participants with explicit knowledge who slept following practice of a continuous tracking task would display off-line enhancement of performance on the tracking task at retention. Conversely, we expected healthy control participants provided explicit instruction who do not sleep between practice and retention would not demonstrate enhanced performance. Because implicit motor learning does not appear to be reliant on sleep for consolidation, we hypothesized that healthy control participants who were not provided with explicit instruction (implicit condition) of the continuous tracking task would display enhanced performance both following a period of sleep and a period of being awake. Enhanced performance would be demonstrated with a reduction in RMSE at retention testing compared to practice. Contrary to our hypotheses, none of the healthy control participants demonstrated off-line motor skill learning of either the implicit or explicit version of the continuous tracking task. Furthermore, neither the spatial or temporal movement components of the tracking task was enhanced at retention testing.

Specific Aim 2: Determine the role of sleep and instruction in off-line motor skill learning in participants with stroke-related lesions in the MCA distribution.

Because the role of sleep in off-line motor skill learning following stroke has never been previously examined, we hypothesized that participants with stroke in the MCA distribution who are given explicit instruction and sleep after practice would demonstrate enhanced performance on a continuous tracking task at retention testing compared to participants who do not sleep. Because preliminary results indicated sleep is important for implicit off-line motor learning for participants with stroke, we hypothesized that people with stroke who are not provided with explicit instructions (implicit condition) would demonstrate enhanced performance of a continuous tracking task compared to participants who do not sleep at retention. As we hypothesized, after stroke, individuals demonstrated sleep-dependent off-line motor learning both when a continuous sequencing task practice was influenced by explicit knowledge and when it was implicit in nature. Furthermore, sleep enhanced both spatial and temporal movements components of the continuous tracking task after stroke.

Four 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 conjunction to the dissertation study with the aim of ascertaining the influence of acquired explicit awareness on motor skill learning (Chapter 2; to be submitted to *Human Movement Science*, in revision). The second manuscript was an invited article based on preliminary data examining the role of sleep in implicit off-line motor skill learning following stroke and in healthy, older adults (Chapter 3; published in *Topics in Stroke Rehabilitation*). The third manuscript utilized the entire dataset of this dissertation research and examined the interaction of sleep and type of instruction on off-line motor skill learning following stroke and in healthy, older adults (Chapter 4; submitted to *Stroke*). The fourth manuscript assessed if particular movement components of the continuous tracking task (i.e. temporal and spatial components) were enhanced off-line by sleep or time for the individuals with stroke and control participants (Chapter 5; to be submitted to *Learning and Memory*).

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. One of the questions that remains is the influence of explicit information on motor skill learning. As discussed in Chapter 1, one of the difficulties in studying implicit skill learning is maintaining the implicit nature of the skill (i.e. insuring that the participants to not become aware of the regularities being learned). Gaining explicit awareness during physical task practice makes it difficult to examine “pure” implicit learning but is also not equivalent to being provided explicit information. Chapter 2 sought to address the potential benefits of acquiring explicit information during physical task practice on motor skill learning in young, neurologically intact individuals and compare change in performance to those individuals provided explicit instruction prior to task practice.

Chapter 2

The Impact of Acquired Explicit Knowledge on Motor Sequence Learning

This work has been submitted for publication to *Human Movement Science*, 2008.

2.1 Abstract

Previous research has demonstrated that individuals can learn motor sequence tasks both implicitly and explicitly. However, the influence of explicit knowledge acquired via implicit physical practice of motor sequences is less understood. In the present study, individuals practiced the Serial Reaction Time (SRT) task during one session and then returned 12 hours later for a retention test. Half of the participants were given explicit instruction regarding the presence of the repeating sequence prior to practice while the other half were not. Individuals were grouped if they were given explicit instruction prior to practice (explicit group, EK), if no instruction was provided and explicit awareness was not acquired (implicit group, IL), and, if no instruction was provided but explicit awareness was gained (acquired explicit knowledge group, AEK). Across practice the IL group performed slowest and showed less change in response time at retention as compared to the EK and AEK groups. Furthermore, the EK and AEK groups behaved similarly; there was no difference between these two groups across acquisition practice or at retention. Our data suggest that explicit knowledge of a repeating sequence during SRT practice, regardless of whether it is provided or acquired, enhanced implicit motor sequence acquisition and learning.

2.2 Introduction

Memory is typically classified into two broad categories: declarative and nondeclarative [134]. Declarative memory can be consciously recalled and includes knowledge of facts and events; nondeclarative memory cannot be conscious recalled and may only be assessed indirectly through change in behavioral performance [134]. A subset of nondeclarative memory, procedural learning can be evaluated through the assessment of motor skills [42]. Although procedural memory is often interchanged with implicit learning and declarative memory with explicit learning, these terms are not always synonymous. The difference between implicit and explicit learning is based on the participant's awareness of the regularities contained in the skill being practiced; explicit learning refers to knowledge of the regularities of the skill to be learned, whereas implicit learning occurs without this awareness [17]. While procedural skill learning is generally implicit in nature, there are exceptions, such as when explicit instructions are provided prior to the start of practice or when explicit awareness of task regularities is acquired through practice [18, 64].

The influence of acquired explicit awareness on motor skill learning is poorly understood, in large part because the literature in this area is highly varied. Some have demonstrated that participants who gained full explicit knowledge of a repeating sequence were able to take advantage of this information to reduce their performance response time (RT) as compared to participants who gained partial knowledge[135]. However, in this work a retention test was not employed, thus the true impact of acquired explicit knowledge on motor learning remains unclear. Others found that the acquisition of explicit knowledge of the regularities of a continuous tracking task did not impair learning of the task but rather affected performance variability [136]. Taken together, the overall impact of explicit knowledge that is acquired via physical practice during motor sequence learning is not known.

Thus, the purpose of this paper is to examine the difference in both motor performance and learning for participants who remained unaware of the presence of the sequence (implicit condition), those subjects who were given no instruction but gained explicit awareness of the sequence via practice (acquired explicit condition), and individuals given explicit instruction prior to the start of practice (explicit condition). Importantly to separate the short-term performance effects of acquiring explicit knowledge during physical practice from the long-term impact on motor learning, we employed a delayed retention test design.

2.3 Method

Participants

Forty-three individuals participated in this study (mean age 27.8 years; range 21-40 years old); one subject was removed from analysis due to computer error during data collection. In accordance with the Human Subjects Committee, each participant signed an institutionally approved informed consent. Participants were excluded if they presented with acute medical problems, uncorrected vision loss, previous history of psychiatric admission or neurological disease, or scored below a 26 on the Mini-Mental State Exam (MMSE). None of the participants reported colorblindness when questioned regarding visual difficulties or displayed difficulties in identifying the correct color during testing. Individuals were recruited at the University of Kansas Medical Center and the local community.

Task

Participants sat in front of a computer with a standard keyboard centrally placed and adjusted for comfort as needed. The most centered letters on the keyboard (v, b, n, and m) were capped with the colors red, yellow, blue, and green, respectively. During serial reaction time (SRT) task practice, only one colored circle was displayed on the computer screen at a time; each maintained its on-screen position during stimuli presentation. Participants responded using the first four fingers of their dominant hand as indexed by the Edinburgh Inventory [137], pressing one of the four keys corresponding to the appropriately colored circle. Participants were instructed to respond as quickly and accurately as possible.

Practice

Fifteen blocks of the SRT task were performed during the practice session; each block consisted of 100 responses. The first block and second to last block (Block 14) of responses contained randomly ordered stimuli for movement. The first random block is to allow participants to familiarize themselves with the task. The second random block (Block 14) is used to assess general improvement or non-specific task learning and allows for a comparison between non-specific task learning and sequence-specific motor learning at retention. The middle 12 blocks and last block (Block 15) consisted of a repeating 10-element sequence (blue-yellow-red-blue-green-red-blue-red-green-yellow) with an ambiguous or minimal probabilistic relationship between the elements. The sequence was designed to contain no more than one trill (e.g. red, blue, red) and have no repeating positions or colors. The transition between the end of one sequence and the beginning of the next within a block were not marked. In total during practice, the10-element sequence was performed 130 times. Participants returned for retention testing 12 hours following practice. Most of the participants slept in between practice and retention; however 14 participants underwent practice and retention testing on the same day with 12 hours (+/- 1 separating the two sessions). Analysis of the individuals who slept and those who did not demonstrated that all of the participants demonstrated an improvement in performance between practice and retention regardless of the presence or absence of sleep between practice and retention. Furthermore, sleep did not influence the amount of explicit awareness acquired. Therefore, the variable of sleep was not considered further. Retention testing consisted of 2 blocks; one random block followed by a repeating sequence block that was used to determine motor sequence learning. Simple (1-choice) response time was also acquired using a 50 stimulus response test with variable inter-stimulus presentation time. Participants responded with the index finger of their dominant hand to press the ‘v’ (red) button each time the stimulus appeared. Simple RT was used to screen for anticipatory responses, particularly in the explicit group (see Data Analysis).

Explicit Instruction

All participants in the explicit condition received instruction prior to practice regarding the presence of the repeating sequence. First, they studied a pictorial representation of, but were not allowed to physically practice, the sequence. Participants could study the sequence for as much time as they wished. Recognition and recall testing prior to practice verified that participants had acquired explicit knowledge regarding the repeating sequence [82]. Ten iterations of a pictorial representation of either the sequence they were instructed to learn (n=3) or a foil sequence (n= 7) were shown; participants had to decide (forced choice) if the sequence was one they recognized as the sequence they explicitly learned. The foil sequences also contained minimal probabilistic relationships between elements with no more than one trill and no repeating positions or colors. Each participant in the EK group passed the recognition test with at least 70% correct before beginning SRT task practice (EK; n=14). None of the EK group participants failed the recognition test and therefore did not required additional instruction. All participants but one scored 100% correct on the recognition test; this individual scored 90% correct.

Recall testing was also conducted prior to practice to determine the ability of the EK group participants to predict which color would come next after being shown 4 lines of the10-element sequence. For example, participants would see the blue circle filled on 1 line, then yellow on line 2, followed by red, and then blue. They would then have to decide which color should appear on line 5 (correct answer = green). This was done for 6 trials with 4 different lines of the sequence each trial. All participants in the EK group correctly predicted the correct color in the sequence at least 4 out of the 6 recall trials with 9 of the 14 participants making the correct prediction for all trials.

Assessment of Explicit Awareness Obtained

Participants in the implicit condition received no explicit instruction on the presence of the sequence prior to practice. The same recognition and recall tests administered to the EK group prior to practice were given to the implicit condition participants *following* retention testing to determine the degree of explicit knowledge obtained. Sixteen of the 28 participants in the implicit condition gained a better than chance amount of explicit knowledge (scored greater than 50% correct on the recognition test and recall test). These participants were placed in the acquired explicit knowledge (AEK) group (n=16) while the individuals who did not meet this criteria remained in the implicit (IL) group (n=12). The EK group did not undergo recognition or recall testing again following retention testing.

Data Analysis

The mean median RT for each block was calculated as the summary score. By taking advantage of their explicit knowledge of the repeating sequence, participants who were provided explicit instruction or acquired explicit awareness during practice could potentially begin the motor response of pressing the next correct colored key prior to the color cue appearing on the screen and thus reduce response time through anticipatory actions rather than improved response time. Therefore, to avoid biasing time data by anticipatory responses, RTs that were faster than the individual's mean simple (1-choice) RT were eliminated from data analysis [138]. As expected, those participants provided explicit instruction had the most trials eliminated and the IL participants the least. Individual data were averaged by group to represent performance for blocks 1-15 during acquisition practice and at a delayed retention test. Acquisition practice performance was examined using a two factor [Group (EK, AEK, IL) X Block (2-13,15)] repeated measures ANOVA with RT as the dependent variable. To assess motor sequence learning, we considered data from the delayed retention test. Because improvements in motor skill during a single practice session may be confounded by temporary changes in performance, learning or the *relatively permanent change* in behavior, is more precisely assessed using a delayed retention test [74, 139]. Sequence learning was assessed by a two factor [Group by Block (Block 14 random, repeated sequence retention block)] repeated measures ANOVA with RT as the dependent variable. Post-hoc testing using Fischer's least significant difference (LSD) was conducted to assess the locus of difference between groups. Linear regression analysis was performed to assess the relationship between performance at retention and amount of explicit knowledge provided or acquired as measured using a recognition test. Analyses were performed with SPSS 13.0[*]. Significance was set at $p<.05$.

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[*] SPSS, 233 S. Wacker Drive, Chicago, Illinois 60606

2.4 Results

Acquisition

Practice benefited participant performance as shown by a main effect of block ($F_{12,468}$=68.867, p<.000) indicating that all the groups became faster with training (Figure 1). However, explicit awareness of the repeating sequence differently impacted acquisition performance (main effect of group, $F_{2,39}$=3.895, p=.029). Post-hoc Fischer's LSD showed that the locus of this effect was a significant difference between the IL and AEK groups (p=.033) as well as between the IL and EK groups (p=.016). There was no significant difference between the AEK and EK groups (p=.841). The group by block interaction was not significant.

Retention

Each group demonstrated learning of the repeating sequence as demonstrated by a main effect of block ($F_{1,39}$=522.727, p<.000; Figure 2). However, a main effect of group ($F_{2,39}$=6.138, p=.005) verified that the differences between explicit conditions noted for acquisition practice were maintained at retention. Again, post-hoc LSD testing demonstrated that the locus of this finding was the significant difference between the IL and AEK groups (p=.025) and also the IL and EK groups (p=.001). The AEK and EK groups did not differ (p=.215). The group by block interaction was not significant.

Relationship between Retention and Amount of Explicit Knowledge

Linear regression analysis demonstrated a moderate relationship between performance at retention and amount of explicit knowledge either provided through instruction or acquired by physical practice of the task or acquired (Figure 2.3; R^2=.337).

2.5 Discussion

This study highlights the difference between acquisition and retention for participants who learned purely implicitly, those who gained explicit knowledge, and individuals who where given explicit instruction prior to practice. Participants in the IL group made the least amount of RT change across acquisition practice and at retention as compared to the EK and AEK groups. While prior studies have demonstrated explicit awareness can be acquired through task practice, this study provides clear evidence that at least for the SRT task participants can utilize this gain of explicit knowledge to enhance motor skill learning. Interestingly, the impact of explicit knowledge for the repeating sequence was similar whether it was acquired (AEK group) or delivered by the experimenter (EK group). This demonstrates that explicit knowledge, either provided or acquired, enhances motor sequence acquisition and learning for the SRT task, perhaps by enabling participants to consciously anticipate and plan for upcoming responses.

Another possible explanation for the larger change in behavior demonstrated by the AEK and EK groups is the individuals' attentional focus during performance of the task or a potential lack of full attention by the IL group. Studies have demonstrated that attending to an external cue versus an internal cue aids skill learning [140, 141]. It is possible that individuals who acquired or were provided explicit knowledge attended to the sequence (an external focus) while the individuals who did not acquire explicit knowledge (IL group) attended to the movement of their fingers (an internal focus) or simply failed to fully attend to the task. The latter premise is supported by post-hoc analysis of performance at the first random block during practice which reveals the IL group performed slower than both the AEK and EK group. These suppositions require verification through future research.

Past work has not ubiquitously demonstrated a benefit of explicit instruction for motor learning. Explicit instruction may either aid [64, 80, 82] or disrupt [79, 110] motor learning in neurologically intact, healthy individuals. The present study confirms that for young, healthy individuals explicit instruction prior to practice of a discrete serial response motor sequence task significantly reduces RT and enhances skill learning. Differences in the reported benefit of explicit knowledge during motor sequence learning between this paper and other research likely stems from the nature and quality of the instruction [142, 143] as well as the task [79, 110, 144, 145]. Individuals in the explicit condition of the present study where told the repeating pattern and did not have to search for an underlying rule [144]. Furthermore, a deterministic sequence was utilized in the present study rather than a probabilistic pattern [110] which may make the explicit knowledge provided or acquired more salient and easier to translate into a motor plan. Task complexity is another possible explanation why the present study found explicit knowledge either provided or acquired enhanced motor skill learning. Other work has found that the learning of other more complex tasks seems to be inhibited by explicit instruction [79]. Complex tasks may require additional cognitive demands and explicit information may "distract" the learner [84]. Taken together, it appears that explicit knowledge may be most beneficial for simple motor sequence learning when participants can both attend to it [146, 147] and successfully integrate it into task practice [148].

The neural networks supporting procedural learning are widely distributed. Imaging studies demonstrate the role of the sensorimotor cortex [50, 51, 54] (particularly M1[62, 63]), premotor cortex [52, 57], supplementary motor areas (SMA)[50, 51], basal ganglia [50-53, 57, 60, 61], prefrontal cortex [50, 51, 57], and cerebellum [52, 55, 57, 61] in procedural learning. While earlier imaging studies have demonstrated dissociable neural system activation during implicit and explicit sequence learning [50-52] and perhaps even competition between the two systems [58], other imaging evidence supports parallel and complementary development of neural networks supporting implicit and explicit sequence learning [60, 61]. Willingham et al.[61] proposed that the dorsal prefrontal cortex might have an integral role in gaining awareness during implicit sequence practice by enabling participants to gradually develop a conscious knowledge of target selection. This conceptualization was supported by Aizenstein et al.[60] who showed prefrontal cortex activity during both explicit and implicit sequence learning, but more extensive activity in the prefrontal cortex during explicit sequence learning. Furthermore, in an elegant study designed to determine the development of explicit awareness during sequence learning, Honda and colleagues[54]demonstrated a positive correlation between brain activity in the dorsolateral prefrontal cortex (DLPFC) and the ability to correctly verbalize the sequence regularities. This supports the role of the prefrontal cortex, and perhaps the DLPFC in particular, as having an integral role in the development of explicit knowledge during implicit motor learning. Our data suggest that these processes likely operate similarly when explicit knowledge is acquired or provided. Though future imaging studies will have to confirm this speculation it appears possible that once explicit knowledge develops through either mechanism it operates similarly through the prefrontal cortex to direct acquisition of implicit motor skills.

One limitation of the present study is our inability to know exactly when explicit knowledge was acquired by the AEK group. Because post-hoc analysis determined that there was no statistical difference between the EK and AEK groups across acquisition, it appears that explicit knowledge may have been acquired at some point near the beginning of practice. The rapid acquisition of explicit awareness has been demonstrated in previous studies to occur as quickly as the first practice block [138, 147]. It is not known if our participants became aware of the repeating nature of the sequence at this early point in practice, however, regardless of when the sequence was recognized knowledge of it enhanced the ability of those individuals to learn the regularities of the repeated sequence.

In summary, our results demonstrated a benefit of explicit knowledge during SRT task learning for young healthy individuals regardless of whether it was acquired during or provided in advance of physical practice. Further, this benefit of explicit knowledge for the SRT task extended to both practice and retention. These data are important as the benefit of acquired explicit knowledge for motor learning has not been previously verified by the use of a delayed retention test. Future research should address both when explicit knowledge is acquired during sequence practice and why some young healthy individuals are able to gain explicit awareness while others cannot, and are thus unable to capitalize on this information to enhance motor sequence learning.

2.6 Figure Legend

Figure 2.1. Acquisition practice RTs by block. Blocks 1 and 14 are random sequence practice (denoted with RN; these blocks were not included in the repeated measures ANOVA), blocks 2-13 and 15 represent repeating sequence practice. All 3 groups significantly improved their RTs with practice, however, between group differences also existed. The implicit group was slower than both the explicit and acquired explicit knowledge groups. Error bars are standard error of the mean (SEM).

