THE RELATION BETWEEN DAYTIME SLEEP AND COGNITIVE FUNCTIONING IN MILD COGNITIVE IMPAIRMENT (MCI) SUBJECTS

A Thesis

by

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ABSTRACT

The current thesis aimed to investigate the relationship between daytime sleep and cognitive functioning in Mild Cognitive Impairment (MCI) subjects and healthy older adults. To explore this, 20 MCI subjects and 16 healthy older adults completed two lab visits with subjective reports, daytime sleep Polysomnography (PSG) measures and a battery of neuropsychological measures. I formulated three main research questions (a) How do MCI subjects and healthy older adults differ in subjective sleep quality? (b) How do MCI subjects and healthy older adults differ in objective daytime sleep parameters? (c) How do MCI subjects and healthy older adults differ in post-nap cognitive changes and how do those changes relate to PSG parameters? Results showed that (a) although self-reported sleep disturbance did not differ in MCI subjects and healthy older adults, within the entire sample, there were some notable correlations between subjective sleep disturbance and cognitive performance; (b) PSG measures suggested that MCI subjects expressed significant less slow-wave sleep (SWS) than healthy older adults and PSG parameters such as the relative amount of stage 2 sleep and SWS were associated with cognitive performance; (c) both MCI subjects and healthy older adults had significant post-nap cognitive improvements and such improvements were associated with PSG parameters such as the amount of stage 2 sleep and k-complex. These findings might be important steps toward a better understanding of daytime sleep activities in MCI subjects and a better identification of PSG parameters and potential mechanisms, which would contribute to future intervention studies and treatment programs.

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NOMENCLATURE

AASM	American Academy of Sleep Medicine
Aβ	β-amyloid
AD	Alzheimers Disease
BH	Body Height
BMI	Body Mass Index
BW	Body Weight
CSF	Cerebrospinal Fluid
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG/EKG	Electrocardiogram
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
ESS	Epworth Sleepiness Scale
ISF	Interstitial Fluid
MCI	Mild Cognitive Impairment
MoCA	Montreal Cognitive Assessment
NREM	Non-Rapid Eye Movement
PET	Positron Emission Tomogram
PSG	Polysomnogram
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid Eye Movement

REML	Rapid Eye Movement Latency
SE	Sleep Efficiency
SL	Sleep Latency
SWS	Slow-Wave Sleep
TMT	Trail Making Test
TST	Total Sleep Time
VSTM	Visual Short-Term Memory
WASO	Wake After Sleep Onset

TABLE OF CONTENTS

Page

LIST OF FIGURES

FIGURE Page

LIST OF TABLES

TABLE Page

1. INTRODUCTION

Mild cognitive impairment (MCI) describes individuals who are exhibiting cognitive impairment in the absence of functional impairment [1]. MCI is often viewed as a translational stage from normal aging to Alzheimers disease (AD). At this time, MCI is diagnosed based on the criteria from Diagnostic and Statistical Manual of Mental Disorders [2] and/or international working group of MCI [3]. These criteria stated that MCI mainly involves problems with memory that are greater than normal age-related changes, while individuals generally preserved activities of daily living and not clinically demented.

In addition to the abovementioned criteria of MCI, sleep disturbances have been documented as one of the core symptoms observed in MCI subjects [4]. The prevalence of sleep disturbances in MCI is estimated to vary between 22% to 59% depending on the diagnostic criteria [5]. In addition, research has argued that the presence of sleep disturbances has been shown to increase the likelihood of progression to AD [6, 7].

As sleeping becomes a significant challenge for MCI individuals, the frequency of napping was consistently found to be increased [8]. Yet, the extent to which naps would impact cognitive functioning is still under debate. There have been discrepancies in the studies examining the effects of napping in both MCI and normal-aging groups. Some studies support the notion that napping has restorative functions for cognition and may even slow the progression of AD [9, 10]. On the contrary, research reported that excessive napping was associated with worse nocturnal sleep quality and an eventual decrease in cognitive functioning [11]. The mixed evidence of both positive and negative effects of napping on MCI subjects might be partially attributed to limitations in the measurement of napping. Napping can vary in characteristics such as duration, timing, and sleep stages, most of which cannot be completely or accurately captured by subjective measures or reports from caregivers [8]. Little is known about objective napping parameters and their associations with cognitive performance. Understanding this relationship may provide not only a deeper understanding of napping behaviors in this population, but it may also offer possibilities for early

diagnosis and potential treatment with the aim of delaying or preventing the progression of AD.

To this end, the current study proposes to examine sleeping and napping behaviors and how napping parameters affect cognitive performance in individuals with MCI compared to normal-aging individuals. This will be accomplished by using PSG system, cognitive tasks, as well as self-reports, which will provide information about sleeping and napping behaviors in MCI subjects and might contribute to new insights for potential treatment programs.

2. LITERATURE REVIEW

2.1 Alzheimer's Disease (AD)

Alzheimers disease (AD) is a degenerative disorder that is characterized by memory loss and confusion and impairment of at least one additional cognitive domain [12, 13]. The World Alzheimer Report 2018 reported that 50 million people worldwide are living with AD, and this number is estimated to triple to 152 million by 2050 [14]. This implies there will be one new case of AD every 3 seconds around the world [14]. National estimates of the prevalence of AD indicated that about 14% of people age 71 and older in the United States have AD [15].

Memory disturbances are the most common symptoms in AD and, as the disease progresses, subjects always present with worsening executive functioning, compromised language (e.g. naming or semantic problems), loss of visual orientation, loss of motivation, and eventually, poor self-care and behavioral issues [16]. Those AD symptoms are placing substantial medical, social, psychological and financial burdens on individuals, their families and their communities. AD individuals commonly need assistance with daily instrumental activities such as shopping, and managing personal finances. In the later stages of AD, they might even need help with basic daily living activities such as eating, dressing, and toileting [17]. Furthermore, the symptoms of AD further attributed to their caregivers emotional strain (i.e. stress, depression) [18, 19] and physical exhaustion, as well as reduced caregiver employment and income, but also increased hospital stay and even nursing home placement [20]. These AD-related burdens, together with increases in AD cases, are stressing the U.S. healthcare system [21]. The total cost of Americans with AD was estimated at US$277 billion in 2018, which included only direct (medical and social care) costs [21], and does not to mention indirect costs such as unpaid caregiving by family and friends.

2.2 Mild Cognitive Impairment (MCI)

The field of aging and AD is moving toward the early identification of impairment, and the construct of Mild Cognitive Impairment (MCI) has played a pivotal role in that effort [6]. MCI

was proposed to describe individuals who are neither cognitively normal nor diagnosed with AD, but who are exhibiting cognitive impairment in the absence of functional impairment [1, 22]. MCI is often viewed as a transitional stage from normal aging to AD [23, 24], with an age-related conversion rates across studies being estimated ranging from 60.5% to 100% to AD in 5 to 10 years without treatment [24]. The prevalence of MCI varies among different age groups: 6.7% for ages 60-64, 8.4% for ages 65-69, 10.1% for ages 70-74, 14.8% for ages 75-79, and 25.2% for ages 80-84 [25].

The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) defined MCI using the term age-related cognitive decline, which is objective decline in cognitive function not otherwise specified [2]. Research studies relied on different sets of diagnostic criteria for MCI, one of the frequently used criteria is the original clinical criteria proposed by Petersen [23] and was later adopted by the international working group of MCI [3]. They recommended the following criteria: (1) Memory complaints, preferably corroborated by an informant; (2) memory impairment documented according to appropriate reference values (i.e. memory impairment relative to age-matched and education-matched healthy people); (3) essentially normal performance in nonmemory cognitive domains; (4) generally preserved activities of daily living; (5) not clinically demented [3, 23]. These criteria have been extensively used since they were developed. Most individuals experience some changes in cognition as they age, however, it is important for clinicians to determine that the described deficits are beyond what one would expect for normal aging. Moreover, the clinician must also assess the persons daily activities to be certain that the individual is still performing well in daily life.

Although the core features observed in MCI are reduced memory functioning, there has been an increasing awareness of additional neuropsychiatric symptoms, which is a branch of medicine dealing with nervous system related mental disorders [26]. The neuropsychiatric symptoms include the most common mood and behavioral symptoms such as depression, anxiety, irritability, apathy, and agitation, and less frequent symptoms like disinhibition, hallucinations, delusions, and aberrant motor behaviors [6, 7, 27]. The presence of those neuropsychiatric symptoms has been shown to

increase the likelihood of progression to AD [6, 7]. In addition, sleep disturbance, though not formally included as a DSM key diagnostic criterion, has been documented as one of the four core symptoms of MCI [4]. The prevalence of sleep disturbances in MCI subjects is estimated to vary between 22% to 59% depending on the diagnostic criteria used [5]. Published studies on MCI subjects were primarily based on subjective reports (i.e. interviews) by subjects or their caregivers [28]. Means and colleagues [29] reported that healthy subjects tend to overestimate their sleep quality. Hence, it is possible that subjective reports might underestimate the prevalence of sleep disturbances in MCI. For example, in Bombois and colleagues [28] study with 65 MCI subjects, they found an extremely high prevalence of sleep disturbances (95.4%) with polysomnographic (PSG) recordings.

Many of the symptoms of MCI are the same as those present in subjects with AD, but to a lesser extent. Therefore, like all other types of dementia, MCI is associated with worse health-related quality of life of individuals. With those symptoms, MCI individuals might require help and support with daily living activities such as transportation, taking medication, or cooking as well as the psychological symptoms such as depression and apathy. MCI individuals experience substantial burdens on their lives and the lives of their caregivers. According to interviews and assessments on MCI subjects, they reported frustration at skill loss, changes in family/social roles, embarrassment, emotionality, and concerns of being a burden [30]. Furthermore, MCI imposes substantial and clinically significant psychological and physical burdens on the caregivers [31]. The burdens of caregivers commonly contain social and economic stress, family and job conflicts, lack of social support, and psychological symptoms such as depression and anxiety [32]. The caregivers also reported a lack of information, support and practical methods in assisting their family or friends with MCI [32].

MCI has been studied intensively over the past decades. Clinicians, researchers, patients and families started to recognize this condition. As the importance of detecting MCI becomes more accepted, these individuals might benefit more from currently available treatments for AD, especially for those individuals who are highly likely to progress to AD [33]. Additionally, the investigation

of MCI might lead to novel treatments that could delay the onset of AD. As estimated by Gauthier and colleagues [6], treating MCI may result in short-term economic benefits of US$5,300 per subject per year. Given the limited success of treatment for AD and emerging evidence for the association between MCI and AD, an understanding of the features of MCI may be crucial for the treatment and prevention of AD.

2.3 Problem Summary

In sum, there are indications that further investigation of MCI might provide valuable markers or significant symptoms in characterizing this preclinical phase of AD. Since sleep disturbance is already considered an important symptom in the context of aging, AD and MCI subjects, the main aim of this review will be to summarize the current literature on the evidence of sleep disturbance in MCI.

As part of this objective, the review will also include evidence of sleep disturbance in AD. While the behaviors and mechanisms associated with AD are well established, little is known about the range of behaviors and mechanisms inherent in subjects with MCI. Considering the relationship between AD and MCI as well as the similarity of behaviors, information regarding AD will help us understand the potential underlying mechanisms of behaviors of MCI or at least provide us with valuable directions. Therefore, studies regarding the behaviors of AD will also be included in the review.

The first part of the review will provide an overview of the sleep architecture and general functions of sleep after which I will summarize the current evidence on sleep disturbance in both AD and MCI subjects. Lastly, the focus will be summarizing current theories on the mechanism relating to sleep disruptions and cognitive decline.

2.4 Basics of sleep

2.4.1 Sleep architecture

Sleep is a physiological process characterized by several cycles consisting of different sleep stages. Over the years, a large number of studies have focused on defining sleep architecture us-

ing polysomnography in order to better identify the characteristics and functions of sleep. Normal human sleep consists of two distinct states: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep could be further divided into three stages: stage 1, stage 2 and stage 3 [34, 35]. Stage 3 is often referred to as slow-wave sleep (SWS) as well. In adult humans, sleep contains about four or five cycles per night from REM sleep to NREM sleep, with each cycle lasting about 90-120 minutes.

Before a description of sleep architecture, it is important to define terms used to characterize the electroencephalographic (EEG), which are frequency, amplitude, and morphology. EEG measures changes in electrical potential on the scalp, which reflect fluctuations resulting from membrane potentials integrated across neurons of the brain. Frequency refers to rhythmic activity in brain waves and is measured by Hertz (Hz; in cycles per second). Amplitude refers to the magnitude of electrical potential changes between peaks and troughs and is measured in microvolts. Morphology reflects both frequency and amplitude. It defines a particular shape of EEG wave or group of waves, which will be described later for specific characteristics of sleep such as sleep spindles or K-complexes.