Figure 2.2 Motor sequence learning demonstrated by delayed retention testing. Motor sequence learning was indexed by the comparison between random and repeating sequence performance. Regardless of knowledge condition all groups learned the repeating sequence. Consistent with acquisition practice data the explicit groups (acquired explicit knowledge and explicit) demonstrated more change in performance than the implicit group. Error bars are SEM.

Figure 2.3. Regression analysis assessing the relationship between performance at retention and amount of explicit knowledge suggests that learning a simple motor skill is aided by explicit knowledge either provided or acquired (R^2=.337).

Figure 2.1

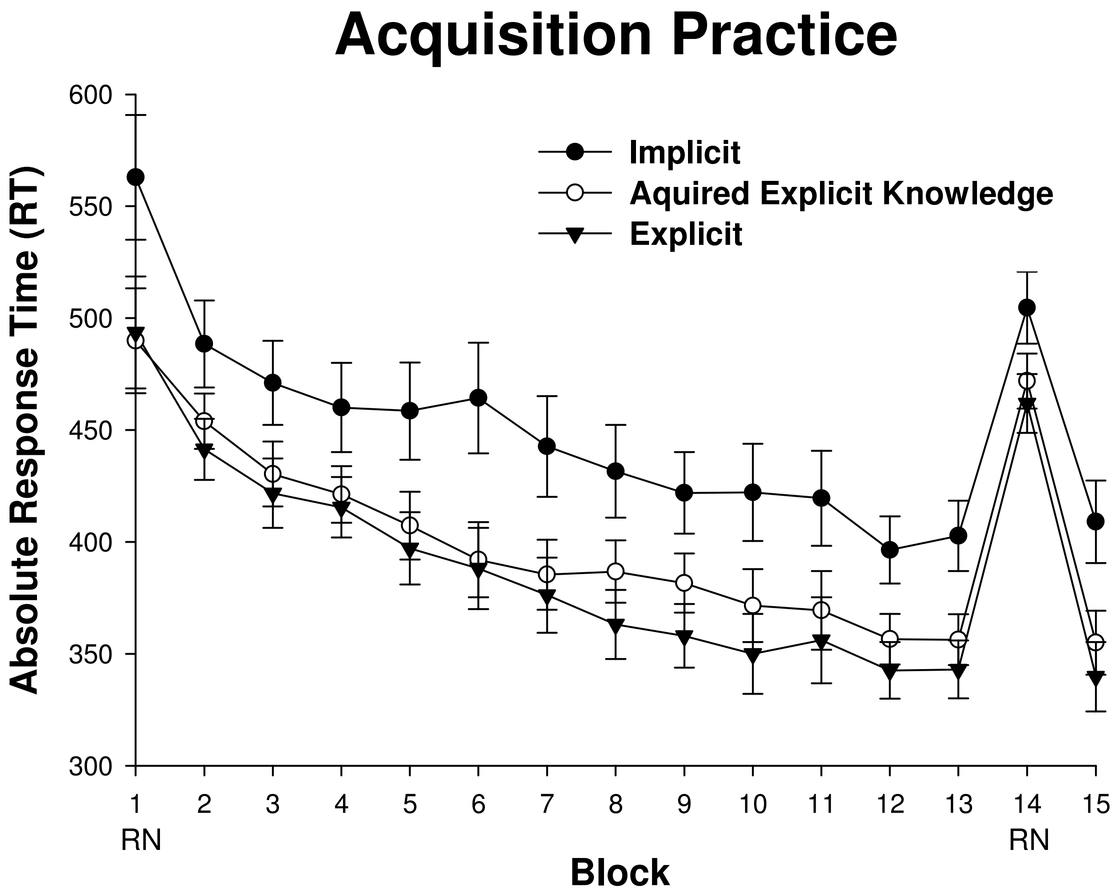

Acquisition Practice
Implicit
Aquired Explicit Knowledge
Explicit
Absolute Response Time (RT)
600
550
500
450
400
350
300
1
RN
2
3
4
5
6
7
8
9
10
11
12
13
14
RN
15
Block

Figure 2.2

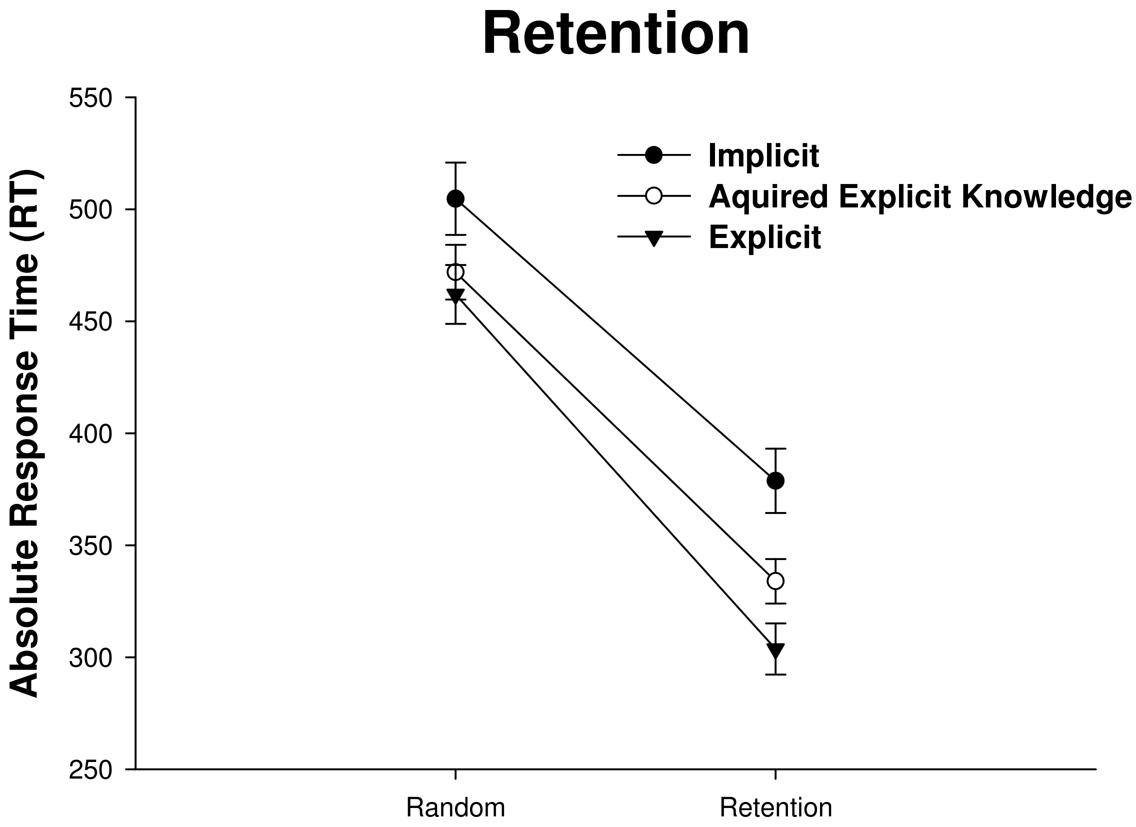
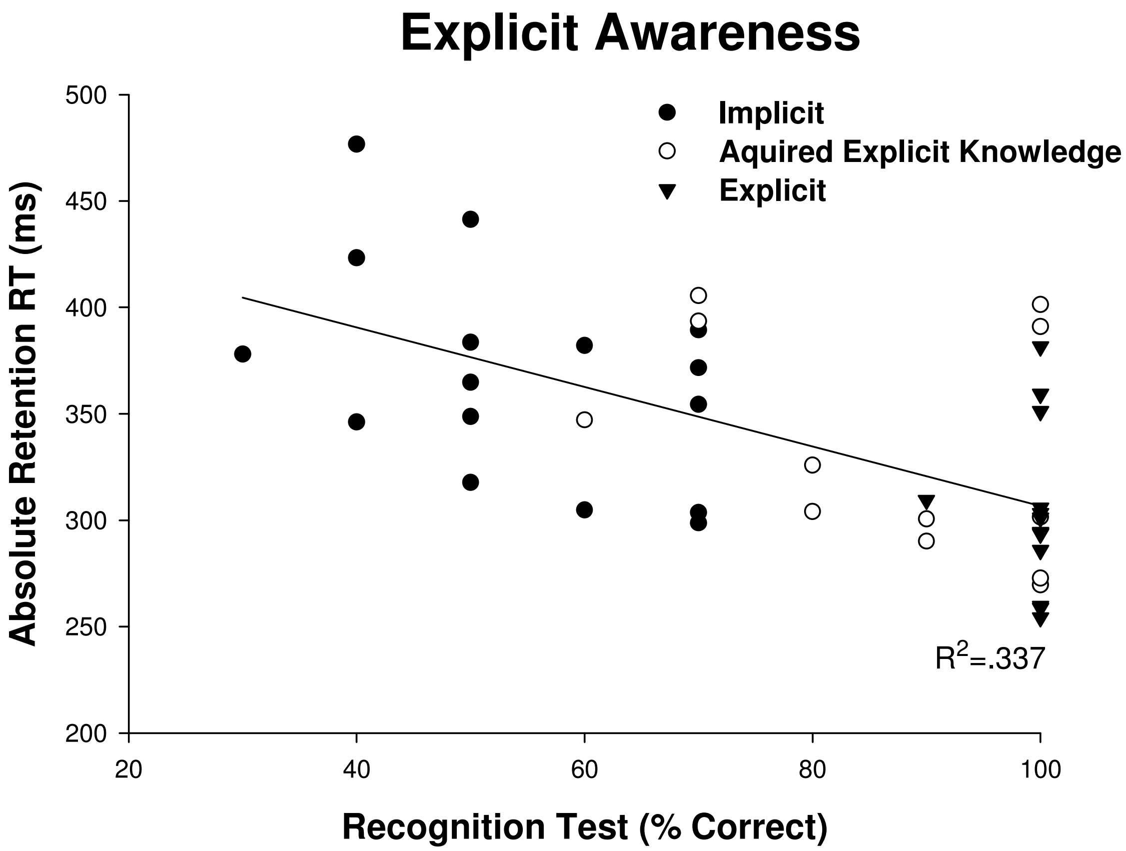

Retention
Absolute Response Time (RT)
550
500
450
400
350
300
250
Random
Retention
Implicit
Aquired Explicit Knowledge
Explicit

Figure 2.3


Explicit Awareness
● Implicit
○ Aquired Explicit Knowledge
▼ Explicit
Absolute Retention RT (ms)
500
450
400
350
300
250
200
20
40
60
80
100
Recognition Test (% Correct)
R^2=.337

Chapter 3 Preface

Chapter 2 provides evidence that explicit knowledge of a repeating sequence during a simple motor task practice, regardless of whether it is provided or acquired, enhances implicit motor sequence acquisition and learning. This work provides concurrent evidence that explicit awareness is often easily acquired during implicit practice of a simple motor task. Therefore, we elected to utilize a more complex task, a continuous tracking task, to assess sleep-dependent off-line motor learning to allow a more accurate assessment of implicit off-line motor learning. Chapter 3 sought to examine the influence of sleep on off-line implicit motor learning following stroke and in older, healthy adults.

Chapter 3

Sleep Enhances Implicit Motor Skill Memory Consolidation in Individuals Post-stroke

This work was published in *Topics in Stroke Rehabilitation*, 2008, p.1-12.

3.1 **Abstract**

While sleep has been demonstrated to be critical for learning and the consolidation of memories in neurologically-intact individuals, the importance of sleep for learning in neuropathological populations remains unknown. To assess the influence of sleep on implicit motor skill learning post-stroke, 18 individuals with stroke and 18 neurologically intact age-matched individuals were assigned to either the sleep group (slept between practice of a continuous tracking task and retention testing) or the no-sleep group (stayed awake between practice and retention testing). Only the individuals post-stroke who slept in between practice and retention testing demonstrated implicit motor learning at retention testing. The individuals with stroke who did not sleep and the age-matched control groups failed to demonstrate learning at retention. These findings provide evidence that after stroke individuals can enhance implicit motor skill learning and motor memory consolidation by sleeping between practice and retention tests. These data suggest that ensuring adequate sleep between rehabilitation therapy sessions and normalizing sleep cycles following stroke may be important variables that can positively influence implicit motor learning after stroke-related brain damage.

3.2 Introduction

A wide base of literature has demonstrated that sleep is critical for motor learning and the consolidation of memories for young, neurologically intact individuals[12-16]. The transformation of memories from a labile state to a more permanent and resistant form without further practice is known as memory consolidation[8]. Memory consolidation can result in stabilization of the memory or an enhancement of skill, referred to as off-line learning[149]. The importance of sleep for motor learning and memory consolidation in neuropathological populations such as stroke has not been well characterized. It is known that individuals with stroke are able to learn new implicit motor skills[27-31]. However, the influence of sleep on memory consolidation and thus, implicit motor learning following a stroke remains in question. The purpose of this present study is to examine the role on sleep in learning an implicit motor tracking task in individuals with chronic stroke.

For young, neurologically intact individuals, sleep enhances perceptual[65-68] and motor[12-16] task learning even when no additional practice has taken place. Participants who practice a task and then sleep perform better on the task following a period of sleep versus a similar length of time when they are awake. Importantly, it is sleep and not circadian rhythm that enhances motor consolidation and learning; improvements in a finger sequencing task are noted after sleep whether or not sleep occurs at night or during the day[16]. Even a short nap of 60-90 minutes can produce an improved performance on both motor[69, 70] and perceptual[71] memory tasks in young, neurologically intact participants.

Participants' awareness regarding the regularities of the motor skill to be learned may influence the beneficial influence of sleep on memory consolidation[18]. Explicit learning occurs when participants have awareness of the regularities contained in the skill being practiced while implicit learning occurs without this awareness[17]. Motor learning is typically implicit, but may become explicit if verbal instructions are given or if participants acquire explicit awareness of the regularities in motor responses during practice[18, 44]. In healthy individuals[18], participants without awareness of the sequence they were practicing demonstrated implicit motor learning following a period sleep *and* a similar length of time when they were awake. In contrast, participants who were given explicit instructions regarding the sequence they were trying to learn only demonstrated motor learning if they slept after practice; in this instance memory consolidation was not enhanced by time. These data imply that for young, healthy people implicit memory consolidation is time dependent while explicit memory consolidation is sleep dependent.

Careful examination of prior studies reporting a benefit of sleep for motor learning[12-16] reveals that, even when it was not the stated goal of the research, participants largely had explicit awareness of the skill being learning. However, a study by Cohen et al[116] suggests that different aspects of implicit motor learning are preferentially benefited by sleep. Using the serial reaction time (SRT) task and having the participants switch to the untrained hand at retention testing, these authors found that only the goal or spatial regularities of the task was enhanced by sleep following practice whereas the mirror finger movement sequence was enhanced over the day without sleep. This suggests that distinct aspects of an implicit motor memory may be supported by different mechanisms of off-line learning, thus providing a potential explanation for the variety of findings in the learning literature[17].

The majority of studies to date examined sleep-dependent performance enhancement in young, neurologically intact individuals. Little work has examined sleep-dependent memory consolidation in older individuals. Hornung, Danker-Hopfe, and Heuser[72] suggest that because people experience both sleep and memory changes with advancing age, the relationship between sleep and memory in older individuals must be considered. Older adults demonstrate a lack of sleep-dependent enhancement on both an explicit and implicit version of a sequence learning task[21] and also on a declarative memory word-pair associations task[22]. Additional support for the impact of sleep on older adults comes from data that showed improving REM sleep parameters using medication enhances word recall performance[73].

While few studies have examined the influence of sleep on learning in older adults, even less is known about the role of sleep in learning in neurologically impaired individuals. People who have had a stroke are able to learn new skills[27-31] particularly implicit motor tasks[80, 82, 108]. However, little is known about the importance of sleep for implicit motor sequence learning. In a pilot study conducted in our lab[150], individuals who were post-stroke exhibited enhanced implicit motor learning following sleep but not following a similar period of being awake. Despite limited number of participants, our initial work provides evidence that for implicit motor sequence learning, sleep may have a differential effect on people with stroke as compared to healthy adults.

Because many individuals post-stroke experience sleep disturbances, the potentially confounding role of sleep on motor learning is critical issue. It is estimated that 20 to 40% of people with stroke experience some type of sleep-wake disorder, including insomnia, excessive daytime sleepiness/fatigue, or hypersomnia[32]. More specifically, data suggest that nearly 60% of people 3-4 months following stroke suffer from insomnia[33]. Furthermore, sleep architecture changes after stroke, including a decreased total sleep time and sleep efficiency, and increased waking after sleep onset[34-36]. Individuals with an acute stroke also demonstrate a reduction in REM sleep[92] and NREM sleep stages 2-4[34]. Alterations in sleep architecture persist with 53% of individuals with chronic stroke (5-24 months post-stroke) showing abnormal EEG patterns during sleep as compared to published norms[37]. Considering the large number of people with stroke who are suffering from sleep disturbances, as well as evidence supporting the role of sleep in memory consolidation, increasing our understanding of the effect of sleep on learning following stroke may provide new avenues for treatment to enhance motor function after stroke.

To examine the role of sleep in implicit motor learning and memory consolidation following stroke, we examined motor learning of a continuous tracking task. Continuous tracking was originally developed by Pew[77] and has since been used by others[78-82] to examine implicit motor sequence learning. Currently it is unclear whether sleep differentially benefits discrete or continuous motor skills. Discrete movements have with an obvious beginning and end (e.g., kicking or throwing a ball), whereas continuous movements have no obvious start and finish (e.g., walking, swimming or jogging)[74]. To date studies of the effect of sleep on motor learning have only considered young neurologically intact individuals as they learn discrete tasks: a finger-to-thumb opposition task[12, 16], a sequential finger-tapping task[13-15], and the SRT task[18]. It is not known whether findings from these discrete tasks will generalize to continuous motor skills. Due to the rapid execution of discrete movements, these skills likely rely on a pre-planned motor program, whereas continuous tasks may be underpinned by the use of ongoing feedback that corrects movements on-line. It is possible that the relative motor control demands of discrete versus continuous tasks may stimulate a differential effect of sleep on learning.

Finally, continuous implicit motor tasks tend to block the acquisition explicit awareness[82,78,79]. Individuals frequently gain explicit awareness during the practice of discrete motor tasks[135, 147] making the assessment of implicit motor learning difficult. Furthermore, continuous tracking task may be considered more complex than a simple discrete movement owing to the additional degrees of freedom[84]. Interestingly, past work noted that the more complex the task was, the greater the off-line improvements following sleep[85]. This suggests that “real-life” complex tasks may benefit even further from sleep-dependent enhancements.

In the current study, participants with stroke used their less-affected, ipsilesional hand to perform the continuous tracking task. Using the less-affected hand allowed the assessment of motor learning without the confounding issue of impairment in motor execution. Using the hemiparetic hand could inflate the difference between participants with and those without a stroke, simply due to the impairment of participants with stroke to perform the movement, rather than to a deficit in motor learning. Furthermore, bilateral hemisphere activity has been demonstrated to be necessary for learning a motor sequence[108] and neuroimaging studies have demonstrated bilateral brain activation during sequence learning tasks[56, 59, 61, 151].