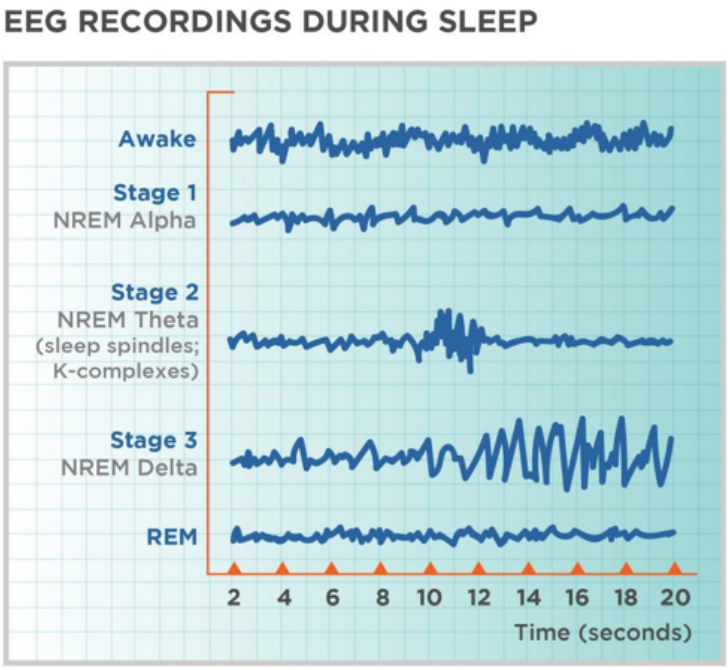

Figure 2.1: EEG wave pattern of different sleep stages. Adapted from [36]

Stage 1 accounts for 3%-8% of sleep time, which is composed of mostly alpha activity (8-13 Hz), theta activity (4-8 Hz), and vertex sharp waves (50-200 ms) toward the end of the stage. Changing from waking to NREM sleep stage 1, the frequency of brain waves become slower gradually. It changes from wake EEG (i.e. beta (14-25 Hz) and gamma (25-80 Hz)) with eyes open to alpha rhythm with eyes closed, and finally to theta rhythm with vertex sharp waves. Along with slower EEG, electromyographic (EMG) activity decreases as well. Electrooculography (EOG) demonstrates slow lateral eye movements. Body temperature begins to drop and muscles relax. Stage 1 sleep is a transitional period from wakefulness to sleep, which can be easily awakened.

Stage 2 sleep often begins after 10-12 min of stage 1 and occupies about 45%-55% of sleep time. In stage 2, the mean frequency of brain waves further decreases, while the amplitude increases. The main rhythm of stage 2 is theta activity (4-8 Hz). Delta waves (0.5-4 Hz) may sometimes appear in stage 2 sleep. EMG activity is further decreased compared to wakefulness

and NREM stage 1. Starting from stage 2 of NREM sleep, EOG does not register eye movements. NREM stage 2 is characterized by two distinctive EEG morphologies: the sleep spindle and K-complex. A sleep spindle is described as clusters of spikes with sigma waveform (12-14 Hz), which lasts more than 0.5 s and has a waxing and waning appearance. Although the mechanism underlying spindles in the human brain is largely unknown, sleep spindles are often correlated with cognitive functioning, learning, and memory [37]. Researchers believe that when spindles occur, the brain disconnects from outside sensory input and begins the process of memory consolidation. A k-complex is a large negative (upward) wave followed by a large positive (downward) wave, both lasting at least 0.5s. A k-complex was described to represent a sort of built-in alertness system that keeps individuals ready to awaken if necessary [38].

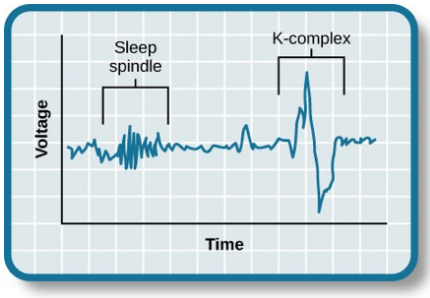

Figure 2.2: Sleep spindle and k-complex of sleep stage 2. Adapted from [36]

Stage 3 sleep or slow-wave sleep (SWS) comprises 15%-20% of total sleep time. SWS is described as moderate amounts of very low-frequency, but high-amplitude activities - delta waves (0.5-4 Hz). EOG does not register eye movements. EMG activity is largely decreased compared to NREM stage 2. In SWS, compared to waking, it shows a largely declined heart rate, blood pressure and respiration rate. Slow-wave sleep is thought to have the primary function of allowing cerebral restoration brain recover from daily activities and to be involved in maintenance and consolidation of memory [39].

REM sleep occupies 20%-25% of total sleep. After 60-90 min of NREM sleep, the first REM

sleep episode occurs. During REM sleep, the brain waves consisted of a mixed activity with slow alpha (1-2 Hz slower than wake alpha) and theta rhythms (4-8 Hz). REM sleep is characterized by rapid eye movements in all directions along with a rise in blood pressure, heart rate and respiration rate compared to other sleep stages, but as noted by previous research, muscle atonia. Despite those activities, the body paralyzed. The REM sleep stage is linked to vivid dreaming. REM sleep is also found to facilitate learning and memory and it is mainly associated with the consolidation of nondeclarative memory, such as riding a bike.

Table 2.1: Characteristics of sleep stages

Sleep Stage	EEG Activity	Muscle Activity
Stage N1 (3%-8%)	alpha (8-13 Hz) theta (4-8 Hz) vertex sharp waves (50-200 ms)	EMG decreases EOG: lateral/slow eye movements drop of body temperature
Stage N2 (45%-55%)	theta (4-8 Hz) sleep spindle (12-14 Hz) k-complex (0.5s)	EMG continues to decrease no EOG
Stage N3 (15%-20%)	delta (0.5-4 Hz)	EMG largely decreased no EOG
Stage R (20%-25%)	slow alpha (1-2 hz) theta (4-8 Hz)	muscle atonia EOG: rapid eye movements rise in blood pressure, and heart rate

Note: EEG = electroencephalographic; EMG = electromyographic; EOG = electrooculography.
The table describes the characteristics of sleep stages for an average healthy adult. Sleep stages could vary between individuals, especially for older adults.

The NREM-REM sleep cycle occurs about every 90 min and adults have approximately four to six cycles per night with the ratio of NREM and REM sleep varying in each cycle. Slow-wave sleep happens more in the first third of the night and REM sleep appears more in the last third cycles. Researchers have observed individual variability in sleep patterns from both experimental and clinical settings. When considering normal nighttime sleep, the most studied characteristic is sleep duration. The discussion on sleep duration was mainly between short sleepers and long sleepers since the 1970s [40]. It has been reported that, when compared to long sleepers, short sleepers have a significant reduction in NREM stage 2 and REM sleep while they have similar

amounts of SWS [41]. Such sleep pattern variability has been attributed to both non-biological factors (i.e. differences in circumstances and habits) [42] and biological factors, which was even proved to be genetically related [43].

2.4.2 Functions of sleep

Sleep is an essential physiological process with important restorative functions. Allan Rechtschaffen, a noted pioneer in the field of sleep research, from the University of Chicago Sleep Laboratory said that If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made. Research in various populations suggested that sleep disturbance is integral to neuropsychological function and mood. For instance, sleep disturbance or fragmentation is associated with impaired attention, processing speed, memory, executive functioning, as well as mood changes, fatigue, and decrements in daytime alertness [44]. Moreover, in older adults, inadequate sleep was found to be related to significant morbidity and mortality [45]. Although sleep consists of a large proportion of human life time and it seems clear that without enough sleep there will be significant impairment in cognition and mood, the function of sleep still remains unclear. There were many hypotheses about the role of sleep, such as homeostatic restoration, thermoregulation, tissue repair, immune control, and memory processing [46]. In the last decade, an increasing number of research reported a bidirectional and symbiotic association between sleep and memory processing, especially memory consolidation [46, 47, 48]. Several reports revealed that SWS (0.5-4 Hz), as well as REM sleep, appear to be very important to memory consolidation [49, 50, 51, 52, 53]. Research with positron emission tomography (PET) scanning further reported that there was a reemergence of hippocampal activation specifically during SWS [53, 54]. Besides the role of SWS in memory, studies also demonstrated an association between sleep spindles in NREM stage 2 and memory processing [55, 56, 57, 58]. Research investigating the role of sleep on memory has become gradually more complicated and further contribution is needed to deeper explore the characteristics and mechanisms.

2.4.3 Measures of sleep

Identification of sleep disturbances requires validated tools that can characterize sleep architectures and detect changes in sleep. Since the late 1960s, Polysomnography (PSG) was used as the primary tool for recording sleep in the laboratory setting. During a polysomnography recording, standard electroencephalography (EEG) and other physiology measures (i.e. electrooculography [EOG], and electromyographic [EMG], electrocardiogram [ECG / EKG]) are recorded. EEG is the most common objective tool used in sleep research. It is an electrophysiological monitoring method of recording the brains electrical activity over a period of time. Those measured brainwaves are divided into bands based on their frequency, which are combined with physiology measures to categorize sleep into discrete stages. Since 2007, most sleep laboratories adopted terminology and scoring rules from the American Academy of Sleep Medicine (AASM) manual for scoring sleep stages and other associated events. Even though PSG is the recognized gold standard measure for sleep, the experiment can be hard to perform. Subjects might experience difficulty with laboratory procedures. Moreover, EEG scoring of sleep might be difficult with older adults, especially those with sleep disturbances, due to diffuse slow activity on EEG during sleep and wakefulness [59]. Therefore, wrist actigraphy is sometimes used as an alternative objective measure to provide quantification of sleep versus wake for 24-h periods. In addition, subjective sleep questionnaires are always used as additional measures. In subjects with AD and MCI, the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Sleep Disorders Questionnaire, and the consensus sleep diary are widely used.

2.5 Theories on how sleep relates to cognition

Over the last few decades, brain research has attempted to define the relationship between sleep and neural functions especially with memory and existing data most strongly supporting the beneficial functions of sleep in memory and general neural function [60]. In more recent years, the theory has been split into three subdomains: (1) a theory that centers on homeostasis, which demonstrated that sleep reverses the exhaustion and overelaboration of neural networks during

wakefulness [61]; (2) a theory stating that sleep consolidates memories for long-term storage [47]; (3) a theory that focuses on the restorative function of sleep enhanced removal of waste products (such as β-amyloid) accumulated during sleep [62].

2.5.1 Homeostasis

The *synaptic homeostasis theory* proposed that sleep, especially slow-wave sleep, may have beneficial effects through promoting a homeostatic regulation in synaptic strength [61]. As the brain learns and adapts to the environment during wakefulness, there are new connections between neurons and great increases in synaptic strength. However, such increases will result in energetically unsustainable neurons since stronger synapses cost more energy and occupy more space. Those changes will affect subsequent learning as those synapses cannot be further potentiated. Thus, the hypothesis states that sleep is associated with synaptic downscaling, which further ties to the beneficial effects of sleep on performance. It further states that the homeostatic regulation of slow-wave sleep is related to the amount of synaptic potentiation. Specifically, the higher the amount of synaptic potentiation during wakefulness, the more slow-wave activity in the subsequent sleep. It also predicts that inadequate sleep will result in synaptic overload, which could lead to cognitive and emotional impairments.

2.5.2 Sleep dependent memory consolidation theory

The *sleep dependent memory consolidation theory* has been supported by a wealth of evidence, which states that sleep promotes the long-term consolidation of memories. Reviews of literature consistently demonstrated a robust beneficial effect of sleep on memory consolidation, especially for procedural memories [48]. The mechanism proposed as underlying effects for memory consolidation is hippocampal-dependent processing. During waking performance of tasks and novel experiences, signature firing patterns of hippocampal and cortical networks occur. Those firing patterns expressed in wakefulness appears to be replayed during sleep. In other words, there appears to be a recurrence of hippocampal activation during sleep just like the activation during wakefulness. It is further hypothesized that the amount of reactivation in the hippocampus was

proportionally associated with the performance improvement the next day.