The purpose of the present study is to assess the influence of sleep on implicit motor learning and memory consolidation in individuals with chronic stroke. Because implicit motor learning does not appear to be reliant on sleep for consolidation but rather is time dependent[18], we expected that the age-matched healthy control participants would show implicit motor learning both after sleep and following a period of being awake. Based on our preliminary work[150], we hypothesized that individuals with stroke would differ from their healthy counterparts and demonstrate implicit motor learning after sleep but not following a similar period of being awake.

3.3 Method

Participants

To examine the role of sleep on motor skill learning, we recruited 18 participants who were post-stroke (ST, mean age 66.0 years old, stdev 11.96) and 18 age-matched neurologically intact individuals (AM, mean age 65.6, stdev 12.26) who served as the healthy control group. Individuals were excluded if they presented with acute medical problems, uncorrected vision deficits, untreated sleep disorders including sleep apnea or narcolepsy, uncontrolled depression, previous history of psychiatric admission or neurological disease other than stroke, or scored below a 26 on the mini-mental status exam[152]. Individuals were instructed to refrain from alcohol and/or caffeine for 12 hours prior to and during testing.

To better characterize the upper extremity function of the participants post-stroke, the Orpington Prognostic Score[153] and the upper extremity motor portion of the Fugl-Meyer Assessment of Physical Performance (FM)[154] were administered. No difference existed between the stroke groups for the Orpington Prognostic Score (p=.456) or the FM (p=.499; Table 3.1). The Stanford Sleepiness Scale[155] measured level of sleepiness prior to the practice session and the retention session; groups did not differ for the Stanford Sleepiness Scale at these two time points (p=.260 at practice session; p=.147 at retention; Table 3.2). Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI)[156], and depression was indexed using the Geriatric Depression Scale (GDS)[157]. There was no difference between the groups for PSQI (p=.538) or the GDS (p=.264; Table 3.2). Last, to better characterize the sample populations sleeping habits and schedule, individuals were asked to maintain a sleep log for a week prior to testing. When a sleep log was not maintained, the fourth question for the PSQI was used to ascertain the average amount of sleep obtained. There was no significant between group difference for average amount of sleep (p=.742; Table 3.2). The Edinburgh Inventory (EI)[137] determined that all participants except one were right hand dominant (Table 3.2).

Participants were recruited at the University of Kansas Medical Center, the University of British Columbia, and the local community. Individuals post-stroke were pseudo-randomly assigned to either the sleep group (slept in between practice and retention testing) or the no-sleep group (stayed awake between practice and retention testing). Neurologically intact individuals were placed into either the sleep or no-sleep group based on subject-wise age-matching (+/- 5 years) and were also matched for hand-use.

Lesion Location

Lesion location was derived from medical records, MRI scans, and the University of Kansas Medical Center's Stroke database, for 15 of the 18 stroke participants (Table 3.3). Based on this information, the individuals post-stroke all presented with lesions located in the cortex and/or sub-cortical structures in the distribution of the middle cerebral artery (MCA). Because of the diverse nature of the descriptions obtained from medical records we classified lesion location using the scheme outlined by Bamford, Sandercock, Dennis, Burn, and Warlow[158, 159].

Task

A continuous tracking task was used to index motor skill learning. Participants were seated facing a computer screen with a curser and a target displayed in easy view. Participants used a joystick to control the curser to match the target as it moved in a pseudo-sine wave pattern. Only the target and the participants' curser position were visible at any given moment; no other part of the wave was visible to avoid the delivery of visually based feedforward and/or feedback information. Following every trial, real-time position data was stored for future analysis. Stroke participants used their less-affected upper extremity and healthy controls were matched for arm use.

Participants practiced the task either in the evening (sleep group) or in the morning (no-sleep group) and then returned 12 hours later (+/- 1 hour) for retention testing. At the first session, participants practiced 10 blocks of 10 trials per block; each trial consisted of both a random segment and a repeated segment of a wave counterbalanced in order (12.5 seconds each segment; trial length 25 sec with 2 seconds stable mid-position target in between trials). To determine off-line improvement in performance related to sleep, participants underwent a delayed retention test consisting of 1 block of the tracking task (10 trials, each consisting of both a random segment and a repeated segment of a wave). Participants received no explicit instruction regarding the presence of the sequence; they were simply told that they were participating in a tracking test and asked to continually track the target cursor with movements of the joystick as accurately as possible.

Following retention, participants completed explicit recognition tests where they simply watched the computer screen while a wave segment was played. The participants were asked to state whether or not the segment was one that they recognized. Ten recognition tests were conducted; 3 of the actual practice repeated segment and 7 foils consisting of a random segment that had not been viewed previously. The purpose of the recognition test was to ascertain the degree of explicit awareness obtained through implicit motor practice.

Outcome Measure

Root Mean Square Error (RMSE) was calculated for each repeated and random segment on each trial[78, 82]. Median RMSE was calculated for both repeated and random segments of each block. To determine the effect of off-line learning attributable to sleep or time, a learning score was calculated by subtracting median repeated sequence RMSE from the retention block from the last repeated sequence block performed during the practice session.

Data Analyses

To assess the change in performance on the continuous tracking task from the last practice block to retention for each group, a paired t-test was performed for each group. To determine differences in participants' ability to correctly identify the repeated and random segments during recognition testing, a one-way ANOVA was conducted with number correct on the recognition test the dependent variable. Alpha was set at .05. An effect size (ES) was calculated to assess a real and meaningful difference between the sleep and no-sleep participants in both the age-matched and stroke groups[160].

3.4 Results

Off-line learning

Only the individuals with stroke who slept in between the practice session and retention testing demonstrated implicit motor sequence learning of the experimental continuous tracking task. This was shown via significant off-line improvements in tracking error from the end of practice to retention testing that were only associated with sleep (p=.018). The individuals post-stroke who stayed awake between the practice and retention did not demonstrate implicit motor sequence learning that was related to time between the sessions (p=.467). A large effect size of .764 indicates a real and meaningful difference between the amount of change that was associated with the stroke sleep and stroke no-sleep groups[160]. Neither of the age-matched control groups performed better at retention (p=.702 for AM sleep group; p=.458 for AM no-sleep group, Figure 3.1). A small to moderate ES of .410 between the AM sleep and AM no-sleep groups indicates that despite a lack of significant improvement in performance from practice to retention testing, there was a difference between these two groups. This between group difference was related to the increased amount of errors made by the AM sleep group at retention (Figure 3.1).

Acquisition of explicit knowledge

There was no difference in the ability to correctly identify the repeated and random segments between groups during the recognition test conducted following retention testing ($F_{3,32}$=.477; p=.701). Furthermore, each group performed at a chance level (50% correct or less) during explicit testing, indicating that none of the groups gained explicit knowledge during implicit task practice (ST sleep group 42.4% correct, ST no-sleep group 46.7% correct, AM sleep and no-sleep groups 51.1% correct).

3.5 Discussion

We sought to determine the role of sleep in implicit motor skill learning following stroke. We discovered that contrary to what has been demonstrated in healthy young adults, after stroke implicit motor sequence learning is preferentially enhanced by sleep. Furthermore, our findings provide concurrent evidence that healthy older adults are not reliant on sleep for implicit motor memory consolidation.

Individuals with stroke are able to learn new implicit motor skills[27-31]. Furthermore, people are able to learn implicitly following lesions in the MCA distribution affecting the sensorimotor cortex[108] or basal ganglia[82, 131-133]. One of the likely reasons that people with a stroke in the MCA distribution may be able to learn new motor skills is the wide distribution of the neural architecture that supports motor learning which includes the sensorimotor cortex (SMC), the cerebellum, and the basal ganglia[47]. Lesions that completely disrupt motor learning are highly unlikely. Robertson et al.[128] found that interfering with the function of the primary motor cortex (M1) using transcranial magnetic stimulation immediately following motor practice of a discrete sequence results in disruption of implicit skill learning when consolidation occurred during the day (i.e., retention test in the same day). However, this effect was not noted when consolidation was accompanied by sleep (i.e., retention test delivered the next day). Because in Robertson et al.'s work the same amount of time elapsed between practice and retention testing regardless of whether or not sleep occurred, these effects are not likely related to the length of intervening time. It appears that M1 is important for implicit skill learning that occurs over the day; sleep related off-line improvements in implicit motor skill do not seem to be entirely reliant on the function of M1. Interestingly, the data from Robertson et al. also demonstrate that different neuronal circuits must support off-line implicit motor learning that is sleep related as opposed to time reliant for memory consolidation. None of the participants in the current study had a lesion that was isolated to M1. However, each individual studied did present with damage in the MCA distribution where M1 is located. In addition the most clinically common location of stroke is in the region of the MCA[38]. Our finding that sleep aided implicit motor sequence learning after stroke suggests that after damage to a portion of the MCA distribution other interconnected neural regions that support implicit motor learning (e.g., the basal ganglia or cerebellum) might participate in sleep-dependent implicit motor skill consolidation. Two studies[75, 120] that have utilized neuroimaging techniques to elucidate changes in the representation of motor memory following sleep have demonstrated wide spread changes in brain activity associated with motor memory consolidation, thus providing some support that damage to one area may not eliminate sleep dependent memory consolidation in others. This contention is further supported by Maquet et al.[117] who showed that areas of the brain activated during acquisition of a probabilistic implicit motor SRT task were re-activated during rapid eye movement (REM) sleep after training. The areas that were re-activated included the cuneus, striate cortex bilaterally, the mesencephalon (all areas outside the MCA distribution) and the left premotor cortex.

Our findings support that of others demonstrating that healthy older adults are not reliant on sleep-dependent memory consolidation to implicitly learning a motor sequencing task[21] or a memory word-pair associations task[22]. The healthy control participants in our study were neurologically normal yet their implicit motor sequence learning was not enhanced by sleep. It may be that with age alterations in sleep characteristics limit the benefit of sleeping for implicit motor sequence learning. With advancing age, total sleep time decreases as does the percentage of time spent in REM and slow wave (SWS) sleep[23, 24]. While the amount of time spent in Stage-2 non-REM sleep remains fairly stable[23], there is a reduction in the number of sleep spindles that occur with age[25, 26]. Consensus is building that developing memory for perceptual-motor tasks similar to the one employed in the present research requires stage-2 and/or REM sleep for consolidation. For example, overnight improvement in the performance of a finger-tapping task was found to correlate with the amount of stage-2 NREM sleep[13], whereas overnight improvement in a similar finger-to-thumb opposition task correlated with the amount of REM sleep[16]. Furthermore, sleep spindles which are characteristic of stage-2 NREM sleep have been demonstrated to play an important role in sleep-dependent memory improvement[69, 90, 91]. If REM sleep and sleep spindles have a facilitating effect on implicit motor skill learning, perhaps the reduction in these two sleep parameters explains the lack sleep dependent off-line learning by the healthy older adults in this study.

Because the control participants were age-matched to the stroke participants, there must be a unique characteristic of the neurologically damaged brain that can promote sleep dependent implicit motor memory consolidation. Little research has characterized the sleep architecture of chronic stroke survivors which makes ascertaining the relative role of the various sleep stages on implicit motor learning after stroke somewhat difficult. Vock et al.[37] found that 53% of people with chronic stroke demonstrate abnormal sleep architecture as compared to published norms. In Vock's study, 15 chronic (5-24 months) stroke patients ranging in age from 18 to 75 years with an average age of 49 year old spent 16.6% of total sleep time (TST) in REM sleep. This is only slightly less than the published norm for a healthy 49-year-old individuals (~ 20% of sleep period time (SPT))[23]. The chronic stroke individuals in the Vock et al. study[37] spent 60.9% of TST in stage-2 NREM sleep which is higher than the published norm for a healthy 49-year-old individual (~52% of SPT)[23]. Maintenance REM sleep and increasing in stage-2 NREM sleep by individuals with chronic stroke may explain the sleep dependent skill enhancement demonstrated by the stroke participants in the current study. Supporting this contention, Gottselig, Bassetti, and Achermann[36] found that spindle frequency activity significantly increased from acute (<10 days) to the chronic (>60 days) stroke. Further studies are needed to characterize the sleep architecture of chronic stroke participants to more fully support this contention.

One of the limitations of the present study is it was not conducted in a sleep lab, and, we cannot therefore ensure the amount or quality of sleep the participants obtained, particularly over the night between practice and retention. We addressed this limitation by asking participants to maintain a sleep log for a week prior to testing as well as used the PSQI to index quality of sleep. No difference in average sleep prior to participating in the study or scores on the PSQI was found between the groups. The benefit of having participants not sleep in a sleep lab is that it provides testing of their "natural" sleep cycle and provides evidence that sleep-dependent skill enhancement can occur in "every day life".

Because we used a task that has not been previously employed to assess sleep-dependent learning in the past it is somewhat difficult to ascertain whether our findings are unique to the continuous tracking task. Different motor control methods are used for a continuous task as compared to a discrete task; further our tracking task may represent a more complex motor problem than previously used discrete tasks. Because we are interested in extrapolating our findings to formulate clinically relevant conclusions we choose to use a continuous task with greater complexity. Indeed, it is possible that previous work using simple finger sequencing tasks may not be useful for forming generalizing conclusions that may be utilized in formulating therapeutic approaches. Our findings that sleep benefited implicit motor sequence learning of a continuous tracking task after stroke lay the groundwork for future research to investigate the role of sleep in functionally relevant contexts.

One might argue that time-of-day of testing or circadian rhythm may have been a factor in the results of our study. Evidence suggests that the performance of older adults on memory exams deteriorates when testing occurs in the evening compared to earlier in the day[161, 162]. However, this time-of-day effect likely depends on the type of memory under consideration. Improved retrieval of implicit motor memory has been shown to occur at non-optimal times (i.e. in the evening for older adults) which is in contrast of explicit memory which is better retrieved at optimal times (i.e. in the morning for older adults)[163]. If time-of-day of testing had indeed been a factor influencing implicit learning of our experimental motor task, we would have expected those individuals who underwent retention testing in the evening (no-sleep group) to have performed better than those who underwent retention testing in the morning (sleep group); this was clearly not the case. Furthermore, there was no difference between the groups on the Stanford Sleepiness Scale at practice session or retention testing regardless of time of day the testing occurred.

Clinical Implications

Understanding the role of sleep in memory consolidation and implicit motor learning in the damaged brain has tremendous implications for rehabilitation. If sleep does aid implicit motor skill learning, therapy may need to be conducted in the evening or late day prior to sleeping for the night; alternatively, a nap may become a standard part of rehabilitation programs. Furthermore, studies have demonstrated that individuals in a hospital, including rehabilitation patients[164 165], report sleep disturbances and a reduction in quality of sleep. Therefore, a new added emphasis may also be placed on ensuring adequate sleep following stroke by altering the environment (i.e. ensuring quiet to promote sleep in the hospital or reducing disturbances while patients are asleep) or addressing underlying conditions limiting sleep such as depression.

If sleep does have an impact on implicit motor learning following stroke the manner in which other researchers perform their studies may need to be shifted. For example, sleep may be the reason that motor skills improve between sessions when sleep is permitted (i.e., when overnight delays are built into research designs) rather than the number of practice sessions, the amount of practice in a session, or the type of practice. Thus, sleep could potentially represent either a confounding or beneficial variable in the experimental designs of those who study learning. Future research may have to explicitly address the impact of sleep in experimental designs.

3.6 Conclusion

The results of our study provide evidence that individuals with stroke benefit from sleep to enhance implicit motor skill learning and consolidation. This sleep-dependent skill enhancement was not found for age-matched, neurologically intact individuals. The findings from our work suggest that during rehabilitation and recovery from stroke emphasis should be placed on promoting both adequate sleep and improved sleep quality in individuals post-stroke. This approach may be particularly critical during rehabilitation when re-learning of old skills or learning new skills is the focus. Furthermore, researchers should consider sleep as a factor in learning studies. Future work is needed to more precisely ascertain which neurobiological mechanisms enable the stroke-damaged brain to benefit from sleep when the healthy brain is unable to do so.

	Time post-stroke (month)	**Fugl-Meyer**	**Orpington**	**Side of Lesion**
Stroke Sleep	87.56 (60.9)	43 (16.1)	2.36 (.68)	3 Left; 6 Right
Stroke No-sleep	69.78 (43.5)	48.25* (15)	2.65 (.91)	3 Left; 6 Right

Table 3.1. Descriptive information for stroke participants. Data are mean (standard deviation).

	Sex	Age	UE Used	Hand Dominance	MMSE	SSS 1	SSS 2	PSQI (n=35)	GDS (n=34)	Average sleep**
Stroke Sleep	5 male; 4 female	65.4 (7.1)	3 Left; 6 Right	9 Right	29.11 (.93)	1.56 (.88)	2.00 (1.22)	4.75 (2.31)	6.13 (3.56)	7.48 (1.42)
Stroke No-sleep	3 male; 6 female	66.6 (16)	3 Left; 6 Right	1 Left; 8 Right;	28.38 (1.5)	2.56 (1.01)	3.11 (1.27)	7.11 (4.48)	6.67 (6.54)	7.43 (1.10)
AM Sleep	5 male; 4 female	66.1 (7.3)	3 Left; 6 Right	9 Right	29.67 (.71)	2.22 (1.30)	2.11 (.78)	5.44 (3.78)	3.33 (2.83)	6.92 (.84)
AM No-sleep	3 male; 6 female	65.1 (16.3)	3 Left; 6 Right	9 Right	29.78 (.67)	2.33 (1.12)	2.33 (1.0)	5.67 (2.40)	3.5 (3.02)	7.17 (1.36)

Table 3.2. Descriptive information for participants. Data are mean (standard deviation). UE Used= upper extremity used during tracking task; MMSE=Mini-mental Status Exam; SSS1=Stanford Sleepiness Scale taken at practice session; SSS2=Stanford Sleepiness Scale taken at retention testing; PSQI= Pittsburgh Sleep Quality Index; GDS= Geriatric Depression Scale; Average sleep=average amount of sleep participants received the week prior to testing determined by sleep log.