2.5.3 Waste-clearance theory

The *waste-clearance theory* states that the restorative function of sleep might be a consequence of removing potentially neurotoxic waste products accumulated during wakefulness [62]. The human brain has such high metabolic rate, and relative fragile neurons to toxic waste products during waking. Proteins like β-amyloid (Aβ), α-synuclein, and tau are accumulated in the interstitial space surrounding the brain cells. Those proteins were linked to neurodegenerative diseases like AD and MCI [63, 64, 65]. However, the brain lacks a conventional lymphatic system like other organs of the body to clean the waste products. Fortunately, cerebrospinal fluid (CSF; fluid in the brain and spinal cord) recirculates through the brain and interchanging with interstitial fluid (ISF; a thin layer of fluid which surrounds the body's cells) to remove the proteins like Aβ. The convective exchange of CSF and ISF happens around the cerebral vasculature, in which CSF flood around arteries and ISF influx around veins. This is called the glymphatic system or glymphatic clearance pathway. It is further supported by biological evidence that wakefulness is associated with the accumulation of waste products like Aβ and such glymphatic pathway reduces the clearance of exogenous A by 65% [62] during sleep, which suggests that the movement of CSF and ISF is substantially contributing to the removal of neurotoxic waste products. Moreover, the cortical interstitial space is estimated to increase by 60% during sleep, which enhances the rate of clearance of Aβ and other compounds. This theory aims to explain the question of why sleep is restorative, or conversely, why a lack of sleep impairs brain function. It further predicts that all kinds of insomnia can lead to cognitive impairment or even death within months or years [62, 66, 67].

2.5.4 Summary

The theories mentioned above are not necessarily mutually exclusive and subject to ongoing discussion and elaboration [60]. Those theories were supported by data on the effects of sleep from healthy adults, yet inconsistencies remain. Researchers could understand the mechanisms of sleep and further validate them in their own studies.

2.6 Nocturnal sleep & MCI

2.6.1 Sleep in normal aging

Aging is associated with neural progressive impairment of the functional capacity, including the circadian cycle [68]. In other words, the neural systems, which regulate and maintain the sleep-wake cycle, might be impaired as we age [68]. It has been estimated that at least 50% of older adults complain about their sleep quality, especially on initiating and maintaining sleep [45]. The quality of sleep changes with aging, and excessive daytime sleepiness (EDS) and insomnia are frequently reported in older adults. Most surveys inquiring about sleep reported that more than one-third of older adults reported early morning awakening, increased awakenings during nocturnal sleep and/or difficulty maintaining sleep on a regular basis [69]. The sleep of older adults is also characterized by changes in sleep architecture include a reduced percentage of slow-wave sleep (SWS) and rapid eye movement (REM) sleep and spectral power in sleep electroencephalogram (EEG), as well as a reduction in number and amplitude of sleep spindles and k-complexes [70]. Overall, older adults have reduced sleep time and worse sleep quality, which is typically not due to less time in bed, but instead due to increased awakenings and/or difficulties of maintaining sleep [71].

2.6.2 Sleep in AD

People often have more complaints on their sleep quality as they grow older. Sleep disturbances are even more common in patients with neurodegenerative disorders such as AD. Nocturnal and daytime sleep disturbances affect up to 44% of AD subjects in the clinic and community-based samples [72]. Sleep disturbance is even proposed as one of the neuropsychiatric syndromes in dementia to be included in the DSM-V for AD diagnosis, along with psychosis, depression, and agitation [5]. AD subjects claimed that they suffer from a number of sleep disturbances including insomnia, frequent awakenings during nocturnal sleep, evening agitation, decreased nocturnal sleep, and increased daytime sleep [16]. Based on the analysis of self-reported questionnaires (i.e. Pittsburgh Sleep Quality Index [PSQI], Epworth Sleepiness Scale [ESS], Sleep Disorder Question-

naire) or physician diagnosis (i.e. apnea hypopnea index [AHI] scores), a meta-analysis demonstrated that sleep disturbance has a predictive role in developing dementia [73]. Specifically, they found that the risk of developing AD was 1.49-times higher in individuals with sleep disturbances [73]. The broad-based effect on multiple cognitive functions in AD subjects also confirmed that poor self-reported sleep quality and sleep complaints (i.e. shorter sleep time) was associated with the poorer cognitive performance [74].

Other than self-reports, objective measures of sleep disturbance may be more helpful in identifying specific target symptoms and the relationship between sleep disturbance and AD. A number of studies have been conducted to evaluate sleep characteristics in subjects with AD using tools such as Polysomnography or actigraphy. AD subjects often have more disrupted nocturnal sleep (i.e. reduced PSG total sleep time, lower PSG sleep efficiency) than age-matched normal-aging older adults [59]. A PSG total sleep time (TST) reduction might due to the difficulty of maintaining sleep (e.g. increased arousal) after sleep onset and increased PSG sleep latency (SL) [59]. Additionally, despite the discrepancies, most studies found decreased PSG slow-wave sleep (SWS) and reduced sleep spindles and k-complexes [16, 59]. Studies also demonstrated alterations in PSG REM sleep [59, 75]. While REM sleep duration is decreased, the total number of PSG REM sleep episodes remain intact [59]. Additionally, researchers also found slower EEG waves (i.e. alpha and theta rhythm) during REM sleep for AD subjects compared to normal-aging older adults [59, 76].

Subjects with AD often have dramatic sleep architectural abnormalities [45] than age-matched controls. Signature findings include decreased sleep efficiency and total sleep time, increased arousal and awakening, a reduction in sleep spindles and k-complexes, and alterations in REM sleep [16, 45, 59]. Even a number of clinical sleep disorders (i.e. insomnia, hypersomnia, nocturnal agitation, and abnormal nocturnal behaviors) have been related to subjects with AD. Some studies even proposed sleep disturbance to be a major risk factor for increasing AD in older healthy adults [59]. Further studies will need to further establish sleep characteristics in this growing population, which would contribute to sleep evaluation and management.

2.6.3 Sleep in MCI

Similar to subjects with AD, MCI individuals are also characterized by an increased prevalence of sleep disturbance. The review paper by Beaulieu-Bonneau & Hudon [5] reported that sleep disturbances have been consistently reported to be one of the most common neuropsychiatric symptoms of MCI. Among the fifteen studies being reviewed, a similar prevalence was obtained from clinical samples (prevalence of 17% - 57%) and population-based studies (prevalence of 14% - 59%). They further summarized that the most commonly reported sleep disturbances were waking up too early, trouble staying asleep and sleeping too much or increase in naps [5]. In one of the population-based studies [77], they evaluated 320 subjects with MCI by asking them to rate the frequency and severity of their neuropsychiatric symptoms. They concluded that sleep disturbance was among the three most frequent clinically significant symptoms (sleep disturbance, apathy, depression). A longitudinal study by Lobo and colleagues [78] surveyed and followed 4061 healthy older adults (over 55 years old) for two years. The results indicated that the presence of sleep disturbances was associated with the incidence of MCI and considered to be one of the risk factors.

Along with the high rates of sleep disturbance reported in MCI with detailed self-report measures and sleep diaries, objective measures of sleep using polysomnography (PSG) have also been implemented to explore the features of sleep disturbance in subjects with MCI. Common PSG assessed sleep parameters include sleep latency (SL; latency to persistent sleep), sleep maintenance (WASO; wake after sleep onset), sleep efficiency (SE = [total sleep time/total recording time]), total sleep time (TST), the amount of time spent in each sleep stage (Stage 1, 2, SWS, NREM, and REM), the latency after sleep onset to REM sleep and the percentage of each stage were also calculated.

Several PSG sleep parameters of MCI subjects were identified by previous studies. Compared to normal-aged peers, most studies showed that MCI subjects expressed longer PSG sleep latency [24, 79, 80, 81], and a decrease in their PSG total sleep time [24, 68, 79, 82]. They also experienced lower PSG sleep efficiency than the normal-aging group [24, 83]. Studies using large community

samples of older adults also confirmed that lower PSG sleep efficiency [84] and less PSG slow-wave sleep [24, 82, 85] consistently related to cognitive impairment. Moreover, MCI subjects were found to have significantly increased PSG REM sleep latency [24, 85, 86] and significantly shortened PSG REM sleep time [68, 82, 87]. To date, no studies have been conducted on examining the difference between sleep spindles and k-complexes between MCI and normal-aging peers.

Most studies consistently found sleep disturbances in MCI subjects [24, 68, 85]. The few studies that did not show significant changes in sleep parameters of MCI mainly focused on total sleep time, SWS, and REM sleep. To the best of our knowledge, three studies observed no significant difference in total sleep time between MCI and their normal-aging peers [80, 83, 85]. Another study demonstrated that REML (rapid eye movement sleep latency), percent of rapid eye movement (REM%), and SWS showed no changes [24].

In sum, previous studies revealed subtle differences in sleep quality between MCI subjects and their peers. In general, the objective measures validated the findings from subjective reports, though studies were not always in agreement with what metrics showed impairment. Despite inconsistent results, most studies reached the same conclusions: compared with normal-aging older adults, the MCI subjects expressed more SL, less TST and SE, and shorter SWS and longer REML. The existing articles that demonstrated inconsistent results may not be comprehensive enough [24], though do call for further exploration of sleep parameters.

2.7 Daytime sleep (napping) & MCI

2.7.1 Daytime sleep & nocturnal sleep in the general older population

The most recent Sleep in America poll indicated that 40% of respondents reported intentionally napping at least once in the previous week, with an average nap duration of 79 minutes [88]. Additionally, 11% of those respondents took naps on at least five of the past seven days [88]. As sleeping becomes a significant challenge for older adults (estimated 57%) [89], the frequency of napping was consistently found to be increased with age [90]. One in four older adults reported intentionally napping daily [89]. The average nap frequency in older adults is at least once per

week with an average duration between 23.3 to 45 minutes per day [89].

People vary in the frequency of napping and also the improvements in alertness and cognitive performance they experienced. The degree of benefit from a nap can be influenced by a number of factors such as the duration of the nap, the timing of the nap, and the presence of sleep inertia. Sleep inertia is the delay of thinking and performance abilities upon awakening due to sleep and is typically found as a result of awakening from SWS [90, 91]. Other individual characteristics (e.g. age, sex, and experience of sleep loss) and test characteristics (e.g. task difficulty, and test timing) might also affect the benefit of naps. Moreover, studies found that habitual nappers (i.e. individuals who naps one or more times per week for 30 min to 2 h for at least 2 years) [92] may benefit more from napping [90].

Napping has been shown to benefit young adults who generally get sufficient sleep on a nightly basis. In general, napping may be beneficial in terms of alertness, mood, and cognitive performance [90]. As older adults experience more sleep disturbance and have more time to nap after retirement, it is possible that napping could be even more beneficial for this group. Takahashi [93] reviewed that older adults with and without sleep disturbances would benefit from appetitive naps. Several studies confirmed that napping improves cognitive performance for older adults. Studies demonstrated that a 30-min to 4-hour nap improved participants alertness, concentration, and coordination [90, 94, 95]. Campbell and colleagues [96] reported that napping improved performance on the Stroop task and a logical reasoning task. Furthermore, Mednick and colleagues [97] found that a 60-90 minute nap could generate both SWS and REM which would improve learning and memory performance in a manner similar to nocturnal sleep. However, few studies reported that napping would result in shorter nocturnal sleep and decreased sleep efficiency [98, 99], which will further affect well-being and daytime function in such populations. One of the limitations was that most studies typically rely on survey and interview data to describe the characteristics of napping and nighttime sleep.

2.7.2 Daytime sleep in AD

A growing body of studies investigated the association between sleep disturbances and the risk of AD, however, less attention was paid on napping. Interestingly, within those limited amounts of studies, both positive and negative effects of napping were found in AD subjects. Aligning with most napping studies on healthy older adults, some findings suggest that napping might be effective in improving cognitive performance and decrease fatigue [100]. For example, Owusu and colleagues [101] demonstrated that moderate-duration naps (31 - 60min) had significant larger benefits for habitual nappers than non-nappers in an AD sample. In particular, habitual nappers had significantly improved performance on a delayed word recall task and better self-rated memory. Additionally, studies also find napping to be helpful in adjusting the sleep-wake biorhythm for AD individuals. For example, Katagi and Miyai [102] assessed 23 female older adults with mild-to-moderate AD for eligibility and randomly allocated them into a nap study group or a non-nap control group. They found that subjects who took a 30-min nap for four weeks showed significantly increased sleep efficiency and reduced nighttime awakenings compared to the non-nap group. An observational study compared AD subjects who nap and did not nap and concluded that those reporting frequent napping 60 min had a decreased speed of decline as measured by Mini-Mental State Exam Scores [10]. On the other hand, data from nursing homes reported that AD residents with excessive daytime napping often showed further fragmentation of night sleep quality and decreased social activities [103]. Woods and colleagues [104] also indicated that excessive daytime napping (> 2 hrs nap per day and an average of 13 hrs in bed at night) contributes to circadian-rhythm or sleep-wake cycle disturbances.

The mixed evidence of both positive and negative effects of napping on AD subjects might be partially attributed to limited measures of napping. Napping can vary in characteristics such as duration, timing, and sleep stages, which cannot be completely captured by subjective measures or reports from caregivers. Therefore, certain types of napping may improve cognitive performance and well-being among AD subjects.

2.7.3 Daytime sleep in MCI

There is a dearth of research investigating napping behaviors in MCI subjects, especially the studies using objective measures such as the PSG system. Among those limited studies, some longitudinal studies found that napping might have a restorative function for MCI subjects. For example, Asada and colleagues [9] followed 337 subjects with MCI for 5 years to study their napping habits. The results revealed that habitual (3 or more days per week) napping for up to 60 minutes was associated with an 84% decreased risk for developing AD. Another study investigated the role of napping in 275 MCI individuals for over 10 years also concluded that napping was associated with less future cognitive decline [10]. Moreover, Keage and colleagues [10] found that both moderate (30-60 min) and long (>60 min) naps were protective against cognitive decline with the naps lasting over an hour showing the strongest positive effects. Schneider and colleagues [105] measured EEG activity during a 90-min nap on 18 MCI subjects. They reported that subjects had significantly improved performance in the picture recognition task after the nap. However, the association between napping and cognitive decline is still under debate. Cross and colleagues [11] measured 111 MCI subjects napping by actigraphy and sleep diaries over 14 days. They found that although napping might not affect nocturnal sleep quality, excessive napping (over 2h per day) might have negative effects on cognitive performance, such as verbal memory and psychomotor speed tasks. There have always been debates over the restorative function of napping. To the best of the authors knowledge, no study has conducted a detailed investigation using PSG napping parameters and their associations with cognitive performance.

2.7.4 Theories on how daytime sleep affects AD & MCI

Besides theories explaining the restorative function of sleep, there are multiple extended mechanisms that may help to explain the observed associations between napping and neuropsychological function. First, aligning with the theories about the mechanism of sleep, napping might be a marker of neurodegenerative disease. Based on the waste-clearance theory, sleep was found to be effective in cleaning waste products including β-amyloid and the disturbance of sleep could

lead to cognitive impairment [62]. While, excessive napping has been linked to the disturbances in nighttime sleep and therefore more deposition of β-amyloid [101]. Therefore, high frequent naps have the potential of resulting in cognitive impairment like AD and MCI. Second, napping, especially unintended napping, has been characterized as a marker of Excessive Daytime Sleepiness (EDS). It is hypothesized that EDS might be the factor that drives the association between napping and neuropsychological performance. A number of previous studies have linked EDS to cognitive decline [106, 107, 108], and individuals that are habitual nappers are more likely to have EDS [109]. Third, napping was also found to be associated with other medical conditions including type-II diabetes [110], higher incidence of cardiovascular disease [111], and greater risk of obesity [112]. Those conditions were highly correlated with cognitive deficits themselves [101]. Thus, napping was hypothesized to affect cognition through those medical conditions. In sum, the findings highlight napping might be a highly correlated factor of cognitive impairment just like nocturnal sleep.

2.8 Study purpose

The main purpose of the current proposal is to examine napping behaviors in MCI subjects and compare them to their normal-aging peers. Napping is common in older adults, especially MCI subjects who experience more sleep disturbance. Yet, the extent to which naps would impact cognitive functioning, nocturnal sleep and overall well-being is still unclear. There have been discrepancies in studies examining the effects of napping in both MCI and normal-aging groups. Some studies support the notion that napping has restorative functions for cognition and may even slow the progression of AD. On the contrary, other studies reported that excessive napping was associated with worse nocturnal sleep quality and a decrease in cognitive functioning. The discrepancy in studies might partially due to the differences in measurements. Therefore, the effects of napping may require further investigation with objective measures such as PSG systems. Moreover, the quality of napping was proposed to be a potential factor that might impact the effects of napping. According to studies examining MCI subjects, disturbed napping behavior was found in comparison to their normal-aging peers [24]. Thus, it is worth comparing MCI subjects with their

normal-aging peers on their napping quality and how that might influence the effects of napping. The proposed study will utilize 2 experimental groups: nap control and nap MCI. A sleep EEG analysis will be conducted to define PSG napping parameters for both groups, and the results will be related to before-and-after nap cognitive performance across groups.

There are three specific aims of the current study. The first aim of the study is to examine the severity of sleep disturbance in MCI subjects and their normal-aging peers using subjective reports. More specifically, the study will assess (1a) the differences in subjective sleep quality between groups; and (1b) how subjective sleep quality relates to baseline cognitive performance separately for each group. The second aim of the study is to investigate napping parameters using objective measures and how those parameters differ in MCI subjects and their normal-aging peers. In particular, the study will assess (2a) the differences in objective napping parameters between groups; and (2b) how objective daytime sleep parameters relate to baseline cognitive performance separately for each group. The third aim of the study is to examine whether the effects of napping would differ in MCI subjects and their normal-aging peers. In particular, the study will assess (3a) the differences of post-nap cognitive performance changes between groups; and (3b) how cognitive performance changes relate to objective daytime sleep parameters separately for each group.

3. METHODS

3.1 Participants

A total sample of 37 older adults (21 MCI, 16 healthy control) meeting inclusion criteria were recruited from College Station - Bryan area, TX. Subjects were recruited through the subject database in the Center for Translational Research in Aging and Longevity (CTRAL) at Texas A&M University and mass emails sent to the university as well. Subjects were matched on sex, age, and Body Mass Index (BMI). Inclusion criteria for the current study included: (1) healthy male or female without any clinically diagnosed sleep disorders; (2) fluent English speaker; (3) individuals are regular napper or at least are able to nap if needed; (4) ability to walk, sit down and stand up independently; (5) for the subjects with MCI, their Montreal Cognitive Assessment (MoCA; description see measurements section) test score should be between 19 and 26, while, for the subjects with normal-aging, their MoCA test score should be equal to or greater than 26; (6) willingness and ability to comply with the protocol. A priori power analysis for ANOVA designs indicated that at least 17 subjects are needed in each of the two groups to have 80% power of detecting a large-sized effect when employing the traditional .05 criteria of statistical significance. This study was approved by Texas A&M University Institutional Ethics Committee (IRB), and all subjects gave written informed consent.

3.2 Study design

The current study investigates napping behaviors and cognitive functioning in healthy older adults with mild cognitive impairment (MCI) and their normal-aging peers. Subjects were blinded for their study group (i.e., uninformed of group assignment). The contains combinations of between-subject and within-subject variables. The between-subject variable was symptom group (MCI or normal-aging older adults), and the within-subject variable was time (before or after napping).

3.2.1 Procedure

The study included 2 sessions. The first session was called the screening session, in which subjects completed demographic information and all neuropsychological assessments to confirm study eligibility. Subjects were also given the opportunity to familiarize themselves with the environment and given the chance to take a practice nap (nap with the PSG system but without collecting any data). Within the following weeks before their second session, subjects were given a sleep diary for them to complete over 7 days. One day before the second session, subjects were contacted to ensure accurate completion of the sleep diary, and ascertain their visit on the following day. The second session was the study session, in which subjects took a nap with the laboratory sleep measures and they completed a set of neuropsychological assessments both before and after their naps.

Once a signed consent form was obtained, the subjects were screened for eligibility based on the inclusion criteria. Based on the Montreal Cognitive Assessment (MoCA) score, subjects were assigned into either the MCI group ($18 < \text{MoCA} < 26$) or the normal-aged group ($\text{MoCA} \geq 26$). Bodyweight, height, and vital signs were assessed as well. Also, a set of neuropsychology assessments were obtained from the subjects. Subjects were asked to sign a medical release form based on their willingness, which helped determine study eligibility and can be used for later analysis. Additionally, subjects were given the chance to take a practice or an adaptive nap based on their willingness. The purpose of the adaptive nap was to familiarize the subjects with the environment and equipment in order to minimize the effect of the first-night effect (FNE) [113]. People often experience troubled sleep in a novel environment, this is called the first-night effect (FNE) in human sleep research and has been referred to as a typical sleep disturbance [113]. To avoid this and for the best practice, most human sleep research would perform an adaptive sleep before formal experiment proceeds.

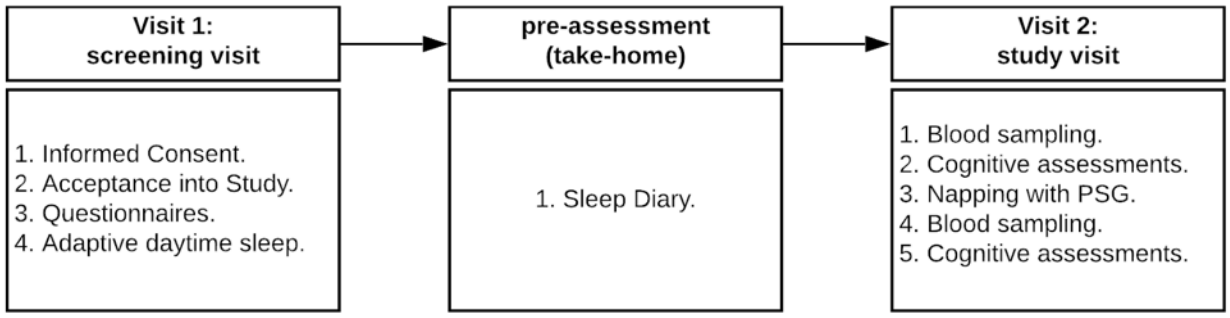

Figure 3.1: Schema of the study procedure

3.3 Measurements

3.3.1 Subjective sleep measures

Pittsburgh Sleep Quality Index (PSQI) is widely used to assess subjective sleep quality. The 19-item PSQI [114] is a self-rated questionnaire that inquiries about the subjects sleep quality for the past month. There are seven components: sleep duration, sleep latency, sleep disturbance, sleep efficiency, subjective sleep quality, daytime dysfunction, and use of mediation. A global score calculated based on those components is used to evaluate subjects sleep quality, with scores of 6 or more indicate poor sleep quality. The internal consistency of the PSQI is good, with a Cronbachs alpha value of 0.83 [114]. According to the original manual of the PSQI, Buysse and colleagues [114] suggested using the global PSQI score to distinguish good and poor sleepers. However, the previous findings [115, 116] raised the question about whether it is appropriate to use a single global score to differentiate good from poor sleep quality and further recommended two or three-factor models to better capture subjects sleep quality.

3.3.2 Objective daytime sleep measures

Laboratory-based Napping Parameter Measures. All napping sessions were take place at the sleep laboratory in the Center for Translational Research in Aging and Longevity (CTRAL) at Texas A&M University. During the nap session (up to 120 min), PSG with 30-s epochs will be recorded for subjects using the Compumedics (Victoria, Australia) system. EEG was recorded

from 11 scalp sites (FP1, FP2, Fz, F3, F4, C3, Cz, C4, O1, Oz, and O2) being placed according to the extended 10-20 system. Additionally, 3 chin electromyography (EMG) channels, 2 electrooculogram (EOG) channels for left and right eyes (E1, E2), 2 electrocardiogram (ECG/EKG) channels, and 2 respiration bands were applied to extend the stability of the measurement.

3.3.3 Cognitive performance measures

Making a distinction between MCI and normal aging can be a challenge as forgetfulness or having difficulty recalling would also be a part of normal aging. Besides the cognitive screening of MCI (i.e. The Montreal Cognitive Assessment [MoCA]), neuropsychological testing generally used to help to verify MCI [117] includes memory (i.e. visual memory), attention (i.e. Trail Making Task), and executive functions (i.e. Stroop Color-Word Interference Test).

The Montreal Cognitive Assessment (MoCA) is a cognitive screening test designed to assist for the detection of MCI and early AD. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation [118]. The time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points: a score below 26 is considered MCI, furthermore, a score below 19 is always considered AD. To better adjust the MoCA score for lower educated individuals, 2 points will be added to the total score for those with 4-9 years of education and 1 point for 10-12 years of education [119]. For the current study, the score of MoCA is not for diagnostic purposes and will not be shared with the subjects. It will only be used to characterize subjects into study groups. The internal consistency of the MoCA was good, with a Cronbachs alpha of 0.83 [118]. Additionally, the MoCA detected MCI with 90%-96% sensitivity and specificity of 87% with a 95% confidence interval [118].