*n=8 due to one participant hurt her involved wrist and was unable to complete portion of test

Subject Number Sleep Group	***Lesion Side***	***Lesion Classification***	***Specific Lesion Location***
Sleep 1	Left	Sub-cortex	Putamen, corona radiata
Sleep 2	Right	Sub-cortex	Basal ganglia
Sleep 3*	Left	Sub-cortex	Posterior limb of the internal capsule
Sleep 4	Right	Cortex	Frontal, parietal, superior temporal cortices
Sleep 5	Right	Cortex & Sub-cortex	Caudate head, lentiform nucleus, posterior-superiorfrontal lobe
Sleep 6	Right	Sub-cortex	Posterior limb of internal capsule
Sleep 7	Right		Not Available
Sleep 8	Right	Cortex & Sub-cortex	Frontal and parietal cortex, basal ganglia
Sleep 9	Left	Sub-cortex	Lentiform nucleus, deep cerebral white matter
Subject Number No- Sleep Group	***Lesion Side***	***Lesion Classification***	***Specific Lesion Location***
No sleep 1	Right	Cortex	Temporal-parietal-occipital cortex
No sleep 2	Right		Not Available
No sleep 3	Left	Sub-cortex	Lenitiform nucleus, putamen, claustrum, insula
No sleep 4	Left	Cortex & Sub-cortex	Middle cerebral artery
No sleep 5	Right	Sub-cortex	Posterior limb of internal capsule
No sleep 6	Right	Cortex & Sub-cortex	Insular, parietal cortex
No sleep 7	Right		Not Available

No sleep 8	Left	Sub-cortex	Thalamus and posterior limb of internal capsule
No sleep 9	Right	Sub-cortex	Basal Ganglia and insula

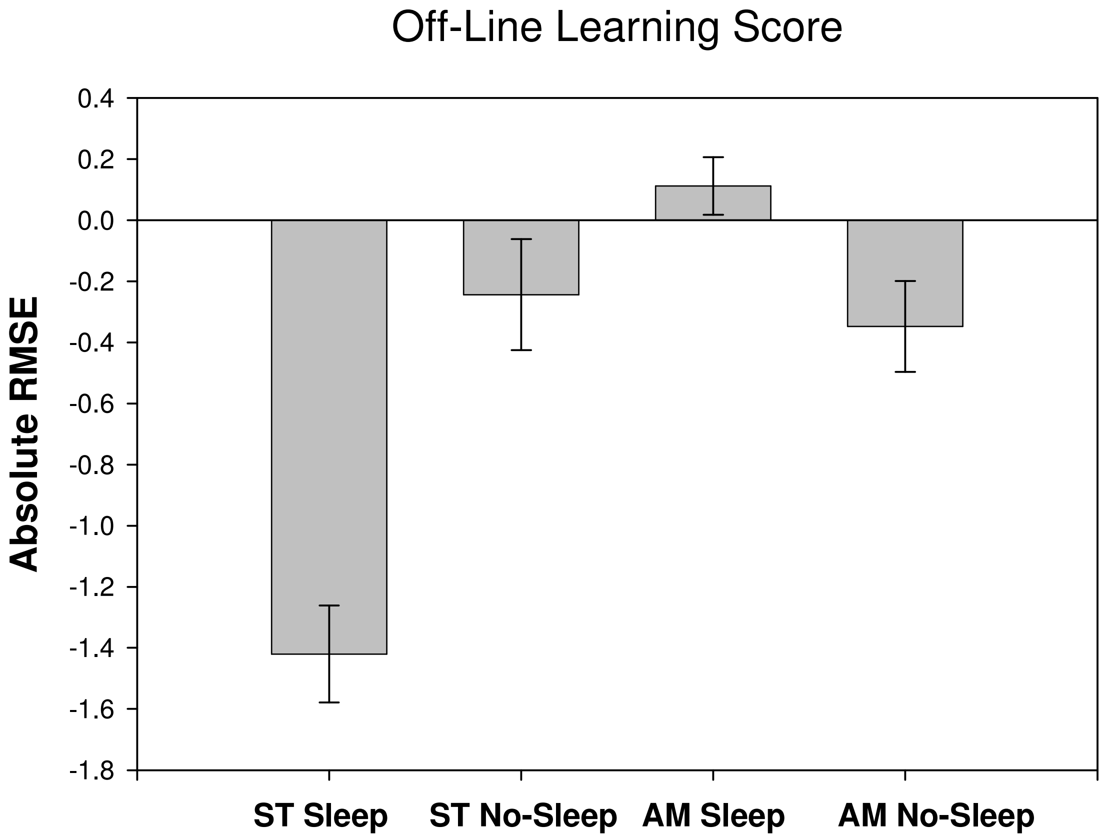
Table 3.3. Lesion location for 15 of the 18 participants of this study. Lesion location derived from medical records, MRI scans, University of Kansas Medical Center's Stroke database.

*Bilateral lesions noted on MRI scan; clinically relevant lesion in left sub-cortex involving the posterior limb of the internal capsule, other foci noted in left insula and right head of the caudate. Additionally, right cerebellar atrophy was apparent.

3.7 Figure Legend

Figure 3.1. Off-line learning for each group. Off-line learning was calculated by subtracting the RMSE of the repeated sequence at retention testing from the last repeated sequence from practice. A negative score indicates an improvement or less error at retention as compared to the last block of practice. Error bars are SEM.

Figure 3.1.


Off-Line Learning Score
Absolute RMSE
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
ST Sleep
ST No-Sleep
AM Sleep
AM No-Sleep

Chapter 4 Preface

Chapter 3 assessed sleep-dependent off-line motor learning for individuals post-stroke and healthy older adults on an implicit version of a continuous tracking task using a subset of participants. Chapter 4 utilized the entire set of participants and extends our work into the realm of off-line explicit motor learning. As mentioned previously, one benefit of utilizing a continuous tracking task to assess off-line motor learning is participants seldom gain explicit awareness of the repeated sequence, thus allowing for an assessment of "pure" implicit off-line motor learning. Another benefit of the continuous tracking task is researchers can manipulate instruction to also examine sleep-dependent explicit off-line learning. Therefore, we utilized both an implicit and explicit version of a continuous tracking task to examine the interaction of sleep and type of instruction on off-line motor skill learning following stroke and in healthy, older adults.

The statistical plan to analyze the data for the presented work included an omnibus 3-way Group (Stroke, Control) by Sleep (yes, no) by Instruction (explicit, implicit) ANOVA to determine whether or not sleep differentially effects individuals with stroke from healthy controls. Alpha was set at .05. No interactions or main effects were significant. Contrasts or a parameter estimate were then conducted to test individual hypotheses.

Hypothesis 1: Participants with explicit knowledge who slept following practice of a continuous tracking task would display improved learning compared to participants who do not sleep.

This hypothesis was assessed using a contrast between the healthy control participants given explicit instruction who slept following practice and who do not sleep. This contrast was not significant at p=.748.

Hypothesis 2: Participants who are not provided with explicit instruction (implicit condition) of the continuous tracking task would display improved learning both following a period of sleep and a period of being awake.

This was assessed using a parameter estimate, and, contrary to our hypothesis, neither of the control groups regardless of sleep or staying awake between practice and retention demonstrated off-line learning of the implicit version of the continuous tracking task (sleep/implicit p= 701, no-sleep/implicit p= .472)

Hypotheses 3: Participants with stroke in the MCA distribution who are given explicit instruction and sleep after practice would demonstrate improved learning of a continuous tracking task compared to participants who do not sleep.

This was assessed using a contrast between post-stroke participants given explicit instruction who sleep following practice and those who do not sleep. This contrast was not significant at p=.176.

Hypothesis 4: People with stroke who are not provided with explicit instructions (implicit condition) would demonstrate improved learning of a continuous tracking task compared to participants who do not sleep.

This was assessed using a contrast between stroke participants given no explicit instruction (implicit condition) who sleep following practice and those who do not sleep. This contrast was not significant at p=.506.

Hypothesis 5: There will be a significant difference on learning of a continuous tracking task between the participants with stroke who are not given explicit instruction (implicit condition) nor sleep following practice and the age-matched controls.

This will be assessed using a contrast between stroke participants and healthy control participants given no explicit instruction and do not sleep following practice. This contrast was not significant at p=.875.

Because we were ultimately interested in whether or not each group displayed off-line motor learning of the tracking task rather than the differences in off-line learning between groups, we conducted further analysis using parameter estimates to determine the significance of change in motor behavior associated with motor memory consolidation that occurred off-line during either sleep or with time for each of the control and stroke groups in the implicit and explicit conditions. This data is presented in the following chapter.

Chapter 4

Sleep to Learn After Stroke:

Implicit and Explicit Off-Line Motor Learning

This work has been submitted for publication to *Stroke*, 2008.

4.1 Abstract

After stroke, many individuals experience persistent motor impairments as well as altered patterns of sleep. Because sleep has been demonstrated to be important for motor skill learning and memory consolidation in healthy, neurologically intact individuals, examining the role of sleep in motor skill learning post-stroke is a critical issue. Other learning variables, such as type of instruction, may interact with sleep to influence sleep-dependent motor learning and memory consolidation. Forty individuals post-stroke and 40 control participants practiced a continuous motor tracking task and then either slept (sleep condition) or stayed awake (no-sleep condition) for a similar period of time before retention testing to assess off-line motor learning. Half of the individuals in both the sleep and no-sleep condition were explicitly instructed regarding the presence of a repeating sequence embedded in the motor tracking task (explicit condition) while the other half were not (implicit condition). After stroke, individuals demonstrated sleep-dependent off-line motor learning of both the implicit and explicit version of the continuous tracking task; however, individuals with stroke who stayed awake between practice and retention testing did not demonstrate an improvement in motor performance at retention. Neither sleep nor instruction differentiated the performance of the healthy control participants. After stroke, individuals benefited from sleep to enhance implicit and explicit motor skill learning and memory consolidation. These data suggest that motor recovery after stroke may be facilitated by sleep.

4.2 Introduction

Patterns of sleep are shifted after stroke. Acutely, individuals with stroke demonstrate reduced total sleep time and efficiency[34-36] and decreased proportions of REM[92] and non-REM sleep[34]. Sub-acutely, 57% experience persistent insomnia 3-4 months after stroke[33]. Sleep patterns do not appear to normalize with time; sleep EEG characteristics differ from normal in 53% of individuals with chronic stroke[37].

Sleep is important for motor skill learning and memory consolidation for young, neurologically intact individuals; participants who sleep in-between practice and retention testing demonstrate enhanced performance as compared to participants who stay awake[12-16]. The impact of sleep on learning in young, healthy individuals appears to be dependent on the memory systems invoked. Learning and memory can be broadly sub-divided into explicit and implicit systems. *Explicit memories* may be consciously recollected, meaning that for motor skills the patterns or regularities of a movement is explicitly known. In contrast, *implicit memories* develop without any conscious awareness for motor task regularities[166]. For young, healthy individuals, sleep beneficially affects motor learning when participants have explicit knowledge of the rules or regularities of the task being practiced, whereas implicit memories are consolidated over time with sleep playing a lesser role[18].

In contrast to young, neurologically intact individuals, sleep does not enhance learning and memory consolidation in older, healthy adults for either implicit or explicit motor[21], or explicit word-pair associations memory consolidation[22]. After the brain is damaged by stroke, the role of sleep in motor skill learning is less clear. Our preliminary work showed that individuals post-stroke demonstrated improvements in motor performance attributable to sleep for an implicit motor tracking task[167]. These sleep-dependent enhancements in motor function occurred “off-line” with no additional physical practice. Presently, we do not know if similar off-line motor learning might occur during explicitly instructed motor learning.

After stroke, many individuals suffer from persistent motor impairments[168]. Thus, examining methods that hasten or increase the efficiency of motor skill learning following stroke is an important clinical endeavor. Therefore, the purpose of the current research was to consider the influence of sleep and type of instruction (explicit instruction vs. implicit learning) on off-line motor learning in individuals with chronic stroke.

4.3 Methods

Participants

Forty-one individuals post-stroke (ST, mean age 62.6 years old, stdev 12.3) and 40 age- and sex-matched neurologically intact individuals (CT, mean age 62.3 years old, stdev 12.4) participated in the study. One ST individual was removed from data analysis due to being labeled an “extreme outlier” by SPSS boxplot analysis[169]. Participants were recruited from the University of Kansas Medical Center and the University of British Columbia as well as local communities. Individuals with acute medical issues, uncorrected vision, untreated sleep disorders, uncontrolled depression, history of psychiatric admission or other neurological disease, or who scored below a

26 on the mini-mental status exam (MMSE)[152] were excluded. Three ST individuals experiencing aphasia completed the 3-step instruction portion of the MMSE to participate. All participants were instructed to refrain from alcohol and caffeine for 12 hours prior to and during the testing period.

To assess level of sleepiness, the Stanford Sleepiness Scale[155] was administered prior to practice and retention testing. To characterize the participants' sleep habits and quality, the Pittsburgh Sleep Quality Index (PSQI)[156] was administered, and individuals were instructed to maintain a sleep log for the week before testing. The Geriatric Depression Scale (GDS)[157] assessed for possible depression. All participants but two were right hand dominant (Table 4.1) as determined by the Edinburgh Inventory (EI)[137]. The Orpington Prognostic Score[153] and the upper extremity motor portion of the Fugl-Meyer Assessment of Physical Performance (FMUE)[154] were utilized to characterize upper extremity function for the individuals post-stroke (Table 4.2).

Lesion Location

The location of stroke lesion was determined using magnetic resonance imaging when possible. Medical reports were obtained when safety criteria or participant preference prevented brain imaging. In total, lesion information was available for 30 of the 40 individuals with stroke (Table 4.3). Lesion location was classified according to the scheme outlined by Bamford, Sandercock, Dennis, Burn, and Warlow[158, 159, 167] with all ST participants presenting with lesions in the cortex and/or sub-cortical structures of the middle cerebral artery (MCA) distribution except two with lesions in the posterior cerebral artery (PCA) distribution and one with a lesion in the pons.

Task

ST participants were assigned pseudo-randomly to either practice a continuous tracking task in the evening and undergo delayed retention testing designed to assess off-line motor learning the following morning (sleep groups) or to practice the tracking task in the morning and undergo retention testing the evening of the same day (no-sleep groups). Twelve hours (+/- 1 hour) elapsed between practice and retention testing for both the sleep and no-sleep groups. The CT participants were assigned to groups based on subject-wise age- (+/- 5 years) and sex-matching. The less-affected, ipsilesional hand was used by the ST participants to perform a continuous tracking task to allow motor learning to be assessed without being overshadowed by motor execution impairments[80, 82, 108]. CT participants were matched for hand-use.

Participants sat in front of a computer screen and used a joystick placed at a comfortable position to continuously track a target moving up and down as a pseudo-sine wave through a sequence of 10 reversals in direction[78, 82]. The participants only saw the target (white box) and their own cursor position (red circle); there was no visual feedback via a residual trace on the screen. Participants practiced 100 trials (10 blocks of 10 trials each) at the first session. For each trial, participants tracked two sequences, one random and one repeated presented in counterbalanced order (each sequence was 12.5 seconds long; total trial length 25 sec; 2 second stable target between each trial). Participants underwent a 10 trial (1 block) delayed retention test 12 hours (+/- 1 hour) following practice with the sleep groups sleeping between practice and retention and the no-sleep groups staying awake. Real-time position data was stored following each trial.

Explicit Instruction

Prior to the start of the first session, half of the participants in the sleep and no-sleep groups received instruction regarding the presence of the repeated pattern (explicit groups; Table 4.4). Participants in the explicit groups were: 1) verbally instructed that a repeated sequence existed along with random sequences, 2) shown a pictorial representation of the repeated sequence with the instruction that only one point of the sequence would be visible at a time, and 3) watched on the computer the repeated sequence with only the target moving to simulate the actual task. Participants were allowed to watch the repeated sequence on the computer as many times as they requested until they indicated that they could recognize the pattern.

To ensure the acquisition of explicit knowledge for the repeating sequence following explicit instruction, participants underwent a recognition test consisting of watching the target move on the computer screen. Participants had to decide (forced choice) if the sequence displayed was the same repeating sequence shown to them or not. This procedure was performed with 10 sequences; 3 of the repeating sequence and 7 foils (random sequences not previously viewed). Participants had to demonstrate 80% correct recognition or this process was repeated until they gained explicit knowledge of the repeating sequence.

The implicit condition groups did not receive any instruction regarding the repeating sequence embedded in the task. They were instructed to track the target cursor as accurately as possible.

Assessment of Explicit Awareness

Following retention testing, all participants underwent a recognition test to determine if 1) explicit knowledge was retained for the explicit instruction groups and 2) the degree of explicit awareness obtained during task practice for participants in the implicit groups. The recognition test was conducted as described above.

Outcome Measure

Tracking accuracy indexed by Root Mean Square Error (RMSE) of each trial was calculated[78, 82]. For each block, participants' median RMSE was calculated[78, 80, 82]. Off-line learning demonstrating change in motor behavior associated with either sleep or time was calculated by subtracting the median retention block RMSE from median RMSE in the last practice block.

Data Analyses

Motor performance during practice was assessed using a two factor repeated measures ANOVA (Group x Block [1 – 10]) with RMSE as the dependent variable. Parameter estimates were performed to determine the significance of change in motor behavior associated with motor memory consolidation that occurred off-line during either sleep or with time for each of the CT and ST groups. Differences in group characteristics were assessed with one-way ANOVAs. To assess the level of explicit knowledge maintained by the explicit groups at retention, a one-way ANOVA was conducted with number correct on the recognition test at retention as the dependent variable. A one-way ANOVA also assessed the level of explicit awareness acquired by the implicit groups using number correct on the post-retention recognition test as the dependent variable. Alpha was set at .05. To verify that between group differences were meaningful, an effect size (ES) between the sleep and no-sleep participants in the CT and ST groups for implicit and explicit conditions was calculated[160].

4.4 Results

Motor Performance

All of the groups demonstrated a practice-related improvement in performance for the repeated sequence as indicated by the presence of a main effect of block (ME block, $F_{9,648}$=9.317, p<.000). Although group differences did exist (ME group, $F_{7,72}$=3.829, p=.001), there was no interaction (Group by Block, $F_{63,648}$=.904 p=.685).

Off-line Motor Learning

Sleep had a significant positive impact on off-line motor sequence learning (i.e., less tracking error at retention that at the last block of practice) for individuals with stroke regardless of type of instruction (implicit group p=.002; explicit group p=.007; Figure 4.1a). Allowing motor consolidation to occur while participants with stroke were awake did not induce any off-line motor learning regardless of the type of instruction provided (implicit group p=.503; or explicit group p=.153; Figure 4.1a). None of the control groups demonstrated off-line motor learning regardless of sleep or type of instruction (CT sleep/implicit p= .701, CT sleep/explicit p= .126, CT no-sleep/implicit p= .472, CT no-sleep/explicit p=.100; Figure 4.1b).

Effect size calculations indicated real and meaningful differences existed between off-line motor learning for individuals with stroke who slept compared to those who stayed awake regardless of instruction. A large effect size (ES) of .761 was noted for the ST implicit groups (ST sleep/implicit compared to ST no-sleep/implicit) and small to moderate ES of .360 for the ST explicit groups (ST sleep/explicit compared to ST no-sleep/explicit)[160]. For the control groups, a moderate ES (.450) was found for the CT implicit groups (CT sleep/implicit compared to CT no-sleep/implicit) owing to the *worse* performance of the CT sleep/implicit at retention (see Figure 4.1b). This finding is not unusual in motor learning studies[28] and likely reflects the presence of a combination of temporary performance effects and longer-term behavioral change at the end of practice. A negligible ES of .0397 for the CT explicit groups (CT sleep/explicit compared to CT no-sleep/explicit) indicates no meaningful difference in off-line motor learning between these groups.

Explicit Knowledge Maintenance

All of the explicit groups maintained knowledge of the repeated sequence at the recognition test following retention testing (ST sleep/explicit group 80% correct, ST no-sleep/explicit group 70% correct, CT sleep/explicit group 85 %, and CT no-sleep/explicit group 92% correct). Although it cannot be determined if participants were able to operationalize explicit information to benefit motor tracking, they did in fact retain this knowledge throughout testing. The explicit control participants generally performed better on the recognition test than the stroke participants, which was confirmed by a significant one-way ANOVA ($F_{3,36}$=3.018; p=.042) with Fisher's LSD post-hoc comparisons indicating a significant difference only between the ST no-sleep/explicit group and the CT no-sleep/explicit group (p=.006).

Acquisition of Explicit Knowledge

Because the acquisition of explicit knowledge regarding the presence of the repeating sequence may interact with sleep[18], we verified that all of the implicit groups had *not* acquired explicit knowledge of the repeating sequence. All in the implicit groups performed at a chance level or below during recognition testing following the retention test (ST sleep implicit group 41% correct, ST no-sleep implicit group 44% correct, CT sleep implicit group 51%, and CT no-sleep implicit group 51% correct). There were no group differences in performance on the post-retention recognition test for the implicit condition groups ($F_{3,36}$=.787; p=.509).