Visual Short-Term Memory (VSTM) is a spatial working memory and item-location binding task [120]. It contains two blocks of practice trials followed by 3 test blocks. Each practice block contains 10 trials, and each of the test blocks contains 40 trials. A schematic of the task is shown in the following figure. In each trial, subjects view 1 or 3 fractal objects, each randomly located on the screen. They are asked to remember both the objects (i.e. color, shape) and their

locations. A blank screening is then displayed for 1 or 4 seconds duration, followed by a test array in which two fractals appear along the vertical meridian. Among those two fractals, one of them is the memory array, which is also called the target fractal whereas the other one is a foil or distractor. The foil is not an unfamiliar object, but is part of the general pool of fractal images presented across the experiment. The fractal stimuli were drawn from a library of 60 pictures (http://sprott.physics.wisc.edu/fractals.htm). Object identity is measured as the proportion of trials where the correct object is selected. Moreover, gross localization error is computed as the distance between the center of the target object for its remembered locations and its original location in the memory array. It is only measured on the trials where an object is correctly identified. Working memory impairments are commonly found in subjects with AD [121]. The VSTM task was designed by Masud Husains team from the University of Oxford specially for subjects with AD. Their findings were in line with the role of the medial temporal lobes, especially in the hippocampus. Such impairment in working memory needs further investigation in MCI subjects.

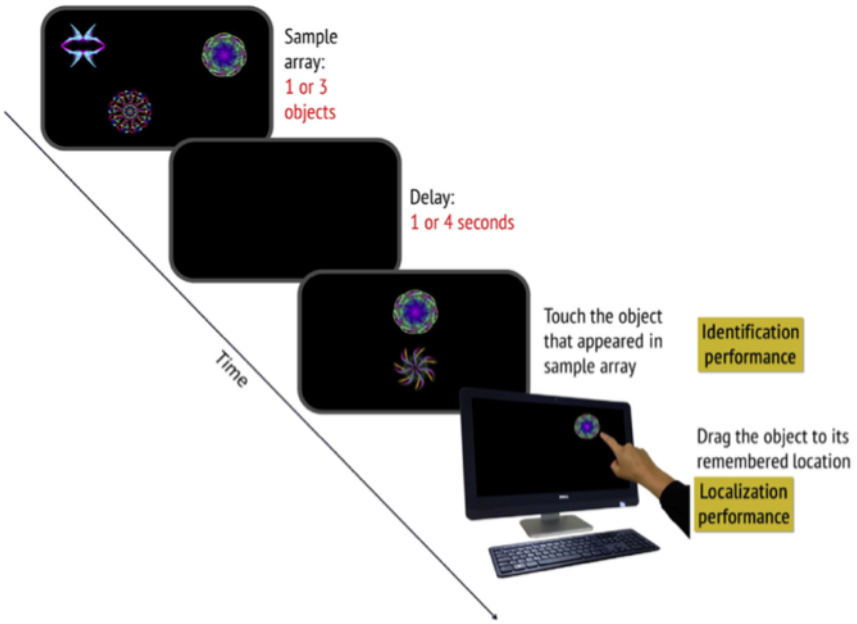

Figure 3.2: Schema of VSTM task. Adapted from [120]

Trail Making Test (TMT) is a neuropsychological test for visual attention and task switching [122]. The test can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning. The test was programmed in Windows and subjects will use Windows Surface book and surface pen to complete the task. It consists of two parts in which the subject is instructed to connect a sequence of 25 consecutive targets as quickly as possible while still maintaining accuracy. In part A, the targets are all numbers (i.e. 1, 2, 3, etc.) and the subjects need to connect them in sequential order; while in part B, the targets alternate between numbers and letters (i.e. 1, A, 2, B, etc.) in which subjects need to connect a number and then a letter in sequential order. If the subject makes an error, the test administrator corrects them before the subject moves to the next target. Both completion rate and error rate will be recorded. Although the main symptom for MCI subjects is memory loss, the presence of processing speed decline and executive functioning deficits and is widely recognized [123]. The Trail Making Test is one of the most commonly used tasks for assessing cognitive processing speed and executive functioning [124] and other studies have applied it in MCI subjects [123, 125].

Stroop color-word test consists of two subtasks [126]. The stimulus material of each of the subtasks is shown on a white sheet of paper that is landscape oriented. In the first subtask, the displayed color words (non-capital letters) are printed in the congruent color, for example, the word yellow printed in yellow ink. The second subtask contains color words printed in an incongruous ink color (non-capital letters), for example, the word yellow printed in red ink. The subjects are instructed to name the ink color of the printed words as quickly and as accurately as possible in both subtasks. There is no time limit to complete the tasks. The complete time and error rate will be recorded. The administrators do not point out errors made during the test. Perry and Hodges [127] reviewed attention and executive deficits of subjects with cognitive impairment, they suggested that those subjects had trouble shifting attention and presented declined abilities for competing processes. Researchers later followed their findings and further investigated attention and executive deficits using Stroop tasks [128, 129].

3.3.4 Bodyweight (BW) and body height (BH) measures

Bodyweight was measured using a beam scale to the nearest 0.1 kg. Body height was measured with the subject barefoot or wearing socks only and standing, and was determined to the nearest 0.5 cm. Body Mass Index (BMI) was a value calculated based on the weight and height of a person. It is defined as the body mass (weight; in kilograms) divided by the square of the body height (in meters), and in units of kg/m^2.

3.4 Analysis plan

All cognitive functioning and sleep data were examined for outliers and normality of the distribution. Subject who had a study variable that is more than 5 standard deviations from the group mean were excluded from the analyses. Variables with significantly non-normal distributions were transformed (e.g. square root transform, log transformation) prior to analysis.

3.4.1 Daytime sleep analysis

Sleep architecture evaluation was based on the scoring criteria proposed by the American Academy of Sleep Medicine (AASM) [34, 35]. PSG daytime sleep parameters were defined based on the analysis. For instance, sleep stages (i.e. stage 1, stage 2, SWS, REM sleep), sleep spindles, k-complexes, total napping time, stage latency will be characterized based on AASM criteria.

The analysis of EEG data was based on the features of the sleep stages. The scoring was performed within each epoch (30 sec). Unless features appear of other sleep stages, the epoch was scored the same stage as previous epoch. Scoring stage W with the following criteria: (1) the majority of subjects will demonstrate alpha activity; (2) constant eye blinks or rapid eye movements. Scoring stage N1 with the following criteria: (1) when alpha activity is replaced by low-amplitude theta activity or mixed frequency activity with alpha and theta activities for more than 50% of the epoch; (2) the appearance of slow eye movements; (3) vertex sharp wave might also appear in stage N1, but its not required for an epoch to be scored for stage N1. Scoring stage N2 with the following criteria: (1) the appearance of k-complex or sleep spindle; (2) if the k-complex or sleep spindle appears at the first half of the epoch, the current epoch is scored as stage N2; (3) if the k-complex

or sleep spindle appears at the second half of the epoch, the following epoch is scored as stage N2. Scoring stage N3 with the following criteria: (1) an epoch is scored as stage N3 if more than 20% of the epoch consists of slow delta activity. Scoring stage R with the following criteria: (1) low amplitude theta activity or mixed-frequency activities (alpha, theta) without k-complex or sleep spindle; (2) low chin EMG movements for the majority of the epoch; (3) if those REM activities appear in any position of the epoch, the epoch is scored as stage R.

After scoring stages, quantitative analyses were performed using PSG parameters, including the length of sleep onset/sleep latency, total sleep time, number of arousals, the length of sleep stages, the percentage of sleep stages, number of k-complex, and number of sleep spindle. Those parameters were compared between the groups.

Table 3.1: Scoring features for sleep stages

Sleep Stage	Features for Scoring
Stage W	1. eye blinks (0.5-2 Hz)) 2. beta (14-25 Hz) 3. gamma (25-50 Hz) 4. rapid eye movements 5. normal or high chin muscle tone
Stage N1	1. alpha (8-13 Hz) 2. theta (4-8 Hz) 3. vertex sharp waves (<0.5 seconds) 4. slow eye movements (>500 msec)
Stage N2	1. theta (4-8 Hz) 2. sleep spindles) 3. k-complexes
Stage N3	1. delta (0.5-4 Hz) in 20% of an epoch)
Stage R	1. slow alpha (1-2 Hz)) 2. theta (4-8 Hz) 3. rapid eye movements (<500 msec)

3.4.2 Statistical analysis

Demographic variables were used to compare healthy controls and MCIs in order to show that those groups do not differ significantly in terms of age, sex, ethnicity, education and BMI. Categorical data (sex, ethnicity and education) was analyzed using Pearson chi-square (X^2) while continuous data (age and BMI)was analyzed using independent sample t-tests.

For all statistical testing, the statistical significance was set at $p < .05$. For statistical testing used to compare group differences, effect size (Cohen's d, η_p^2) was calculated. Interpretation of Cohen's d refers to small effect size as $d = 0.2$, medium effect size as $d = 0.5$, and large effect size as $d = 0.8$ [130]. Interpretation of η_p^2 refers to small effect size as $\eta_p^2 = 0.01$, medium effect size as $\eta_p^2 = 0.09$, and large effect size as $\eta_p^2 = 0.25$ [130]. All analyses were conducted in SPSS [131] and R [132] .

A one-way Analysis of Covariance (ANCOVA) was conducted to determine a statistically significant difference between group on cognitive performance controlling for demographic variables. Effect sizes for the ANCOVA were calculated using partial η^2. The assumptions of ANCOVA are: (1) covariates should not be highly correlated, which was tested by correlation test; (2) residuals should be normally distributed, which was tested by Shapiro-Wilks test; (3) homogeneity of variance, in other words, the variances should be similar for all groups, which was tested by Levene's test. All assumptions were checked before conducting ANCOVA. Benjamini-Hochberg method were applied to adjust for multiple comparisons as needed.

A mixed-effect Analysis of Variance (ANOVA) was applied to compare the mean differences between groups on their pre- and post-test cognitive performance. Effect sizes for the mixed-effect ANOVA were calculated using partial η^2. The assumptions of ANOVA are: (1) continuous dependent variables; (2) both within-subject variables and between-subject variables consist of at least two categories; (3) dependent variables have a normal distribution, which was tested by Shapiro-Wilks test; (4) homogeneity of variances for each combination of the groups for independent variables, which was tested by Levenes test; (5) the variances of the differences must be equal for all groups, which was tested by Mauchlys test of Sphericity. All assumptions were checked

before conducting ANOVA.

Further Pearson partial correlation analyses examined the relationship between sleep/napping parameters and cognitive functioning. Correlation coefficients were used to evaluate the correlation coefficient to determine the strength of the relationship or the effect size. The assumptions of the Pearson correlation are level of measurement, normality of variables, linearity, and homoscedasticity. (1) Level of measurement refers to each variable should be continuous. (2) Normality of variables were tested by Shapiro-Wilk test. Variables were transformed if not normally distributed before the analysis. (3) Linearity assumes a straight-line relationship between each of the two variables. (4) Homoscedasticity assumes that data is equally distributed about the regression line.

4. SUBJECTIVE SLEEP QUALITY IN MCI & HEALTHY OLDER ADULTS

4.1 Introduction

MCI subjects are characterized by increased prevalence (14% - 59%) of sleep disturbances [5]. Although not formally included as a DSM key diagnostic criteria, sleep disturbance has been documented as one of the four core symptoms of MCI [4]. Moreover, sleep disturbances were even considered to be one of the risk factors of developing cognitive impairment [78] and have been shown to increase the likelihood of progression to AD [6, 7].

For older adults, subjective measures of sleep quality, such as self-report questionnaires, are one of the most commonly used measurements due to their efficiency and practicability. Prior community-based studies using subjective sleep measures showed that MCI subjects reported more sleep disturbances than their normal aging peers [5, 77, 78]. Subjective reports showed that there were significant changes in MCI subjects sleep quality when compared to their normal-aging peers [133]. Specifically, MCI subjects experienced a higher fragmentation of sleep, increased awakenings, and increased total sleep time. On the other hand, a number of studies, mainly conducted on clinical samples found no such difference [134, 135]. Those differences might be due to differences in the measurements as well as the sample. Therefore, the current study would first validate the presence of sleep disturbance in our sample.

Over the last two decades, there has been increasing recognition of the integral role of sleep in cognitive functioning. Sleep disturbance was found to be related to impaired attention, reaction time, and working memory [47, 136]. For instance, an increasing number of research reported on the association between sleep disturbance and worsened performance in memory tasks [37, 39, 46]. In particular, the category of spatial working memory, largely dependent on hippocampal function, was found to be a potentially sensitive measure of detecting memory decline [120]. Furthermore, Cain and colleagues [137] found significant impairment in Stroop task performance in subjects with sleep disturbances.

One of the proposed mechanisms explaining the relation between sleep disturbance and cognitive impairment particularly in MCI subjects, is the accumulation of β-amyloid in the brain. In particular, the movement of CSF and ISF is substantially contributing to the removal of neurotoxic waste products such as β-amyloid during sleep. Sleep disturbance might relate to significantly more β-amyloid burden in memory-related brain regions such as the hippocampus [138]. Therefore, the mechanism possibly explains why a lack of sleep might impair brain function.