Participant Characteristics

No group difference in level of sleepiness were detected at the practice session (p=.299) or at retention (p=.174; Table 4.1). There were no significant differences between groups on the PSQI (p=.789), average amount of sleep (p=.425), GDS (p=.227; Table 4.1), or between stroke groups on the Orpington Prognostic Score (p=.920), FMUE (p=.630), or time-post stroke (p=.425; Table 4.2).

4.5 Discussion

Emerging from the literature is a growing consensus of the importance of sleep for motor skill learning and memory consolidation. Over half of all individuals with stroke show changes in sleep architecture[37]. At present it is unclear how changed sleep patterns impact recovery from stroke; however, our data demonstrate that after stroke, individuals *benefit* from sleep to enhance off-line motor learning and memory consolidation whereas control participants do not. Sleep related off-line learning was not dependent on the type of memory system invoked; both implicit and explicit groups benefited from sleep. Regardless of the presence or absence of stroke or the type of instruction none of those who stayed awake (no-sleep groups) between practice and retention testing demonstrated off-line motor learning.

Our findings that the control participants did not show sleep-dependent enhancement of implicit or explicit motor learning provide concurrent support for two prior studies that demonstrated a lack of sleep-dependent enhancement for older individuals on an implicit or explicit version of a sequence learning task[21] and a declarative memory word-pair associations task[22]. Taken together, this emerging body of evidence points to a failure of healthy, older adults to benefit from sleep to enhance motor learning. Older adults demonstrate changes in sleep architecture[23, 24, 25, 26] which may limit the potential benefits of sleep. Increased time spent in REM sleep, greater REM density, and decreased REM latency through the use of donepezil enhanced the performance of older adults on an explicit word recall task[73] suggesting that the underlying factors limiting the benefit of sleep with aging are malleable and capable of being shifted therapeutically.

Previous studies have demonstrated that after stroke individuals can learn new motor skills[27, 28, 31]. Owing to the widely distributed nature of the neural circuit supporting motor skill learning which includes the sensorimotor cortex[50, 51] (particularly M1[62, 63]), premotor cortex[52, 57], SMA[50, 51], and basal ganglia[50-53] total abolition of motor skill learning as a result of stroke is unlikely. All of these brain areas receive their blood supply from the MCA, which is the most often occluded artery during stroke[38]. Our findings that sleep enhanced implicit and explicit off-line motor skill learning and memory consolidation after MCA stroke suggests that some redundancy may exist in the neural regions responsible for motor skill consolidation; disruption in one area apparently does not abolish the ability of other regions to benefit from sleep-dependent changes in motor skill. Neuroimaging studies demonstrate widespread changes in brain activity associated with motor memory consolidation, supporting the contention that a lesion may not entirely eliminate capability for sleep dependent memory consolidation[75, 120].

It is presently unclear why individuals post-stroke benefit from sleep and demonstrate off-line motor learning while healthy control participants do not. One explanation centers on the possibility that after stroke individuals profit from changes in their sleep architecture. Vock et al. [37]demonstrated that individuals with chronic stroke spent nearly the same amount of time in REM sleep as healthy younger people (individuals with stroke spent 16.6% of total sleep time (TST)[37] in REM vs. ~ 20% of sleep period time from published norms from a healthy 49-year-old[23]). Alterations in the percentages of time in different phases of sleep were not limited to REM. After stroke, nearly 61% of TST was spent in non-REM stage-2 sleep[37] which is more than the published norms (~52% for published norms, mean age 49[23]). Sleep spindle frequency also increases significantly from acute to chronic stages of stroke (>60 days)[36]. Perceptual-motor skills have been demonstrated to rely on stage-2[13] (in particular sleep spindles[69, 90, 91]) and/or REM[16] sleep for memory consolidation. It is possible that during the recovery process after stroke, the sleep cycle is shifted allowing the brain to achieve a more optimal state for motor learning. Specifically, it may be that individuals with chronic stroke are able to maintain REM sleep and increase non-REM stage-2 sleep and sleep spindle activity. Combined with motor skill practice, changes in sleep architecture after stroke might provide a platform for enhanced off-line motor skill learning. Future work will have to verify this contention and determine whether any particular EEG characteristics or any specific sleep stage(s) directly relates to the findings of the present study.

In the present study participants post-stroke used their less affected upper extremity for motor practice which corresponds to neural activity primarily in the non-lesioned hemisphere. Following stroke, neuronal function of the non-lesioned hemisphere is shifted. A reduction in transcollosal inhibition from the lesioned hemisphere to the non-lesioned hemisphere[170, 171] can result in hyperexcitability of the non-lesioned hemisphere[172, 173]. This hyperexcitability may create a permissive environment for sleep-dependent memory consolidation. In a series of studies, Huber et al. demonstrated an increase in slow wave activity (SWA) limited to the neural region associated with learning a motor task[174]. Further, potentiating the cortex with TMS also increases SWA specifically in the same region of the brain that is being stimulated by TMS[175]. This suggests that learning a motor skill may create similar changes in neuronal plasticity as does direct potentiation by an exogenous source. Perhaps the hyperexcitability of the non-lesioned cortex after stroke results in enhanced potentiation of the neural circuits involved in motor skill learning and memory consolidation. Future work will have to confirm or refute this possibility, perhaps via pairing motor skill practice with external stimulation to the cortex designed to induce SWA during sleep.

4.6 Summary

After stroke, individuals benefit from sleep and demonstrate off-line motor learning both when continuous sequencing task practice was influenced by explicit knowledge and when it was implicit in nature. Age and sex-matched healthy control participants did not experience sleep- or time-dependent off-line motor learning. Because the characteristics of sleep in individuals with chronic stroke have not been well categorized we can only speculate on the precise mechanism(s) that allow individuals with chronic stroke to benefit from sleep to consolidate motor memories off-line. Future studies will undoubtedly seek to understand the truly remarkable resilience of the post-stroke brain. In the meantime, ensuring adequate sleep after stroke may promote motor and functional recovery in this population.

	Sex	Age	UE Used	Hand Dominance	MMSE	SSS1	SSS2	PSQI	GDS	Average sleep‡
STROKE										
Implicit Sleep	6 male; 4 female	62.9 (10.5)	3 Left; 7 Right	10 Right	29.1 (.88)	1.8 (1.1)	2.1 (1.2)	4.89 (2.2)	5.44 (3.9)	7.26 (1.5)
Explicit Sleep	6 male; 4 female	62.2 (10.3)	4 Left; 6 Right	10 Right	28.9 (1.4)	2.6 (1.1)	1.9 (.99)	5.89 (2.5)	4.44 (4.1)	7.70 (1.1)
Implicit No-sleep	3 male; 7 female	65.4 (15.4)	3 Left; 7 Right	1 Left; 9 Right;	28.6* (1.5)	2.4 (1.1)	2.9 (1.4)	7.4 (4.3)	7.5 (6.7)	7.53 (1.1)
Explicit No-sleep	5 male; 5 female	59.8 (13.7)	7 Left; 3 Right	1 Left; 9 Right;	29.1† (.99)	2.1 (.57)	2.4 (.84)	5.2 (3.94)	4.38 (3.9)	7.80 (1.5)
CONTROL										
Implicit Sleep	6 male; 4 female	63.3 (11.3)	3 Left; 7 Right	10 Right	29.7 (.67)	2.2 (1.2)	2.1 (.74)	5.4 (3.6)	3.8 (3.0)	6.95 (.80)
Explicit Sleep	6 male; 4 female	62.2 (10.9)	4 Left; 6 Right	10 Right	29.7 (.48)	3.1 (1.2)	1.6 (.70)	5.7 (2.4)	2.8 (2.3)	7.30 (.82)
Implicit No-sleep	3 male; 7 female	64.5 (15.5)	3 Left; 7 Right	10 Right	29.8 (.63)	2.2 (1.1)	2.4 (.97)	5.2 (2.7)	3.5† (3.0)	7.2 (1.3)
Explicit No-sleep	5 male; 5 female	59.3 (13.0)	7 Left; 3 Right	10 Right	29.4 (1.3)	2.6 (1.4)	2.2 (.92)	5.6 (3.5)	3.2 (2.2)	7.64 (1.4)

Table 4.1. Descriptive Information. Data are mean (standard deviation). UE Used= upper extremity used during continuous tracking task; MMSE=Mini-mental Status Exam; SSS1=Stanford Sleepiness Scale at practice session; SSS2=Stanford Sleepiness Scale at retention testing; PSQI= Pittsburgh Sleep Quality Index; GDS= Geriatric Depression Scale; Average sleep=average amount of sleep the week prior to testing determined by sleep log.

	Time Post-Stroke (month)	FMUE	Orpington	Side of Lesion
Implicit Sleep	81.1 (60.9)	41.4 (16.0)	2.48 (.75)	3 Left; 7 Right
Explicit Sleep	64.1 (43.4)	47.3 (18.3)	2.68 (.76)	4 Left; 6 Right
Implicit No-sleep	65.0 (43.7)	49.6* (14.5)	2.62† (.86)	3 Left; 7 Right
Explicit No-sleep	66.6 (87.3)	47.0 (18.8)	2.27† (1.1)	7 Left; 3 Right

Table 4.2. Descriptive information for individuals following stroke. Data are mean (standard deviation). FMUE = Upper extremity motor portion of Fugl-Meyer, range 0-66.

*n=9 due to one participant hurt her involved wrist and was unable to complete a portion of this test

†n=9 due to aphasia and unable to complete verbal portion of test

Group	***Subject Number***	***Lesion Side***	***Lesion Classification***	***Specific Lesion Location***
Implicit Sleep	1	Left	Sub-cortex	Putamen, corona radiata
	2	Right	Sub-cortex	Basal ganglia
	3*	Left	Sub-cortex	Posterior limb of the internal capsule
	4	Right	Cortex	Frontal, parietal, superior temporal cortices
	5	Right	Cortex & Sub-cortex	Caudate head, lentiform nucleus, posterior-superiorfrontal lobe
	6	Right	Sub-cortex	Posterior limb of internal capsule
	7	Right	Not Available	
	8	Right	Cortex & Sub-cortex	Frontal and parietal cortices, basal ganglia
	9	Left	Sub-cortex	Lentiform nucleus, deep cerebral white matter
	10	Right	Sub-cortex	Internal capsule, temporal and parietal lobes
Explicit Sleep	1	Right	Not Available	
	2	Left	Sub-cortex	Pons
	3	Right	Not Available	
	4	Left	Cortex & Sub-cortex	Postcentral gyrus, insular cortex, temporal and frontal lobes
	5	Right	Cortex & Sub-cortex	Basal ganglia, frontal lobe
	6	Right	Cortex & Sub-cortex	Parieto-temporal lobe, putamen
	7	Left	Not Available	
	8	Right	Cortex	Superior gyrus of frontal lobe
	9	Left	Not Available	
	10	Right	Not Available	

Implicit No-sleep	1	Right	Cortex	Temporal-parietal-occipital cortex
	2	Right	Not Available	
	3	Left	Sub-cortex	Lenitiform nucleus, putamen, claustrum, insula
	4	Left	Cortex & Sub-cortex	Middle cerebral artery
	5	Right	Sub-cortex	Posterior limb of internal capsule
	6	Right	Cortex & Sub-cortex	Insula, parietal cortex
	7	Right	Sub-cortex	External capsule
	8	Left	Sub-cortex	Thalamus and posterior limb of internal capsule
	9	Right	Sub-cortex	Basal Ganglia and insula
	10	Right	Sub-cortex	Corona radiata, internal capsule
Explicit No-sleep	1	Left	Sub-cortex	Cingulate gyrus, posterior cingulate cortex
	2	Right	Not Available	
	3	Left	Cortex & Sub-cortex	Lingual gyrus, visual association cortex, cuneus
	4	Left	Cortex	Occipital lobe
	5	Left	Cortex & Sub-cortex	Frontal lobe
	6[†]	Right	Sub-cortex	Lentiform nucleus
	7	Left	Not Available	
	8	Left	Not Available	
	9	Right	Cortex & Sub-cortex	Middle cerebral artery
	10	Left	Cortex	Frontal, parietal and anteromedial temporal lobe

Table 4.3. Lesion location participants post-stroke.

*Bilateral lesions noted on MRI scan; clinically relevant lesion in left sub-cortex involving the posterior limb of the internal capsule, other foci noted in left insula and right head of the caudate.

†Addition lesion head of left caudate

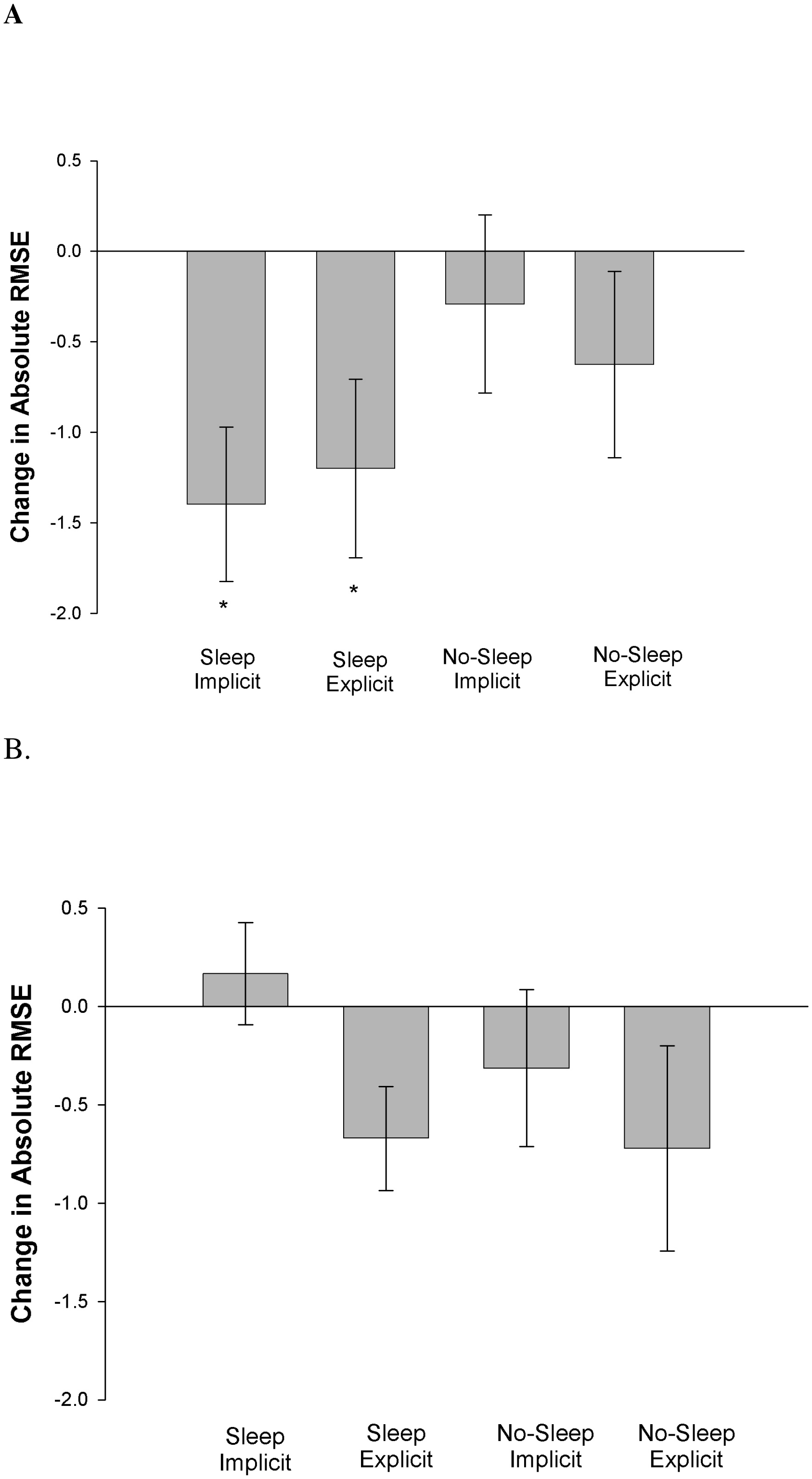
Group by Information Condition		**Session 1**	**Session 2**
Explicit Condition	Information Provided	1. “There is a repeated sequence” 2. Study a pictorial representation 3. Watch the repeated sequence on computer	
	Explicit Knowledge Test	Recognition test prior to practice	Recognition test following retention
Implicit Condition	Information Provided	None	
	Explicit Knowledge Test	None	Subjective and recognition test following retention

Table 4.4. Explicit instruction provided to individuals in explicit condition

4.7 Figure Legends

Figure 4.1. Off-line learning showing the difference in motor performance (tracking errors) between the last practice block and the retention test. A negative score indicates less error attributable to sleep at retention as compared to the last block of practice. Error bars are SEM. * indicates significance. (A) Stroke groups. (B) Control groups.

Figure 4.1.


A
Change in Absolute RMSE
0.5
0.0
-0.5
-1.0
-1.5
-2.0
*
*
Sleep Implicit
Sleep Explicit
No-Sleep Implicit
No-Sleep Explicit
B.
Change in Absolute RMSE
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Sleep Implicit
Sleep Explicit
No-Sleep Implicit
No-Sleep Explicit

Chapter 5 Preface

Chapter 4 demonstrated that individuals after stroke demonstrate sleep-dependent implicit and explicit off-line motor learning whereas individuals following stroke who stayed awake between practice and retention testing did not demonstrate time- or sleep-dependent off-line learning of either the implicit or explicit version of the tracking task. Furthermore, healthy older adults did not experience off-line motor learning regardless of type of instruction provided or the presence or absence of sleep. However, it remains unclear if certain parameters of the tracking task (spatial vs. temporal) are preferentially enhanced via off-line mechanisms for individuals following stroke. One prior study found that only spatial regularities of the SRT task were enhanced by sleep following practice whereas the motor component were enhanced over the day without sleep[116]. This suggests that distinct aspects of an implicit motor memory are supported by different mechanisms of off-line learning. The presented work sought to extend these findings by determining if different movement components (spatial and/or temporal components) of a continuous tracking task are preferentially enhanced off-line by sleep in individuals with stroke and healthy, older adults.

Chapter 5

Sleep Enhances Off-line Spatial and Temporal Motor Learning after Stroke

This work has been submitted for publication to *Learning & Memory,* 2008.

5.1 Abstract

After stroke, individuals demonstrate sleep-dependent off-line learning of a continuous tracking task. However, it remains unclear if particular components of the movement are preferentially enhanced by sleep (spatial vs. temporal elements). To address this question, individuals with chronic stroke and control participants practiced a continuous tracking task in the evening and underwent retention testing the following morning (sleep groups) or practiced the task in the morning and underwent retention testing in the evening (no-sleep groups). Results demonstrate that the individuals who had a stroke and slept between practice and retention testing demonstrated off-line improvements in both spatial and temporal elements of tracking at retention. Participants with a stroke who stayed awake between practice and retention testing did not demonstrate off-line improvements in either spatial or temporal elements of tracking. Control participants did not demonstrate sleep- or time-dependent enhancement of either component of the movement task. This study provides the first evidence that sleep enhances learning of both spatial and temporal aspects of a continuous motor task in individuals following stroke. Emphasizing both spatial and temporal aspects of movement in conjunction with sleep may enhance motor recovery following stroke.