The large variance in the prevalence of sleep disturbance in MCI subjects found between studies might be due to different diagnostic criteria and different types of measurements. The current study would contribute to the qualification of sleep disturbance in MCI subjects using one of the most widely used self-reports, the PSQI. Although studies indicated that the presence of sleep disturbance was associated with the incidence of cognitive impairment [74, 78], most studies exclusively focused on AD subjects. Thus, there has been a lack of research that examines the relationship between subjective sleep quality and cognitive functioning in MCI subjects. Such investigation in comparing MCI subjects and their normal-aging peers might be of particular importance, because knowledge of MCI subjects might prevent the progression of impairment. In addition, to the best of my knowledge, no study has investigated the association of sleep disturbance and spatial working memory tasks in MCI subjects. Therefore, the study will also contribute to the discussion of the role of sleep specifically on spatial working memory for MCI subjects.

The main purpose of this study is to compare subjective sleep quality between MCI subjects and their normal-aging peers. I hypothesize that ***MCI subjects would report more sleep disturbances than their normal-aging peers***. Further, as a secondary aim, I will investigate the relationship between subjective sleep quality and cognitive functioning in both groups. In particular, I hypothesize that ***better subjective sleep quality would relate to better baseline cognitive performance***.

4.2 Methods

This study included baseline data from a project which investigated the effects of daytime sleep in MCI subjects and their normal-aging peers. More information on the full sample, measurements, and analyses were provided in the general methods section (Section 3).

4.2.1 Sample

From the initially measured subjects (N = 37), 36 of them had complete data that could be used for further analysis (1 subject was excluded due to incomplete data on PSQI). All subjects (N = 36) were recruited from College Station - Bryan area, TX. Subjects were classified into either MCI or healthy older adults groups based on their MoCA scores. For those 36 subjects included in analysis, 20 were from the MCI group (average age = 73.57; SD = 6.73) and 16 were from the healthy group (average age = 68.67; SD = 7.36). The basic demographic characteristics of subjects were compared across groups in Table 3.

Table 4.1 displayed demographic information for the sample. There were no significant differences between subject groups in terms of sex and BMI. There were statistically significant differences between groups in their age (p = 0.049). Therefore, due to the MCI being older, age was treated as a control variable for further correlation analysis. As expected, there were significant differences between groups on their MoCA scores (p < 0.001). MCI subjects had significantly lower MoCA scores than their normal-aging peers, which indicated that they tended to experience more cognitive impairment.

Table 4.1: Demographic characteristics by subject group

Variable	MCI (n = 20) n(%) | mean(*SD*)	Healthy (n = 16) n(%) | mean(*SD*)	Chi-square | *t*-test	*p*	Effect Size
Sex			$x^2(1) = 3.11$	0.080	$\phi_{Cramer} = 0.50$
Female	8 (40%)	12 (75%)			
Male	12 (60%)	4 (25%)			
Age	73.57 (6.73)	68.67 (7.36)	*t*(34) = -2.03*	0.049	*d* = 0.69
BMI	26.69 (7.25)	27.64 (8.80)	*t*(34) = 0.36	0.724	*d* = 0.12
MoCA	22.50 (2.09)	26.88 (1.36)	*t*(34) = 7.23***	**<0.001**	*d* = 2.48

Notes: MCI: Mild Cognitive Impairment. BMI: Body Mass Index in units of kg/m^2. MoCA: Montreal Cognitive Assessment.
*p<0.05, **p<0.01, ***p<0.001.

4.2.2 Subjective sleep measures

Subjects subjective sleep quality was assessed by the PSQI. Subjects were asked to report their sleep quality during the past month with a 4-Likert scale ranging from 0 (Not during the past month) to 4 (Three or more times a week). Individuals were characterized as having good or poor sleep quality based on the PSQI score. PSQI measures sleep quality based on 7 components: sleep duration, sleep efficiency, sleep quality, sleep latency, sleep disturbance, use of medication and daytime dysfunction. The main outcome variable, the total PSQI score, will be calculated by the sum of those component scores. Furthermore, previous studies [115, 116] recommended three-factor models to better capture subjects sleep quality. The current study will calculate PSQI factor scores (i.e. sleep efficiency, sleep latency, and sleep quality) based on factors weights [116]. More information about the factors of PSQI is provided in the following figure.

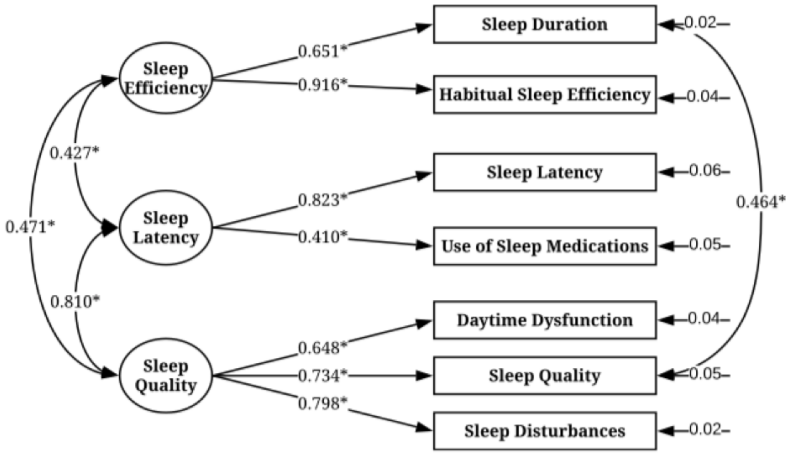

Figure 4.1: PSQI 3-factor model with standardized path coefficients based on Jia et al. Adapted from [116]

4.2.3 Cognitive performance measures

Memory was measured by the Oxford VSTM task. Spatial working memory and item-location binding were assessed through a series of trials containing fractal objects [120]. A schematic of

the task was shown in the following figure. In each trial, subjects viewed 1 or 3 fractal objects, each randomly located on the screen. They were asked to remember both the objects and the locations. A blank screen was then displayed for 1 or 4 seconds, followed by a test array in which two fractals appear. Subjects were then asked to pick out the target object they remembered and drag the object to its displayed location. The VSTM task contained 4 conditions: 1-item with 1-sec delay (1item-1s), 1-item with 4-sec delay (1item-4s), 3-item with 1-sec delay (3item-1s), and 3-item with 4-sec delay (3item-4s). The ***reaction time*** in identifying and localizing the objects as well as the ***accuracy*** of the responses were recorded.

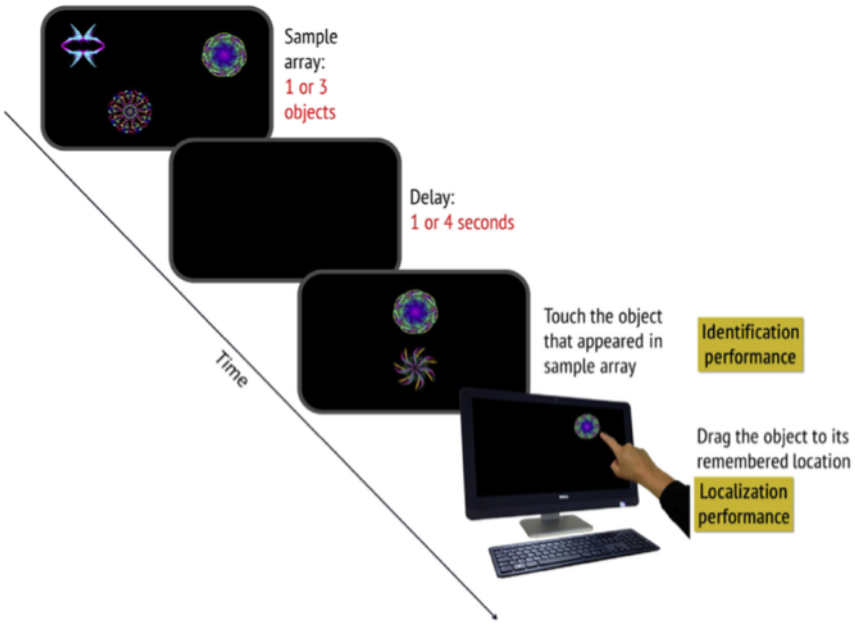

Figure 4.2: Schema of VSTM task. Adapted from [120]

Executive function was measured by the Trail Making Test (TMT) [122] and Stroop color-word test [126]. TMT assessed subjects' visual attention and task switching. The TMT task consisted of two conditions in which the subjects were instructed to connect a sequence of 25 consecutive targets as quickly as possible. One condition included targets with only numbers and the other condition included targets with numbers and letters mixed. The TMT recorded ***reaction time*** and

error rate when they were instructed to trace the targets as quickly as possible. Stroop color-word test assessed subjects' ability to inhibit their automatic response (naming the colors instead of the words). The subjects were instructed to name the color of the printed words as quickly and as accurately as possible. The Stroop test also recorded ***reaction time*** and ***error rate*** when they were instructed to respond as quickly as possible.

4.2.4 Analysis plan

The main analysis examined the group differences in overall sleep quality. To examine such differences, I conducted a one-way ANCOVA to determine the difference between MCI subjects and healthy older adults on the PSQI total scores controlling for sex, age, and BMI. Further exploratory analyses explored the group differences in PSQI factor scores, including perceived sleep quality, sleep efficiency, and sleep latency. To explore the differences of PSQI factor scores between groups, I conducted one-way ANCOVA with Benjamini-Hochberg correction. Effect sizes for ANCOVA were calculated using partial η^2.

The secondary analysis explored the relationship between subjective sleep quality and baseline cognitive performance after controlling for confounding variables (i.e. sex, age, and BMI) for the entire sample. The exploratory analyses firstly explored the relationship between PSQI total scores and baseline cognitive performance. Further exploratory analyses examined the relationship between PSQI factor scores and baseline cognitive performance. Pearson partial correlation tests were implemented. Correlation coefficients were used to evaluate the correlation coefficient to determine the strength of the relationship or the effect sizes.

4.3 Results

4.3.1 Subjective sleep quality outcome (PSQI)

Table 4.2 displayed the results of group comparisons on the PSQI total score and factor scores (i.e. sleep efficiency, sleep latency, and sleep quality) controlling for sex, age, and BMI. The effect of covariate variables were all non-significant. According to the PSQI total score, poor sleepers (defined as PSQI total score > 5) constituted 35% of MCI subjects and 56% of healthy controls.

One-way ANCOVA with Benjamini-Hochberg correction indicated that MCI subjects were not significantly different from their healthy peers in terms of the PSQI total score and the factor scores. The groups did not significantly differ in either the overall subjective sleep quality or any of the factor structures. To further explore the relationship between PSQI total score and MoCA score, Pearson partial correlation was calculated for the entire sample. The results indicated that there was no significant correlation between PSQI total score and MoCA score with Pearson partial correlation $r(31) = 0.17$, $p = 0.322$.

Table 4.2: PSQI total and factor scores for healthy controls and MCI subjects

Variable	MCI (n = 20) mean(*SD*)	Healthy (n = 16) mean(*SD*)	$F(1,34)$	p	partial η^2
PSQI total score	4.95 (2.28)	6.50 (3.63)	0.82	0.373	0.03
Sleep Efficiency (F1)	0.91 (1.00)	1.37 (1.46)	0.44	0.514	0.01
Sleep Latency (F2)	1.07 (0.59)	1.31 (0.71)	0.25	0.621	0.01
Perceived sleep quality (F3)	1.74 (0.76)	2.20 (1.27)	0.60	0.445	0.02

Notes: MCI: Mild Cognitive Impairment. PSQI: Pittsburgh Sleep Quality Index. F1: Factor1, F2: Factor2, F3: Factor3.
Variables that are significantly skewed (Shapiro-test) were log-transformed to normal distribution before conducting t-tests.
Adjusted p-values were calculated based on Benjamini-Hochberg correction.
*p<0.05, **p<0.01, ***p<0.001.

4.3.2 Cognitive performance outcome

Table 4.3 displayed the results of group comparisons on baseline cognitive performance, which further validate that there were differences in terms of baseline cognitive performance between groups. For the majority of task conditions, healthy controls showed better performance (i.e. faster reaction time, higher proportion of correct response) than MCI subjects.

Specifically, (a) for the TMT, in both number and number-letter conditions, healthy controls had faster reaction time than MCI subjects. (b) for the VSTM task, in all 1-item conditions, healthy controls had faster identification reaction time and localization reaction time than MCI subjects. But either identification reaction time or localization reaction time was significantly different for two groups in 3-item conditions. Besides the 1item-1sec condition, healthy controls had a higher

proportion of correct response than MCI subjects in all other conditions. (c) for the Stroop task, healthy controls had significantly faster reaction time than MCI subjects.

Table 4.3: Baseline cognitive performance for healthy controls and MCI subjects

Variable	Condition	MCI (n = 20) mean(*SD*)	Healthy (n = 16) mean(*SD*)	*t*(34)	*p*	Cohen's *d*
TMT RT	number	48.24 (23.79)	34.06 (13.83)	2.27*	**0.030**	0.73
	number-letter	111.86 (69.15)	64.62 (35.48)	2.70*	**0.011**	0.86
VSTM i-RT	1item-1sec	1.44 (0.56)	1.16 (0.22)	2.11*	**0.043**	0.66
	1item-4sec	2.04 (1.50)	1.33 (0.34)	2.17*	**0.039**	0.65
	3item-1sec	2.05 (0.71)	2.05 (0.39)	0.37	0.711	0.00
	3item-4sec	2.33 (0.83)	2.39 (0.67)	-0.45	0.711	0.08
VSTM l-RT	1item-1sec	2.80 (0.93)	2.33 (0.43)	2.18*	**0.037**	0.65
	1item-4sec	3.47 (1.74)	2.57 (0.51)	2.18*	**0.037**	0.70
	3item-1sec	3.62 (1.39)	3.35 (0.63)	0.44	0.662	0.25
	3item-4sec	3.80 (1.26)	3.72 (0.86)	0.01	0.998	0.07
VSTM PCR	1item-1sec	97.94% (0.04)	99.38% (0.02)	-1.60	0.121	0.46
	1item-4sec	91.59% (0.09)	97.08% I(0.05)	-2.36*	**0.025**	0.75
	3item-1sec	80.79% (0.11)	87.08% (0.06)	-2.23*	**0.033**	0.71
	3item-4sec	74.29% (0.09)	82.29% (0.09)	-2.69*	**0.011**	0.89
Stroop RT	word-color	115.68 (37.55)	96.43 (23.57)	2.08*	**0.045**	0.61

Notes: MCI: Mild Cognitive Impairment. PSQI: Pittsburgh Sleep Quality Index. TMT: Trail Making Task. VSTM: Visual Short-Term Memory. RT: Reaction Time. i-RT: identification Reaction Time. l-RT: localization Reaction Time. PCR: Proportion of Correct Response.
Variables that are significantly skewed (Shapiro-test) were log-transformed to normal distribution before conducting t-tests.
Adjusted *p*-values were calculated based on Benjamini-Hochberg correction.
*p<0.05, **p<0.01, ***p<0.001.

4.3.3 Correlation between subjective sleep quality and baseline cognitive performance

To further explore the relationship between subjective sleep quality and baseline cognitive performance, Pearson partial correlations were calculated for the entire sample. The relationship between subjective sleep quality and baseline cognitive performance varies between tasks. Table 4.4 displayed the results of the Pearson partial correlations between subjective sleep quality and baseline cognitive performance.

For the TMT task, results showed that the factor sleep efficiency significantly correlated with TMT reaction time (number-letter condition) after controlling age, BMI and MoCA score (Pearson

partial correlation $r(31) = 0.36$, $p = 0.039$). It suggested that subjects with better sleep efficiency tended to have faster reaction time in TMT.

For the Oxford VSTM task, results showed that for both 3-item conditions, proportion of correct response was significantly related to PSQI total score, factor sleep latency and factor sleep quality. Specifically, for the 3-item with 1-second delay condition, the analyses indicated that after controlling for age, BMI and MoCA score, higher proportions of correct response significantly correlated with better overall PSQI measured sleep quality (Pearson partial correlation $r(31) = -0.40$, $p = 0.022$), shorter sleep latency (Pearson partial correlation $r(31) = -0.35$, $p = 0.049$), and better perceived sleep quality (Pearson partial correlation $r(31) = -0.34$, $p = 0.049$). For the 3-item 4-second delay condition, higher proportions of correct response was significantly correlated with better overall PSQI measured sleep quality (Pearson partial correlation $r(31) = -0.62$, $p < 0.001$), shorter sleep latency (Pearson partial correlation $r(31) = -0.45$, $p = 0.008$), and better perceived sleep quality (Pearson partial correlation $r(31) = -0.71$, $p < 0.001$).

The analysis results showed no significant correlations between Stroop reaction time and the PSQI total or factor scores.

Table 4.4: Partial correlations between PSQI total/factor scores and baseline cognitive performance

Variable	Condition	PSQI total score	Sleep efficiency	Sleep latency	Perceived sleep quality
TMT RT	Number	0.27	0.29	0.07	0.09
	Number-Letter	0.25	**0.36***	0.05	-0.01
VSTM PCR	1item-1sec	-0.30	-0.25	-0.29	-0.13
	1item-4sec	-0.17	-0.11	-0.15	-0.18
	3item-1sec	**-0.40***	-0.20	**-0.35***	**-0.34***
	3item-4sec	**-0.62*****	-0.25	**-0.45****	**-0.71*****
Stroop RT	word-color	-0.01	-0.08	-0.03	-0.03

Notes: PSQI: Pittsburgh Sleep Quality Index. MCI: Mild Cognitive Impairment. TMT: Trail Making Task. VSTM: Visual Short-Term Memory. RT: Reaction Time. PCR: Proportion of Correct Response.
Variables that are significantly skewed (Shapiro-test) were log-transformed to normal distribution before conducting t-tests.
Partial correlations are controlled for age, BMI and MoCA.
*p<0.05, **p<0.01, ***p<0.001.

4.4 Discussion

In this study, the results demonstrated that the healthy group consisted of more poor sleepers (defined as PSQI total score > 5) than the MCI group. In contrast with our hypothesis, our findings suggested that MCI subjects were not statistically significantly different from their normal-aging peers in terms of their self-reported sleep quality.

One possible reason for the difference in our findings is that self-report measures on sleep quality showed great variabilities for subjects, especially on older adults with cognitive impairment. Most studies that found MCI subjects reported more sleep disturbances than their normal-aging peers utilized large community-based studies or longitudinal population studies [77, 78]. Therefore, it is possible that the small sample size of our study is not able to generalize the report variabilities. On the other hand, our data showed similar results to clinical studies with small sample sizes [134, 135]. One of the studies further stated that objective measures such as PSG might be a more reliable measure for evaluating sleep disturbances especially in MCI subjects [135].

Additionally, the differences in self-report may be in part due to the experience that subjects choose to emphasize. Clinical studies reported subjects varying a lot when reporting their sleep behaviors during their visit. For example, subjects might be largely affected by their most recent night's sleep, or they will report more general impressions on their sleep quality of the past week. This might especially be true for MCI subjects considering the inaccuracies in recalling the details of their sleep [139]. Thus, measuring sleep quality over a time period and using additional caregiver reports could minimize the effect of the variability in future studies.

Another possible reason for the difference in our study might be related to subtypes of MCI. Studies further comparing MCI subtypes, amnestic MCI (aMCI) and non-amnestic MCI (naMCI) showed the differences between levels of sleep disturbances. The results indicated that aMCI subjects experienced more disturbed sleep than naMCI subjects [134]. Therefore, the differences in sleep disturbances of MCI subjects might be related to differences in the underlying pathology and disease trajectory for those MCI subtypes [134]. Therefore, additional clinical interviews and diagnoses that help further identifying MCI subtypes are needed to verify these results.

Other findings concern the relationship we observed between subjective sleep quality and baseline cognitive performance. The present study showed that in MCI subjects and their normal-aging peers, overall better sleep quality, shorter sleep latency and better subjective perception of sleep quality were significantly correlated with higher accuracy in more complicated task conditions (3 items) of the VSTM task. Furthermore, better sleep efficiency was found to be significantly correlated with faster reaction time in the number-letter condition of TMT task. These results were similar to previous studies examining the relationship between sleep disturbances and cognition [16, 44, 53].

While several studies have found consistent results regarding sleep disturbances and impaired cognitive performance in normal-aging adults and AD subjects, few have focused on MCI populations. In addition, most previous studies used relatively simple tasks such as word recall or recognition to assess cognitive performance, while in the current study we used a more intensive memory task that targeted not only short-term memory but also spatial memory. The results suggested that the impairment in spatial working memory might be related to sleep disturbances for both MCI subjects and their normal-aging peers.

Our study also found that low sleep efficiency might lead to impairments in executive tasks such as TMT, which was in agreement with previous findings [140, 141]. On the other hand, subjective perceptions of sleep quality and sleep latency were more associated with accuracy in the memory performance. The role of sleep disturbances in cognition still needs more exploration, especially with older adults. The results of the current study suggested that it is worth viewing sleep disturbances with different factors as those factors might be linked to different perspectives of cognition.

There are several strengths of the present study. First, we used a well-validated sleep questionnaire in the United States population which is also reliable in capturing sleep disturbances in older adults [116, 142]. Second, we tried to capture sleep disturbances not only using the global score but also measuring different factors [116]. Last but not least, we conducted a battery of neuropsychological tasks including an intensive memory task. However, several limitations should

also be noted. First, the interpretation of our results is limited by the small sample size of the present study, and further studies with larger sample size are needed to verify the results. Second, although we tried to match subjects in terms of their age, sex and BMI, there might still be other unmeasured confounding factors that affect sleep disturbances, such as sleep environment [143], and pain, anxiety and other medical conditions [144]. Third, further clinical measures and diagnoses are needed to better categorize and identify potential subtypes of MCI subjects since such characteristics might affect the degree of sleep disturbances. Last, the self-report measure on sleep quality might be affected by individual biases. This is particularly noteworthy since we have MCI subjects who potentially interpret sleep disturbances in a different manner. Adding caregiver reports as well as objective measures would definitely benefit in investigating the relationship between sleep disturbances and cognition.

In summary, the main findings showed that there were no significant differences in subjective sleep measures between groups. Building on such findings, the study suggested that objective sleep measures might be potentially more reliable to MCI individuals. Therefore, future studies using objective sleep measures should be applied to further examine sleep disturbances in MCI. The present study has also found a few notable relations between sleep disturbances and cognitive performance in MCI subjects and their normal-aging peers. Those relationships indicated that distinct sleep factors might be associated with cognitive performance. Further studies should explore key sleep factors that might relate to cognitive impairment for MCI subjects using more detailed psychological assessments. Since sleep disturbance is such a common neuropsychiatric symptom related to cognitive impairment, further investigation of sleep characteristics might be able to better explain the relationships and contribute to potential early diagnosis or intervention.

5. OBJECTIVE NAPPING QUALITY IN MCI & HEALTHY OLDER ADULTS

5.1 Introduction

As sleeping becomes a significant challenge for older adults, including both MCI and healthy older adults, the frequency of napping was consistently found to be increased [90]. In general, one in four older adults reported intentionally napping daily [89]. The average nap frequency in older adults is at least once per week with an average duration between 23.3 to 45.0 minutes per day [89].

There is a dearth of research investigating napping quality in MCI subjects, especially studies using objective measures such as the PSG system. Available research directly comparing MCI and AD subjects pointed out that there was no significant difference between the two groups in terms of the PSG parameters [83]. For these reasons, we will also review research in AD subjects as a reference. Previous studies reported that AD subjects experience significantly worse napping quality when compared to their normal-aging peers [100, 101]. In particular, when compared to healthy older adults, AD subjects expressed longer PSG sleep latency, decreased total sleep duration, and lower PSG sleep efficiency. It is likely that MCI subjects would experience worsened napping quality compared to healthy controls just like AD subjects. Therefore, the current study will explore the objective napping quality in MCI subjects and their normal-aging peers.

A growing body of studies investigated the association between sleep disturbance and cognitive performance, however, less attention was paid on napping, especially for MCI subjects. It is known that sleep disturbance affects reaction time, attention, mood, cognitive performance and motor functions for both MCI subjects and their normal-aging peers [47, 136]. Moreover, napping was found to produce similar sleep patterns just like nocturnal sleep [97]. In other words, naps can have a similar impact on cognitive performance as nocturnal sleep due to the fact that they are generating similar patterns of SWS and REM sleep [97].

The waste-clearance theory states that the restorative function of sleep might be a consequence

of removing potentially neurotoxic waste products accumulated during wakefulness [62]. This theory aims to explain why a lack of sleep impairs brain function. It further predicts that sleep disturbances might lead to cognitive impairment [62, 66, 67]. Aligning with the waste-clearance theory of sleep, napping was also proposed to be effective in cleaning waste products including β-amyloid [101]. Thus, disturbed napping might lead to cognitive impairment just like nocturnal sleep. In other words, napping might also be a highly correlated factor of cognitive impairment.