5.2 Introduction

Sleep has recently been noted to facilitate motor learning in individuals with stroke [21, 167]. Off-line motor learning refers to changes in the capability for responding that occur between the last block of practice and a delayed retention test[149]. Off-line learning of continuous tracking tasks has been shown to occur in individuals with chronic stroke but not age-matched healthy controls when a normal night's sleep occurs between practice and retention testing [21, 167]. Though improvements in motor behavior have been related to off-line learning, it remains unclear what particular aspects of motor skill are enhanced by sleep. The purpose of the present study was to investigate whether spatial tracking accuracy, temporal tracking accuracy, or both were enhanced by sleep during off-line motor learning in a group of individuals with chronic middle cerebral artery stroke who practiced a well-described [78, 82] continuous tracking task.

The role of sleep in off-line motor learning of a task where either spatial or temporal accuracy can be improved to facilitate motor learning is largely unknown. One study sought to address this issue by having young, healthy participants practice the serial reaction time (SRT) task using their dominant hand. The participants then switched to their untrained hand at retention testing in order to assess if sleep preferentially enhances the motor or spatial component of movement [116]. The results determined that only the spatial regularities of the task were enhanced by sleep, whereas the motor component improved over the day without sleep. This suggests that distinct aspects of implicit motor memory may be supported by different mechanisms of off-line learning for young, healthy individuals [17].

Emerging evidence suggests that individuals with injured brains may benefit from sleep to enhance motor learning. A recent study demonstrated that individuals with damage to the prefrontal cortex (as a result of either stroke, tumor, or trauma) benefited from sleep to promote off-line learning of a finger sequencing task [176]. Furthermore, recent studies have demonstrated that individuals with chronic stroke also experience sleep-dependent enhancement of motor skill learning [167]. However, it was not clear what aspects of movement (spatial or temporal) facilitated improved motor behavior after sleep.

An emerging body of evidence demonstrates that healthy, older adults do not show sleep-dependent off-line motor learning [21, 167]. The failure of healthy, older adults to benefit from sleep during motor learning may be due to changes in sleep architecture associated with aging [23-26]. However, past work examining motor learning and sleep in older, healthy adults have only considered changes in overall task performance; thus, it is unclear whether a particular element of movement (spatial or temporal) might be enhanced by sleep-dependent off-line learning.

A continuous tracking task has been used previously to examine the role of sleep in off-line motor learning and memory consolidation following stroke and in healthy, older adults [167]. A benefit of utilizing a continuous tracking task is the performance on the task can be decomposed into spatial and temporal components to examine if a particular element is preferentially enhanced off-line during sleep or a similar period of awake in individuals following stroke and in healthy, older individuals. Previous studies have utilized a continuous tracking task to examine motor skill learning following stroke in the cerebellum [81] or basal ganglia [82]. However, the influence of sleep on off-line motor learning was not considered in either of these studies.

The present study sought to extend previous findings that sleep enhances off-line motor skill learning in individuals following stroke [167] and determine precisely which component(s) of skilled movement benefit from sleep. Furthermore, it is possible that even though healthy, older adults have not demonstrated sleep-dependent off-line learning of the tracking task that one component of movement might be enhanced by sleep but then subsequently this improvement is masked by overall lack of performance enhancement. Thus, a second aim of this work was to ascertain the impact of sleep on off-line changes in spatial and temporal aspects of learned movements in healthy older adults.

5.3 Results

Participants in this work practiced a single session of continuous tracking in either the morning (no-sleep groups) or evening (sleep groups). During continuous tracking repeated and random sequences of movement were practiced; motor learning of the repeated sequence was assessed. After a 12-hour period in which individuals either stayed awake or slept according to group assignment, a delayed retention test was administered. Change in motor behavior that occurred during the delay between practice and retention is considered off-line motor learning[149]. Individuals in our stroke groups who slept in between practice and retention testing demonstrated off-line motor learning of our experimental continuous tracking task while those individuals who stayed awake between practice and retention testing did not [167]. Furthermore, none of our age-matched healthy control groups demonstrated off-line motor learning regardless of group assignment (sleep or no-sleep).

Spatial Tracking Accuracy

The stroke group who slept between practice and retention demonstrated a sleep-dependent off-line improvement in spatial tracking accuracy at retention (p=.014; Figure 5.1); those in the no-sleep stroke group did not (p=.556; Figure 5.1). Neither of the control groups demonstrated enhanced off-line spatial tracking accuracy regardless of group assignment (sleep p=.578, no-sleep p=.776; Figure 5.1).

Temporal Tracking Accuracy

Individuals in the stroke group who slept between practice and retention displayed off-line motor improvements in time lag of tracking (p=.036; Figure 5.2). The no-sleep stroke group did not demonstrate off-line motor learning of the temporal aspects of the repeating sequence (p=.962; Figure 5.2). Neither of the control groups demonstrated an off-line improvement in time lag of tracking at retention (sleep p=.964, no-sleep=.703; Figure 5.2).

Lesion Location

All individuals in the stroke groups had lesions in the middle cerebral artery distribution. Owing to the heterogeneous nature of stroke, lesion overlay analysis indicated a larger area of overlap as well as an overall larger size of lesion in the sleep group (Figure 5.3) than in the no-sleep group. Furthermore, the basal ganglia was involved in both the stroke sleep group (Figure 5.3, panel A6) and the no-sleep group (Figure 5.3, panel B4).

5.4 Discussion

The current study is the first to determine which aspects of a continuous task are enhanced during off-line motor learning associated with sleep following stroke. Participants with stroke who slept between practice and retention testing demonstrated enhanced spatial accuracy and shorter time lag of tracking at retention, whereas participants in the stroke group who stayed awake and both healthy control groups did not.

Lesion overlay analysis demonstrated a larger size of lesions for the participants in the stroke sleep group compared to the stroke no-sleep group. One may have predicted that the larger lesions of those in the stroke sleep group would lead to poorer off-line motor learning. However, this was not the case; in fact the opposite was found. The participants in the stroke sleep group were able to profit from sleep to promote off-line learning of the spatial and temporal accuracy components of the continuous tracking task despite more expansive lesions whereas the no-sleep group who had smaller lesions did not demonstrate off-line improvements in spatial accuracy or time lag of tracking. This provides evidence regarding the critical role of sleep in promoting off-line learning of the components of the tracking task regardless of lesion size.

Hypothetically, different neural circuits support learning for spatial and temporal components of movement. Two brain areas purported to have a role in human spatial learning during navigation are the hippocampus and the basal ganglia, in particular, the caudate [177-180]. Furthermore, the caudate has been implicated in learning spatial regularities during motor skill learning [56, 57]. It is interesting that in the current study the stroke sleep group demonstrated off-line improvements in spatial tracking accuracy despite three of the eight individuals in the group presenting with a lesion in the basal ganglia. Furthermore, two of the three individuals with a basal ganglia lesion demonstrated off-line improvement in spatial tracing accuracy. This would suggest that because motor learning is supported by multiple neural regions, disrupting one area due to stroke does not completely abolish off-line motor skill learning.

Because the hippocampus was spared from stroke-related damage in all participants in the stroke sleep group it is possible that this region functioned to support off-line spatial motor learning. Providing support for this contention is evidence that hippocampal activation increased in individuals who slept between practice of a finger sequencing task and retention testing as compared to individuals who stayed awake [75]. While the hippocampus is generally associated with explicit or declarative learning [45, 46], evidence also supports a role for the hippocampus in spatial relational processing [181] and motor sequence learning [59]. Taken together, prior studies suggesting a theoretical role for the hippocampus in spatial learning in conjunction with the findings of our study, suggest that the hippocampus may have supported off-line motor learning of the spatial regularities of our experimental continuous tracking task in individuals with stroke-related damage to their basal ganglia. Future studies, perhaps utilizing fMRI to determine neural areas of activation, are needed to disentangle the neural circuits involved in sleep-dependent off-line motor learning of spatial accuracy during continuous tracking.

While the hippocampus and basal ganglia are involved in spatial learning, the cerebellum has been purported to have a role in the accurate timing of motor responses [182, 183]. For example, past behavioral work by Boyd and Winstein[81] demonstrated that after cerebellar stroke, individuals were unable to improve the time lag of tracking despite several days of motor skill practice. Though sleep was not considered in this work, its findings implicate the cerebellum as a key structure in motor learning that involves temporal accuracy. In contrast, in the current study where the cerebellum as not damaged by stroke, the stroke sleep group demonstrated off-line learning of the temporal movement component of the tracking task resulting in an overnight reduction in time lag of 60 milliseconds. We propose that the cerebellum is an important neural component in sleep-dependent off-line motor skill enhancement, functioning to enhance prediction of, and planning for, upcoming movements and thereby reducing the time lag of tracking. It may be that cerebellar function enabled the stroke sleep group to plan in advance for upcoming target movements, reducing the time of lag between the targets movements and the participants' responses via their curser movements. Supporting this contention are neuroimaging studies showing increase activation of the cerebellum during early motor skill learning with a reduction in cerebellar activation as the skill become automated [55], suggesting that the cerebellum plays a role in the initial enhancement of motor skill, allowing upcoming movements to be anticipated. Once the motor memory is consolidated, the cerebellum appears to be not critical for motor performance. Further supporting this interpretation, are data showing that individuals who slept between practice of a finger sequencing task and retention testing demonstrated increased activation of the cerebellum compared to those individuals who stayed awake [75]. Converging data from past neuroimaging work and the findings from our study portray the cerebellum as a key participant in off-line motor learning of the temporal components of motor tasks.

Neuroimaging techniques have also been utilized to determine which areas of the brain that are activated during motor-skill acquisition are re-activated during sleep [117]. Reactivation during sleep is purported to lead to the modification of synaptic connections that were established during acquisition of the motor skill [117]. Furthermore, functional coupling between neural regions shown via neuroimaging associated with learning a pursuit task [76] and the serial reaction time task [119] was increased during post-training REM sleep. This indicates that cerebral areas reactivated after physical practice during sleep do not act in segregation, but, rather, as a part of an integrated neuronal network [119].

Providing concurrent evidence for wide-spread neural modifications associated with sleep-dependent motor memory consolidation are neuroimaging studies conducted to elucidate changes in motor memory representation following sleep [75, 120]. Of particular interest to the current study, Walker et al.[75] demonstrated enhanced cerebellar, hippocampal, and ventral striatal activity in individuals who slept between practice of a sequential finger-tapping task and retention testing compared to individuals who stayed awake for a similar period of time. Although particular components of the finger-tapping task were not assessed, this study provides evidence that brain regions purported to function to support temporal and spatial learning respectively do, in fact, demonstrate a sleep-dependent increases in activity associated with off-line motor learning.

The control participants in this current study were all healthy individuals with no reported or known neurological disorders or any other obvious health factors that would prevent off-line motor learning. Furthermore, there was no difference between the control participants and those with stroke in average amount of sleep prior to testing, sleep quality as reported by the Pittsburg Sleep Quality Index, or level of sleepiness before to practice or retention testing (assessed using the Stanford Sleepiness Scale). Also, there was no evidence of depression as indexed by the Geriatric Depression Scale in any of our participants. It is therefore surprising that healthy older individuals did not profit from sleep and show off-line motor learning.

The changes in sleep architecture associated with advanced age including a reduction of time spent in REM and slow wave sleep as well as a reduction in the number of sleep spindles [23-26]. These changes in sleep may limit off-line sleep-dependent memory consolidation in older adults as prior studies have demonstrated that sleep spindles [69, 90, 91] and REM sleep [16] are important for sleep-dependent memory consolidation of perceptual-motor skills in young, healthy adults. Support for this contention comes from data showing that therapeutically shifting REM sleep parameters in older adults is correlated with sleep-dependent off-line gains on an explicit word recall task [73].

Because the control participants were age-matched to the participants with stroke, one might hypothesize that individuals with stroke would also demonstrate changes in sleep architecture due to age. Individuals with chronic stroke do appear to demonstrate changes in sleep architecture [37], but rather than a detrimental change associated with limiting sleep-dependent off-line learning as is noted in age-matched older adults, the shift of sleep parameters following stroke appears to be in a beneficial direction. Evidence suggests that individuals with chronic stroke maintain the proportion of REM sleep and increase non-REM stage-2 sleep [37] compared to published norms [23] as well as increase sleep spindle activity [36]. These shifts in sleep architecture associated with chronic stroke may promote sleep-dependent off-line motor learning, including the off-line improvements in spatial accuracy and reduction in time lag of tracking demonstrated in the current study. This contention will need to be verified in future studies that consider these same questions in conjunction with examination of the patterns of brain activation via a sleep lab.

One limitation of the current study was the somewhat heterogeneous nature of lesion locations in the stroke groups. Due to the range of lesion locations, specific examination of the contribution of a particular neural area to changes in spatial or temporal accuracy of tracking was difficult. While producing a circumcribed lesion to study the function of a specific brain area is possible in an animal model, studying focal damage in humans is much more difficult because of the limited number of individuals with focal damage. The use of TMS to create a “virtual lesion” in humans may enable researchers to better pinpoint the neural circuits involved in sleep-dependent off-line motor learning [128] as well as the role of various neural areas in the sleep-dependent off-line learning of the component movements of a motor task. Despite the heterogeneous lesion locations demonstrated by the stroke participants in this current work we were still able to demonstrate that the robust and redundant neural circuits of the human brain allowed individuals with stroke to benefit from off-line motor learning to improve both spatial and temporal accuracy of tracking behavior.

5.5 Conclusion

This study provides the first evidence that sleep rather than time enhances off-line learning of spatial accuracy and reduces the time lag of tracking for a continuous motor tracking task after stroke. We propose that the sleep-dependent off-line improvements in spatial and temporal tracking accuracy for a continuous motor task after stroke was due to the redundant neural circuits involved in motor skill learning, and, in particular, to the likely role of the cerebellum and hippocampus in sleep-dependent off-line motor skill learning.

5.6 Materials and Methods

Participants

Forty-one individuals post-stroke and 40 age- and sex-matched control participants were recruited from the University of Kansas Medical Center, the University of British Columbia, and the local communities to participate in this study. Individuals presented with no acute medical issues, uncorrected vision, untreated sleep disorders, uncontrolled depression, or a previous history of psychiatric admission or neurological disease other than stroke. Participants were also excluded if they scored below a 26 on the mini-mental status exam (MMSE) [152]. However, three individuals with expressive aphasia who were unable to complete the full MMSE performed the 3-step instruction portion to participate. Boxplot analysis determined that the performance of one ST individual was deemed an outlier and this participant's data was removed from analysis [169]. Data reported here are a part of a larger study[184]. Because the individuals with stroke demonstrated off-line learning of both the implicit and explicit version of the tracking task[184], the groups were collapsed across type of instruction into sleep and no-sleep groups. To examine the neural correlates associated with spatial and temporal off-line learning of the movement pattern, only individuals with stroke able and willing to undergo an MRI scan were included in the present analysis as were their matched control participants. In addition, individuals were excluded if MRI scan demonstrated lesions outside the distribution of the middle cerebral artery (three participants) or bilateral lesions (one participant). Data from the remaining 8 individuals in the stroke and control sleep groups and 7 participants in the stroke and control no-sleep groups were used for analysis (Table 5.1). Anatomical MRI scans were transformed into Talairach stereotaxic space using AFNI software [185]. Each participant's lesion was then traced using MRIcro software (C. Rorden, Columbia, SC), and a lesion overlay was produced to represent lesion distribution for the stroke sleep and stroke no-sleep group (Figure 5.3). Lesion location was also classified according as outlined by Bamford, Sandercock, Dennis, Burn, and Warlow [158, 159, 167].

Sleep characteristics of the groups were assessed in three ways: the Pittsburgh Sleep Quality Index (PSQI) [156], the Stanford Sleepiness Scale [155] prior to practice and retention testing, and a sleep log for the week before testing (Table 5.2). There were no significant differences between groups on the PSQI, in level of sleepiness at the practice session or at retention on the Stanford Sleepiness Scale, or average amount of sleep. There were no group differences on the Geriatric Depression Scale (GDS) [157] administered to assess for depression (Table 5.2). For the participants post-stroke, the Orpington Prognostic Score [153] and the upper extremity motor portion of the Fugl-Meyer Assessment of Physical Performance (FMUE) [154] were given to characterize the function of the affected upper extremity (Table 5.2). There were no differences between stroke groups on the Orpington Prognostic Score, FMUE, or time-post stroke. All participants but one were right hand dominant [137].

Motor-skill Task

The continuous tracking task discussed in this current paper to index motor learning and the method to randomize participants into groups has been previously described [167]. To summarize, participants with stroke used their less-affected, ipsilesional hand to practice a continuous tracking task in the evening and then underwent a retention test the following morning with sleep occurring at the participant's home (sleep group) or participants practiced the tracking task in the morning and then underwent retention testing the evening of the same day (no-sleep group). The same amount of time elapsed between practice and retention testing regardless of group (twelve hours +/- 1 hour). Control participants were matched for age, sex, and hand-use. All participants were asked to avoid ingesting alcohol and caffeine for 12 hours prior to and during testing.

Outcome Measures

Tracking accuracy was indexed by calculating the Root Mean Square Error (RMSE) for each trial; subsequently median RMSE was determined for each block [78, 82]. A time series analysis deconstructed overall tracking accuracy into spatial and temporal components by serially correlating the data points from the participant's tracking pattern with the target pattern until a maximum correlation coefficient was achieved (Figure 5.4). The distance or number of data points the participant's tracking data was moved along the target data represents time lag of tracking and is a measure of temporal tracking accuracy of the movement sequence [78, 82]). This score was converted to milliseconds by multiplying the number of data points moved by 20 milliseconds. The RMSE that remained following the lag correction represents spatial tracking accuracy. An off-line learning score was then calculated for both the adjusted RMSE (spatial tracking accuracy) and time lag of tracking (temporal tracking accuracy) by subtracting the retention block RMSE from the last practice block for each of the components.

Data Analyses

To determine the significance of off-line change in spatial accuracy and time lag of tracking on the tracking task from practice to retention attributable to sleep or time, parameter estimates were performed for the control and sleep groups. A repeated measures ANOVA model was used to generate parameter estimates. Alpha was set at .05.

Group	***Subject Number***	***Lesion Side***	***Lesion Classification***	***Specific Lesion Location***
Sleep	1	Right	Sub-cortex	Basal ganglia
	2	Right	Cortex	Frontal, parietal, superior temporal cortices
	3	Right	Sub-cortex	Posterior limb of internal capsule
	4	Right	Cortex & Sub-cortex	Frontal and parietal cortex, basal ganglia
	5	Right	Cortex & Sub-cortex	Internal capsule; temporal and parietal lobes
	6	Left	Cortex & Sub-cortex	Postcentral gyrus, insular cortex, temporal and frontal lobes
	7	Right	Cortex & Sub-cortex	Parieto-temporal lobe, putamen
	8	Right	Cortex	Superior and middle temporal gyrus of frontal lobe
No-sleep	1	Right	Cortex	Temporal-parietal-occipital cortex
	2	Left	Sub-cortex	Lenitiform nucleus, putamen, claustrum, insula
	3	Right	Sub-cortex	Posterior limb of internal capsule
	4	Right	Cortex & Sub-cortex	Insular, parietal cortex
	5	Left	Sub-cortex	Thalamus and posterior limb of internal capsule
	6	Right	Sub-cortex	Corona Radiata and upper portion of internal capsule
	7	Left	Sub-cortex	Cingulate Gyrus; Posterior cingulate cortex

Table 5.1. Lesion location participants after stroke.

	Sex	Age	MMSE	SSS1	SSS2	PSQI	GDS	Average sleep‡	Time Post-Stroke (month)	FMUE	Orpington
STROKE											
Sleep (n=8)	6 male; 2 female	59.5 (12.5)	28.5 (1.4)	2.50 (1.2)	2.38 (1.2)	4.88 (2.2)	5.25 (3.8)	6.89 (1.3)	79.6 (61.0)	39.0 (17.6)	2.80 (.83)
No-Sleep (n=7)	4 male; 3 female	64.0 (6.1)	29.0 (1.1)	1.71 (.95)	2.43 (.79)	6.14 (3.5)	5.57 (5.6)	7.93 (.68)	42.6 (31.6)	55.4 (12.4)	2.11 (.50)
CONTROL											
Sleep (n=8)	6 male; 2 female	60.0 (12.9)	29.8 (.46)	2.88 (1.36)	2.25 (.71)	6.63 (3.7)	5.86 (1.9)	7.05 (.74)	----	----	----
No-Sleep (n=7)	4 male; 3 female	62.8 (6.2)	30.0 (0.0)	2.71 (1.11)	2.71 (.76)	6.14 (2.9)	4.80 (3.2)	7.12 (1.5)	----	----	----

Table 2 Descriptive Information. Data are mean (standard deviation). UE Used= upper extremity used during continuous tracking task, MMSE=Mini-mental Status Exam; SSS1=Stanford Sleepiness Scale at practice session; SSS2=Stanford Sleepiness Scale at retention testing; PSQI= Pittsburgh Sleep Quality Index; GDS= Geriatric Depression Scale; Average sleep=average amount of sleep the week prior to testing determined by sleep log. ‡ For those participants who did not keep a sleep log, the average amount of sleep filled in for the PSQI was used to calculate an average sleep score

5.7 Figure Legends

Figure 5.1. Off-line learning of spatial tracking accuracy between the last practice block and the retention test. A negative score indicates less spatial tracking error at retention as compared to the last block of practice. Error bars are SEM. * indicates significance.

Figure 5.2. Off-line learning of time lag of tracking between the last practice block and the retention test. A positive score indicates improved time lag of tracking at retention (less lag) as compared to the last block of practice. Error bars are SEM. * indicates significance.

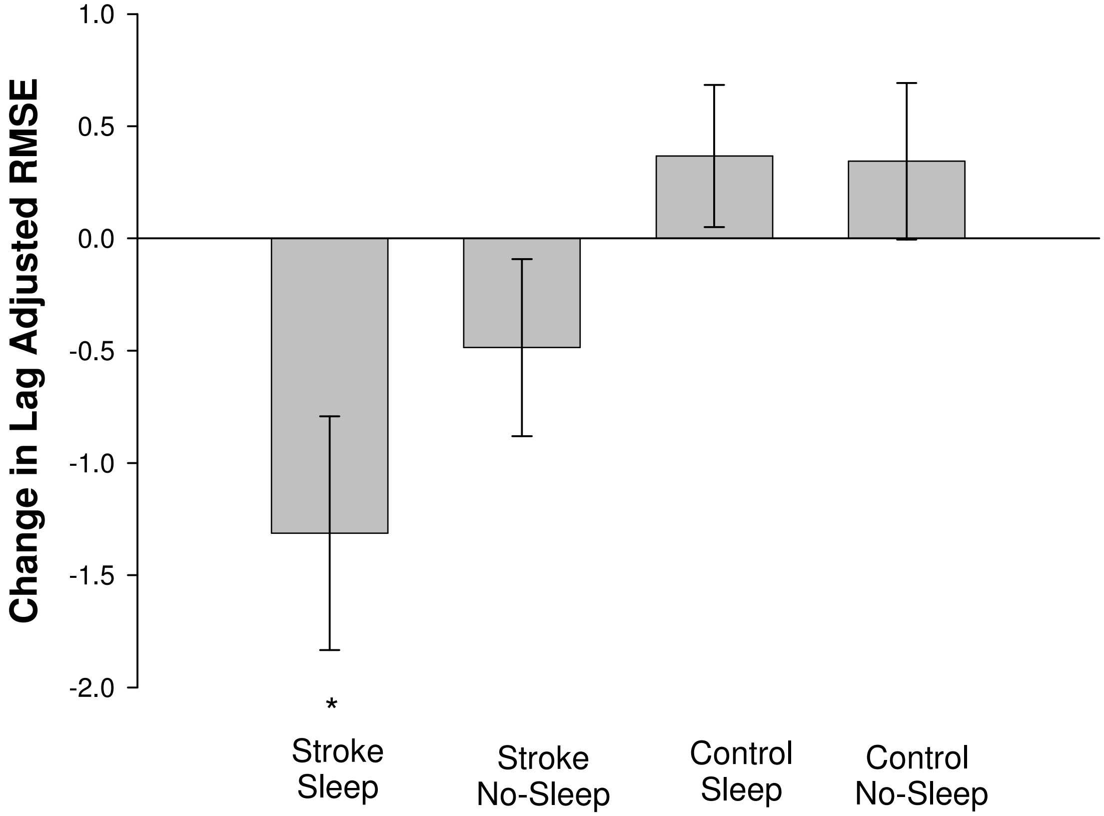
Figure 5.3. Reconstruction of stroke lesion representations. The lesion of each participant with stroke was transcribed from MRI scans, and an overlay of the individuals' lesions in the sleep (A) and no-sleep group (B) was constructed onto an axial template. Lesions were overlaid on the *right* for illustration purposes. Slices are 5 mm apart and arraigned from superior (top left) to inferior (bottom right). The degree of overlap is indicted by the color bar (violet = no overlap, dark blue = overlap of 2 lesions, light blue = overlap of 3 lesions; teal = overlap of 4 lesions). Red arrows indicate maximal areas of overlay.

Figure 5.4. For the time series analysis the participant's response was "slid" along the target, with correlation coefficients calculated serially for every interval the participant response was moved. When the correlation coefficient reached a maximum, the two waveforms were considered a best fit. The magnitude of the distance the participant's waveform was moved was converted to time (ms).

(A) Uncorrected data.

(B) Corrected data after serial correlation.

Figure 5.1



Change in Lag Adjusted RMSE
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
*
Stroke Sleep
Stroke No-Sleep
Control Sleep
Control No-Sleep

Figure 5.2

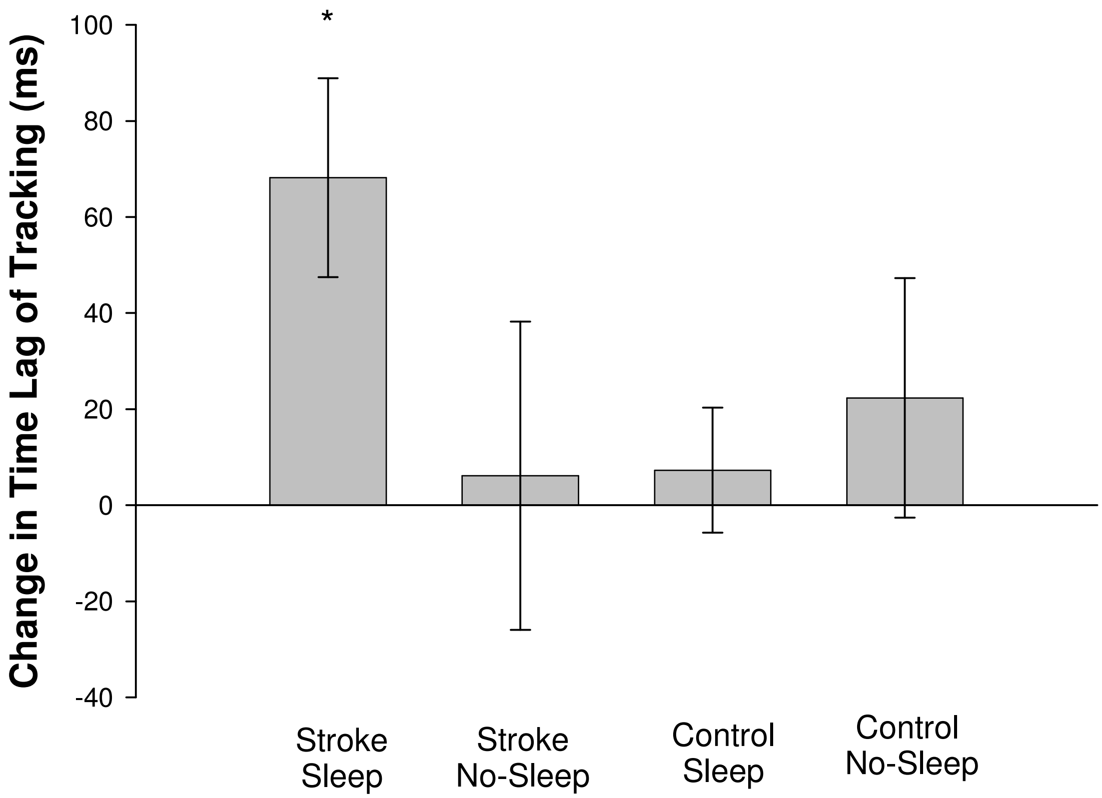

Change in Time Lag of Tracking (ms)
100
80
60
40
20
0
-20
-40
*
Stroke Sleep
Stroke No-Sleep
Control Sleep
Control No-Sleep

Figure 5.3

A.

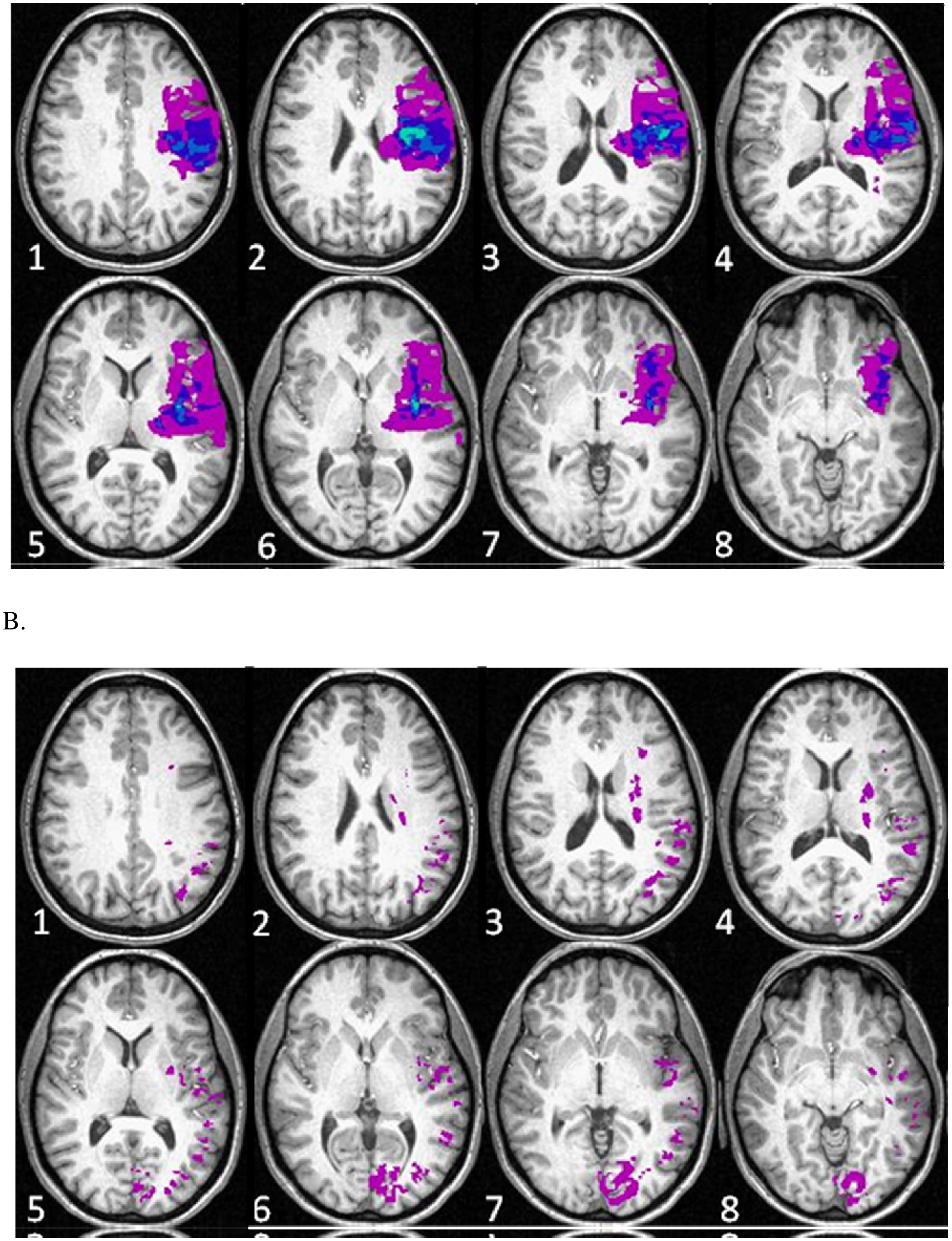
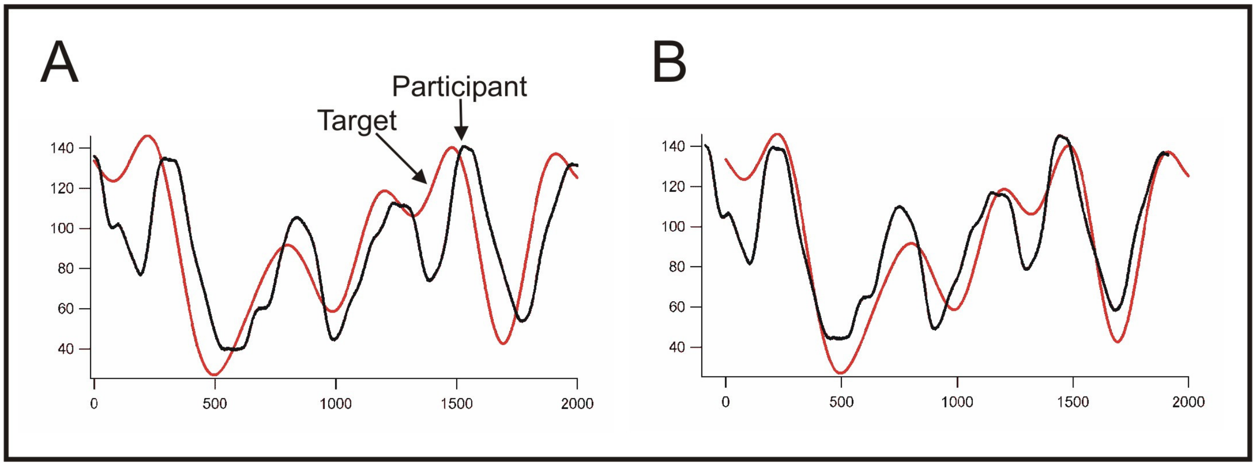


Figure 5.4


A
Participant
Target
140
120
100
80
60
40
0
500
1000
1500
2000
B
140
120
100
80
60
40
0
500
1000
1500
2000

Chapter 6

Discussion and Conclusion

6.1 Summary of Findings

This body of presented work extends the sleep-dependent off-line literature from young, healthy, neurologically intact to healthy, older adults and into a new sample of study: individuals following stroke. Overall, the presented work provides concurrent evidence that healthy, older adults fail to benefit from sleep to enhance motor learning. This is the first body of work to demonstrate that individuals following stroke benefit from sleep to enhance both off-line implicit and explicit motor learning. Possible explanations why healthy, older adults are unable to take advantage of sleep to produce off-line enhancement in motor performance while individuals following stroke are able to will be discussed. The findings of this work have implications for rehabilitation of individuals following stroke.

Chapter 2. The Impact of Acquired Explicit Knowledge on Motor Sequence Learning

The purpose of this work was to examine the difference in both motor performance and learning for participants who remained unaware of the presence of the sequence (implicit condition), those subjects who were given no instruction but gained explicit awareness of the sequence via practice (acquired explicit condition), and individuals given explicit instruction prior to the start of practice (explicit condition). Our results demonstrate a benefit of explicit knowledge to learn a discrete finger sequencing task, the SRT task, for young healthy individuals regardless of whether it was acquired during or provided in advance of physical practice.

Chapter 3. Sleep Enhances Implicit Motor Skill Learning in Individuals Post-stroke

While many studies have demonstrated sleep produces off-line enhancement of motor performance for young, healthy individuals, less is known about sleep-dependent off-line motor learning in healthy, older adults. Furthermore, the influence of sleep on implicit motor learning following stroke had never before been examined. Therefore, purpose of this chapter was to assess the influence of sleep on implicit motor learning and memory consolidation in individuals with chronic stroke and their age- and sex-matched controls. The results of this work provide the first evidence that individuals with stroke benefit from sleep to enhance off-line implicit motor skill learning and provide concurrent evidence that healthy, older individuals do not benefit from sleep to produce off-line skill enhancement of an implicit task.

Chapter 4. Sleep to Learn After Stroke: Implicit and Explicit Off-Line Motor Learning

The purpose of this work was to extend the findings of Chapter 3 to a larger sample as well as determine if the sleep-dependent off-line learning of an implicit motor learning would extend to explicit motor learning. The results demonstrate that after stroke, individuals benefit from sleep to enhance off-line motor learning and memory consolidation regardless of type of instruction provided whereas healthy older adults do not. Furthermore, none of the individuals regardless of the presence or absence of stroke or the type of instruction who stayed awake between practice and retention testing demonstrated off-line motor learning. This work demonstrates that individuals following stroke exhibit sleep-dependent implicit and explicit off-line motor learning and adds to the growing consensus that healthy, older individuals fail to profit from sleep to produce off-line improvements of either implicit or explicit motor skills.

Chapter 5. Sleep Enhances Spatial and Temporal Components of Continuous Tracking Task for Individuals Following Stroke

Learning a motor skill requires the integration of the spatial and temporal components of the task. Because little is known if sleep preferentially enhances certain components of a motor skill movement in any population, the present chapter sought to extend our findings from Chapter 4 that sleep enhances off-line motor skill learning in individuals following stroke and examine if a particular component(s) of a tracking task are enhanced (spatial and/or temporal components) off-line. This study provides the first evidence that sleep enhances both spatial and temporal components of a motor skill following a stroke but not for healthy older adults.

6.2. Possible Mechanisms of Sleep-Dependent Off-Line Motor Skill Learning Following Stroke

Alterations in Sleep Characteristics

Due to the lack of neurophysiological measures, we can only speculate as to why the individuals with damage to their brain were able to benefit from sleep to enhance off-line motor learning while individuals with healthy, intact brains failed to demonstrate off-line motor learning. Because little research has characterized the sleep architecture of chronic stroke survivors, ascertaining the relative role of the various sleep stages on off-line motor learning problematic. However, one possible explanation for sleep-dependent off-line motor learning following stroke is after stroke individuals profit from changes in their sleep architecture. In a study by Vock et al.[37], 15 chronic stroke participants ranging in age from 18 to 75 years with an average age of 49 year old spent 16.6% of total sleep time (TST) in REM sleep. This is only slightly less than the published norm for a healthy 49-year-old individual (~ 20% of sleep period time (SPT))[23]. A shift in the percentages of time spent in different phases of sleep was not limited to REM. The chronic stroke individuals in the Vock et al. study[37] spent 60.9% of TST in stage-2 non-REM sleep which is higher than the published norm for a healthy 49-year-old individual (~52% of SPT)[23]. Further evidence indicating individuals post-stroke experience a shift in sleep characteristics is spindle frequency activity significantly increases from acute (<10 days) to the chronic (>60 days) stroke[36]. Consensus is building that developing memory for perceptual-motor tasks similar to the one employed in the present research requires stage-2 and/or REM sleep for consolidation in young, healthy individuals. For example, overnight improvement in the performance of a finger-tapping task was found to correlate with the amount of stage-2 non-REM sleep[13], whereas overnight improvement in a similar finger-to-thumb opposition task correlated with the amount of REM sleep[16]. Furthermore, sleep spindles which are characteristic of stage-2 non-REM sleep have been demonstrated to play an important role in sleep-dependent memory improvement[69, 90, 91]. Therefore, maintenance REM sleep and an increase in stage-2 non-REM sleep and spindle activity by individuals with chronic stroke may explain the sleep-dependent skill enhancement demonstrated by the stroke participants in the current body of work. Further studies are needed to characterize the sleep architecture of chronic stroke participants to support this contention.

In contrast to the individuals following stroke who demonstrated sleep-dependent off-line motor learning, this body of work provides concurrent evidence that healthy, older adults do not benefit from sleep to enhance off-line motor learning. We speculate that age-related changes in sleep characteristics limit the benefit of sleep for off-line motor learning. With advancing age, total sleep time decreases as does the percentage of time spent in REM and slow wave sleep (SWS)[23, 24]. While the amount of time spent in Stage-2 non-REM sleep remains fairly stable[23], there is a reduction in the number of sleep spindles that occur with age[25, 26]. If REM sleep and sleep spindles facilitate off-line motor skill learning, perhaps the reduction in these two sleep parameters with age explains the lack of sleep-dependent off-line learning by the healthy, older adults in this body of work. Further studies utilizing EEG are needed to assess if these changes in sleep architecture are associated with a failure to demonstrate sleep-dependent off-line motor learning in healthy older adults.

Hyperexcitability of Non-lesioned Hemisphere

Considering that participants in this body of work used their less affected upper extremity to perform the experimental tracking task, examining the neuronal function of the non-lesioned hemisphere is in order. A reduction in transcollosal inhibition[170, 171] can result in hyperexcitability of the non-lesioned hemisphere[172, 173]. Perhaps this hyperexcitability creates a permissive environment in which sleep-dependent memory consolidation can occur. Huber et al. demonstrated learning a motor task resulted in an increase in slow wave activity (SWA) circumscribed to the brain region associated with learning the task[174]. Furthermore, utilizing TMS to potentiate the cortex also resulted in an increase in SWA limited to the same neural region stimulated by TMS[175]. This suggests that motor skill learning and direct potentiation by an exogenous source create similar changes in neuronal plasticity. Perhaps the hyperexcitability of the non-lesioned cortex after stroke results in enhanced potentiation of the neural circuits involved in motor skill learning and memory consolidation enabling individuals post-stroke to benefit from sleep to enhance motor skill learning. Future work will have to confirm or refute this possibility.

Redundant Neural Circuits

Individuals with stroke are able to learn new implicit motor skills[27-31]. Owing to the widely distributed nature of the neural circuit supporting motor skill learning which includes the sensorimotor cortex[50, 51] (particularly M1[62, 63]), premotor cortex[52, 57], SMA[50, 51], and basal ganglia[50-53] total abolition of motor skill learning as a result of stroke is unlikely. The findings of this body of work that sleep enhances implicit and explicit off-line motor skill learning and memory consolidation after MCA stroke provides evidence that redundant neural circuits responsible for off-line motor skill consolidation exists so that disruption in one area does not abolish the ability of other regions to benefit from sleep-dependent to enhance motor skill learning. Two studies[75, 120] that have utilized neuroimaging techniques to elucidate off-line changes in the representation of motor memory following sleep have demonstrated wide spread changes in brain activity associated with off-line motor memory consolidation, thus providing some support that damage to one area may not eliminate sleep dependent memory consolidation in others. Future imaging studies would be needed to elucidate changes in neural activity with off-line motor learning in individuals following-stroke.

6.3 Clinical Implications

Nearly 780,000 individuals in the US suffer a stroke each year [186] with more than half experiencing a persistent loss of function of the affected upper extremity at two years [187] and four years [168] after their stroke. After stroke, learning new motor skills and re-learning motor skills is an important component of recovery of function. Identifying methods to hasten or increase the efficiency of motor skill learning following stroke is an important clinical endeavor. The findings of this body of work indicate that sleep but not time promotes implicit and explicit off-line motor skill learning in individuals following stroke.

The findings of this study may lead to a shift in the standard of therapy provided to individuals following stroke. An emphasis may be placed on ensuring sleep between therapy sessions in order to consolidation what was learned during the therapy session. Therapy may need to be conducted in the evening prior to a night of sleep or a nap between morning and afternoon therapy sessions may become standard. Furthermore, addressing underlying conditions limiting sleep and ensuring adequate sleep following stroke may be warranted.

The findings of this study that healthy, older individuals fail to demonstrate sleep-dependent off-line motor learning may lead to further assessment of underlying sleep conditions in these individuals or to methods to improve sleep architecture. Evidence that improving REM parameters through medication resulted in an enhanced performance of older adults on an explicit word recall task[73] demonstrates that it is likely the underlying changes in sleep architecture due to aging that limits older individuals from profiting from sleep to enhance learning. Perhaps this mounting evidence will result in therapeutic means to enhance learning in older adults.

6.4 Limitations

Setting of Study

All of the testing for this study took place either in a laboratory setting or in the participants' home. While the setting was not controlled for in this study, every attempt was made to ensure a quiet testing environment free of distractions for all participants. A benefit of performing this study in the participants' home is that the findings can be more easily generalized to "real life." Furthermore, the learning of motor skills following stroke will very often take place in a hospital, rehabilitation, or outpatient setting which is often neither quite nor easily controlled.

Participants in this study in the sleep groups slept at home between practice and retention testing rather than in a sleep laboratory. Therefore, although we cannot ensure the amount, type or quality of sleep the participants obtained. This was addressed by having participants maintain a sleep log for a week prior to testing as well as utilized the Pittsburg Sleep Quality Index to index quality of sleep. The benefit of having participants sleep at home is it provides testing of their "natural" sleep cycle.

Medication

Participants were not excluded from participating in the presented study if they were taking medication for depression or for sleep enhancement. Debate remains regarding the possible role of REM suppression by antidepressant medication on memory consolidation[2, 9]. Despite initial suppression of REM sleep by certain classes of antidepressants (including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs)) and certain medications within each class[188], REM sleep often reemerge with chronic medication use[189, 190], suggesting that individuals taking these classes of antidepressants experience REM sleep on a nightly basis. A review by Wilson and Argyropoulos[191] indicates that sleep architecture improves following 3-4 weeks of usage of most antidepressants. Furthermore, questions remain regarding the need of REM sleep or non-REM Stage-2 sleep or a combination of the two stages for procedural memory consolidation. In addition, the "amount" of REM sleep for memory consolidation is unknown. Therefore, the potential transitory suppression of REM sleep is likely a non-issue.

Individuals were also not excluded from participating in the current work if taking medication for sleep enhancement. A study demonstrated that commonly used hypnotic used for sleep enhancement (Zolpidem which is sold under the name Ambien) did not interfere with the sleep-dependent improvement in a declarative memory task[192]. Furthermore, no previous studies demonstrating sleep-dependent enhancement of motor skill learning have explicitly excluded participants taking these types of medications[12-16]. Therefore, there is no current evidence suggesting that the use of these sleep aids will interfere with sleep-dependent memory consolidation. To better characterize our samples' medication usage, we did collect a medication list to ascertain the use of medications by participants in this study.

Time of Day of Testing

A time-of-day effect could possibly influence our findings as evidence suggests that the performance of older adults on memory tests deteriorates when tested in the evening compared to earlier in the day[161, 162]. However, this time-of-day effect appears to depend on the type of memory under consideration. Improved retrieval of implicit memory has been shown to occur at non-optimal times (i.e. in the evening for older adults) which is in contrast of explicit memory which is better retrieved at optimal times (i.e. in the morning for older adults)[163]. If time-of-day of testing had indeed influenced the findings of the presented study, we would have expected to see all of the implicit groups perform better in the evening which was not the case. Furthermore, we would have expected to see only the explicit groups perform better following a period of sleep and retested in the morning, which was also not the findings of this study.

Lesion Location

The participants post-stroke present with heterogeneous lesion locations. Lesion information was available for 30 of the 40 post-stroke individuals with all lesions in the cortex and/or sub-cortical structures of the middle cerebral artery (MCA) distribution except two in the posterior cerebral artery (PCA) distribution and one in the pons. Studying stroke in humans is difficult because of the heterogeneous nature of stroke. While producing a circumcribed lesion to study the function of a specific brain area is possible in an animal model, studying focal damage in humans is much more difficult because of the limited number of individuals with focal damage. The use of TMS to create a “virtual lesion” in humans may enable researchers to better pinpoint the neural circuits involved in sleep-dependent off-line motor learning. Nonetheless, the heterogeneous lesion location demonstrated by the post-stroke participants in this body of work demonstrates the robust and redundant neural circuits of the human brain; despite assorted lesions, the post-stroke participants in this body of work are able to benefit from sleep to enhance motor learning.

Floor Effect

Individuals with stroke often perform with larger error of tracking during motor learning studies even when utilizing their less affected upper extremity to perform the task[81, 82]. This is likely due to motor control deficts of the less-affected upper extremity[28, 193]. The indivdiuals with stroke display increased tracking error across practice compared to the healthy controls in this current body of work (Figure 6.1). All groups do demonstrate improvement in performance across practice as demonstrated by a repeated measures ANOVA main effect of block (p. 92). However, one might suspect the healthy control participants are unable to display off-line motor learning due to a floor effect (i.e. they are performing with the least amount of error possible during practice and, therefore, cannot improve further despite sleep or the passage of time). However, we feel this is unlikely. When examing the participants' data across practice, the least amount of error any participant performed the tracking task for a block of practice was 5 degrees of RMSE. If 5 degrees of RMSE is the least amount of error partcipants can perform the tracking task (note this may not actually be the "best" possible performance but is the best any one participant in this study performed on the tracking task in one block), then all of the control groups could theoretically have improved at retention (i.e. track with less error), and the failure of the control partcipants to demonstrate off-line motor learning was not limited by a floor effect.

6.5 Future Directions

As mentioned above, speculation regarding the neural mechanism for sleep-dependent off-line motor learning following stroke, is just that; speculation. Future studies are needed to determine why individuals with damage to their brain due to stroke are able to benefit from sleep to enhance motor skill learning while age-matched adults with a "healthy" brain fail to do so. Furthermore, as evidenced by the literature review in the introduction, many other variables such as type of task and task complexity may impact sleep-dependent off-line learning. Thus, we propose several extensions from this body of work to address these questions.

Characterization of Chronic Stroke Sleep Parameters

Very little is known about the sleep characteristics displayed by individuals post-stroke. In order to proceed into determining which stages of sleep or changes in sleep parameters are associated with sleep-dependent off-line motor learning, we need to first understand the underlying sleep stage characteristics in individuals with chronic stroke. Therefore, conducting a sleep study assessing the sleep characteristics of individuals with chronic stroke is a paramount first step.

Assessment of Sleep Stage Associated with Off-line Motor Skill Learning

Debate remains in young, healthy individuals which particular stage of sleep is important for a particular memory trace (i.e. SWS important for declarative memory consolidation and stage-2 and REM sleep important for procedural memory consolidation). Other variables including the emotional content of the memory, the cognitive load of the task, or the initial skill level of the learner complicate the issue of which stage of sleep is critical for a particular memory trace. However, no studies have examined which stage of sleep is associated with sleep-dependent off-line motor skill learning following stroke. This could be conducted in a sleep lab using EEG recordings during sleep following practice of a motor task.

Assessment of Neural Activity Changes Associated with Off-line Motor Skill Learning

Two neuroimaging studies demonstrate widespread changes in brain activity in healthy, young adults associated with motor memory consolidation[75, 120]. It is presently unclear the changes in neural activity associated with sleep-dependent off-line motor learning in individuals following stroke. Functional MRI has been utilized in healthy, young individuals and this technique could be extended to individuals post-stroke to determine changes in neural activity following learning a motor skill and sleep.

Exogenous Stimulation to Potentiate or Depress Neural Areas

Evidence suggests that learning a motor skill creates a similar change in neuronal plasticity as does exogenous potentiation by TMS[174,175]. We propose that the hyperexcitability of the non-lesioned cortex due to a reduction in transcollosal inhibition from the lesioned hemisphere after stroke results in enhanced potentiation of the neural circuits involved in motor skill learning and memory consolidation. Pairing motor skill practice with external stimulation via TMS to the cortex to induce changes in sleep architecture during sleep could confirm or refute this supposition.

One limitation of this body of work is the heterogenous lesion location of the stroke participants. One method to examine the role of discrete neural areas in off-line motor skill learning would be to utilize TMS to depress circumscribed cortical areas. Robertson, Press, and Pascual-Leone[128] found that interfering with the function of the primary motor cortex (M1) using TMS immediately following motor practice of a discrete sequence resulted in disruption of implicit skill learning when consolidation occurred during the day (i.e., retention test in the same day), but this effect was not noted when consolidation was accompanied by sleep (i.e., retention test delivered the next day). This would suggest that M1 is important for implicit skill learning that occurs over the day but not with sleep over night. Furthermore, these findings demonstrate that different neuronal circuits support off-line implicit motor learning that is sleep-related as opposed to time-reliant for memory consolidation. Because a wide distribution of cortical regions support motor learning, including the sensorimotor cortex[50, 51] (particularly M1[62, 63]), premotor cortex[52, 57], and SMA[50, 51], disrupting these areas using TMS would help determine their individual role in sleep-dependent off-line motor learning.

Different Tasks

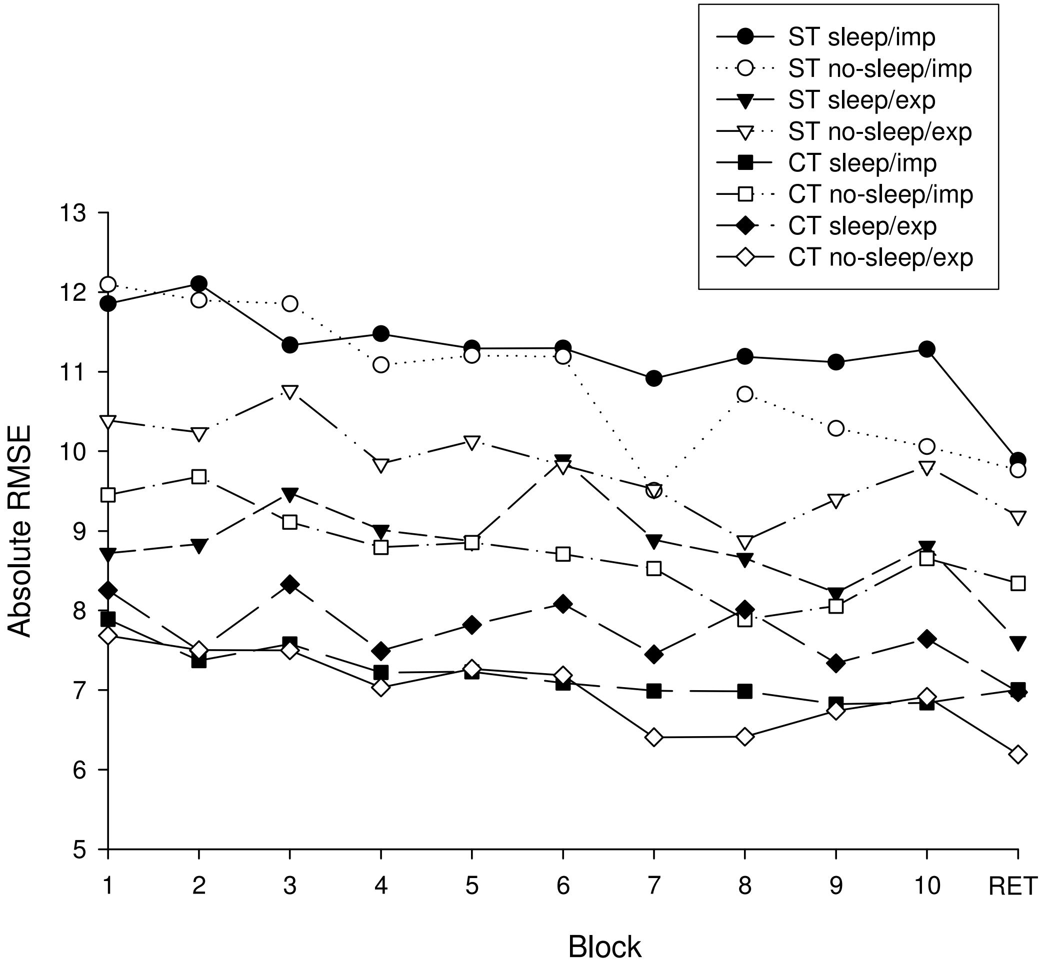
This body of work demonstrates that individuals following stroke benefit from sleep to enhance off-line motor learning on a continuous tracking task. This task was chosen to index off-line motor learning for this body of work for several reasons, including to assess implicit vs. explicit off-line motor learning, to utilize a more ecologically valid task, and to enable the decomposition of overall motor task learning into its component parts. The studies to date demonstrate that while sleep enhances performance on a number of simple discrete tasks in young, healthy adults, sleep may not in fact benefit all kinds of discrete tasks; a probabilistic discrete task was not enhanced by a night of sleep[83]. Therefore, it appears not all discrete tasks experience sleep-dependent consolidation. Furthermore, a continuous task, which was used in the presented work, uses different motor control mechanisms than discrete tasks. Due to the often rapid nature of discrete tasks, these types of skills are thought to rely on a motor program to produce the rapid movement whereas continuous tasks are thought to rely on feedback to correct movements while the movement is being produced[74]. Therefore, these differences in motor control may result in a differential effect of sleep on learning these skills. While perhaps not as ecologically valid as a continuous task, discrete tasks are also performed during daily life, such as dialing a phone number or reaching for a glass. Therefore, future studies are needed to determine if findings from this body of work that individuals following stroke demonstrate enhancement motor performance following sleep will extend to a discrete task.

Interestingly, one study found that the more complex the motor task was, the greater the off-line improvements following sleep[85]. This suggests that “real-life” complex motor tasks may benefit from sleep-dependent enhancement. Future studies are needed to determine if more complex clinically valid continuous tasks, such as walking, are enhanced following sleep in individuals following stroke.

6.6 Conclusions

The body of work presented in this dissertation extends the current sleep literature and examines the influence of sleep and type of instruction on off-line motor skill learning following stroke. The findings of this work demonstrate that individuals following stroke profit from sleep to enhance implicit and explicit off-line motor skill learning. Furthermore, the presented work provides addition support to the credence that healthy, older adults do not benefit from sleep to enhance motor learning regardless of the memory system involved. The discrepancy between the ability of individuals following stroke to take advantage of sleep to enhance motor learning while healthy older adults are unable to do so may be due to shifts in sleep characteristics or neuronal excitability following stroke. Future studies are needed to determine the neural mechanisms of sleep-dependent off-line motor learning following stroke. The findings of this work indicate a need to emphasize sleep following practice of a motor skill to enhance off-line learning of the skill following stroke.

Figure 6.1



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