In addition to the biological mechanisms, age-related changes in sleep parameters have also been reported, which suggested that the reduction of SWS was associated with sleep disturbances [113, 101]. Those studies further supported the notion that SWS might be essential for the consolidation of hippocampal-dependent memory [50]. During SWS, similar firing patterns in wakefulness appeared to be replayed to enhance the consolidation of tasks and experiences learned during wakefulness [50]. Therefore, the declines in SWS appear to parallel with levels of cognitive decline. As napping was found to generate similar patterns of SWS as nocturnal sleep, it might be the case that napping in older adults might also relate to the reduction of SWS and further exacerbate cognitive impairment.

Research on napping in older adults (both MCI and healthy older adults) has been quite limited and data has typically been collected through surveys and interviews. Those measures, however, might not be able to fully capture the characteristics of napping. For example, self-reports might be largely affected by the subjects most recent sleep. This might especially be true for MCI subjects considering the inaccuracies in recalling the details of their sleep [134]. To date, no study has investigated the association between objective napping quality and cognitive performance in MCI subjects. Thus, there is a gap in our knowledge of napping quality in MCI subjects in comparison to their normal-aging peers. As MCI subjects were found to have similar sleep disturbances observed in AD [85], further research offers the possibility for early diagnosis and potential treatment with the aim of delaying or preventing the progression of AD.

The main purpose of this study is to compare the amount of SWS between MCI subjects and their normal-aging peers. I hypothesize that ***MCI subjects would experience less SWS than their***

normal-aging peers. Further exploratory analysis would compare other napping parameters (i.e. stage1%, stage2%, REM%, sleep spindle, k-complex) between MCI subjects and healthy controls. As a secondary aim, I will investigate the relationship between objective napping quality and cognitive functioning in both groups. In particular, I hypothesize that ***better objective napping quality would relate to better baseline cognitive performance***.

5.2 Methods

This study included objective daytime sleep measurements data and baseline cognitive measurement data from a project which investigated the effects of daytime sleep in MCI subjects and their normal-aging peers. More information was provided in the general methods section (Section 3).

5.2.1 Sample

Out of the initially measured subjects (N = 37), 36 of them had complete data that could be used for further analysis (1 subject was excluded due to incomplete data from PSG recording). All subjects (N = 36) were recruited from College Station - Bryan area, TX. Subjects were classified into either MCI or healthy older adults groups based on their MoCA scores. For those 36 subjects included in analysis, 20 were from the MCI group (average age = 73.73; SD = 6.12) and 16 were from the healthy group (average age = 68.67; SD = 6.99). The basic demographic characteristics of subjects were compared across groups.

Table 5.1 displayed demographic information for the sample. There were no significant differences between subject groups in terms of sex and BMI. There were significant differences between groups in their age (p = 0.045). Therefore, due to the MCI being older, age was treated as a control variable for further correlation analysis. As expected, there were significant differences between groups on their MoCA scores ($p < 0.001$). MCI subjects had significantly lower MoCA scores than their normal-aging peers, which indicated that they tended to experience more cognitive impairment.

Table 5.1: Demographic characteristics by subject group

Variable	MCI (n = 20) n(%) | mean(*SD*)	Healthy (n = 16) n(%) | mean(*SD*)	Chi-square | *t*-test	*p*	Effect Size
Sex			$x^2(1) = 3.11$	0.080	$\phi_{Cramer} = 0.50$
Female	8 (40%)	12 (75%)			
Male	12 (60%)	4 (25%)			
Age	73.73 (6.12)	68.67 (6.99)	$t(34) = -2.21$*	0.045	$d = 0.71$
BMI	27.07 (7.46)	27.64 (8.80)	$t(34) = 0.21$	0.962	$d = 0.07$
MoCA	22.70 (2.13)	26.88 (1.36)	$t(34) = 7.13$***	<0.001	$d = 2.34$

Notes: MCI: Mild Cognitive Impairment. BMI: Body Mass Index in units of kg/m^2. MoCA: Montreal Cognitive Assessment.
*p<0.05, **p<0.01, ***p<0.001.

5.2.2 Objective napping measures

PSG with 30s epochs will be recorded for subjects using the Compumedics (Victoria, Australia) system during a napping session (up to 120 min). EEG will be recorded from 11 scale sites (Fp1, Fp2, Fz, F3, F4, C3, Cz, C4, O1, Oz, and O2) being placed according to the 10-20 system. Additionally, 3 chin EMG channels, 2 EOG channels, 2 ECG/EKG channels, and 2 respiration bands will be applied to extend the stability of the measurement.

5.2.3 Cognitive performance measures

Memory was measured by the Oxford VSTM task. Spatial working memory and item-location binding were assessed through a series of trials containing fractal objects [120]. A schematic of the task was shown in the following figure. In each trial, subjects viewed 1 or 3 fractal objects, each randomly located on the screen. They were asked to remember both objects and the locations. A blank screen was then displayed for 1 or 4 seconds, followed by a test array in which two fractals appear. Subjects were then asked to pick out the target object they remembered and drag the object to its displayed location. The VSTM task contained 4 conditions: 1-item with 1-sec delay (1item-1s), 1-item with 4-sec delay (1item-4s), 3-item with 1-sec delay (3item-1s), and 3-item with 4-sec delay (3item-4s). Subjects' ***reaction time*** in identifying and localizing the objects as well as the ***accuracy*** of the responses were recorded.

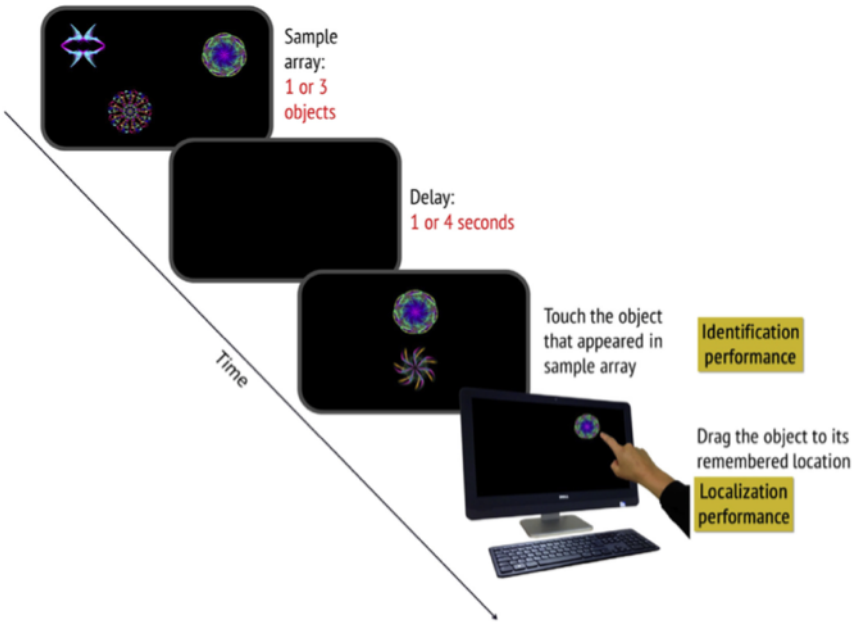

Figure 5.1: Schema of VSTM task. Adapted from [120]

Executive function was measured by the Trail Making Test (TMT) [122] and Stroop color-word test [126]. TMT assessed subjects' visual attention and task switching. The TMT task consisted of two conditions in which the subjects were instructed to connect a sequence of 25 consecutive targets as quickly as possible. One condition included targets with only numbers and the other condition included targets with numbers and letters mixed. The TMT recorded subjects' ***reaction time*** and ***error rate*** when they were instructed to trace the targets as quickly as possible. Stroop color-word test assessed subjects' ability to inhibit their automatic response (naming the colors instead of the words). The subjects were instructed to name the color of the printed words as quickly and as accurately as possible. The Stroop test also recorded subjects' ***reaction time*** and ***error rate*** when they were instructed to respond as quickly as possible.

5.2.4 Analysis plan

The main analysis examined the group differences in SWS. I conducted a one-way ANCOVA to determine the difference between MCI subjects and healthy older adults on the SWS activity controlling for sex, age, and BMI. Further exploratory analyses explored the group differences in

additional PSG measured napping parameters including PSG napping duration, PSG percentage of sleep stages, and the number of sleep spindles and k-complexes per minute in sleep stage 2. To examine those parameters of napping quality, I conducted one-way ANCOVA with Benjamini-Hochberg correction to compare specific differences between groups controlling for sex, age, and BMI. Effect sizes for ANCOVA were calculated using partial η^2.

The secondary analyses focused on examining the relationship between PSG napping quality and baseline cognitive performance (i.e. spatial working memory, TMT, and Stroop test) after controlling for age, BMI and MoCA scores for the entire sample. The Pearson correlation tests were conducted for PSG napping parameters and baseline performance scores. Correlation coefficients were used to evaluate the correlation coefficient to determine the strength of the relationship or the effect sizes.

5.3 Results

5.3.1 Objective napping quality outcome (PSG parameters)

The results showed that MCI subjects had significantly lower percentages of SWS ($F(1, 34) = 5.73$, $p = 0.023$) compared with healthy controls with a medium effect size (partial $\eta^2 = 0.15$).

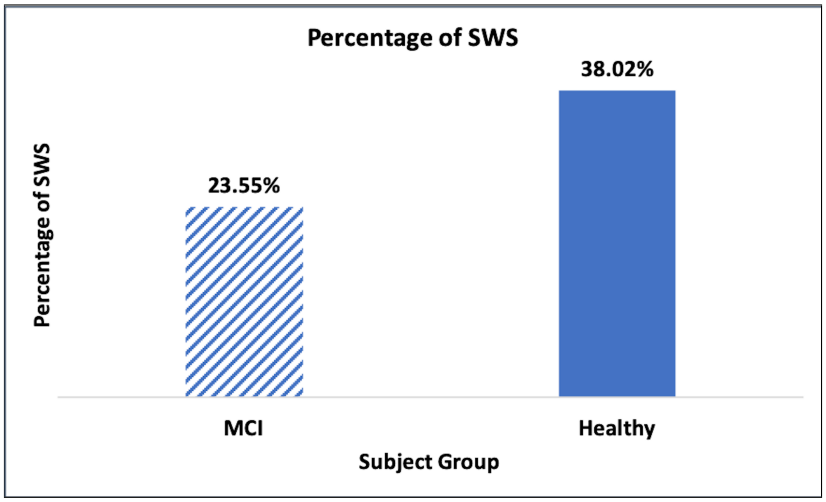

Figure 5.2: Percentage of SWS in MCI subjects and healthy controls

Table 5.2 displayed the comparison of PSG measures between MCI subjects and their normal-aging peers controlling for sex, age, and BMI. The effect of covariate variables were all non-significant. The ANCOVA with Benjamini-Hochberg correction yielded no significant group differences in PSG parameters. However, the results yielded potential differences in those PSG measures when comparing MCI subjects to their normal-aging peers. For instance, MCI subjects potentially experienced higher percentages of stage 1 sleep than healthy controls ($F(1,34) = 3.49$, $p = 0.071$, *adjusted* = 0.144) with a medium effect size (partial $\eta^2 = 0.10$). Additionally, MCI subjects potentially expressed less sleep spindles per minute in stage 2 sleep than healthy controls ($F(1,34) = 4.73$, $p = 0.037$, *adjusted* = 0.144) with a medium effect size (partial $\eta^2 = 0.13$).

Table 5.2: PSG parameters in healthy controls and MCI subjects

Variable	MCI (n = 20) n(%) | mean(*SD*)	Healthy (n = 16) n(%) | mean(*SD*)	$F(1,34)$	p	Adjusted p	partial η^2
SWS (%)	23.55% (0.17)	38.02% (0.21)	5.73	**0.023**	–	0.15
TST (min)	107.72 (31.00)	116.31 (41.28)	1.67	0.206	0.309	0.05
Stage 1 (%)	34.75% (0.19)	23.13% (0.21)	3.49	0.071	0.144	0.10
Stage 2 (%)	24.88% (0.12)	28.51% (0.15)	0.97	0.332	0.398	0.03
REM (%)	11.94% (0.14)	6.74% (0.09)	0.118	0.734	0.734	0.00
# of k-complex/min	1.06 (0.39)	1.23 (0.35)	3.47	0.072	0.144	0.10
# of spindle/min	0.90 (0.31)	1.16 (0.38)	4.73	**0.037**	0.144	0.13

Notes: PSG: Polysomnography. MCI: Mild Cognitive Impairment. TST: Total Sleep Time. SWS: Slow-Wave Sleep. REM: Rapid Eye Movement.
Variables that are significantly skewed (Shapiro-test) were log-transformed to normal distribution before conducting t-tests.
*p<0.05, **p<0.01, ***p<0.001.

5.3.2 Correlation between objective napping quality and baseline cognitive performance

To examine the relationship between objective napping quality and baseline cognitive performance, Pearson partial correlations were calculated for the entire sample. The relationship between objective napping quality and baseline cognitive performance varies between tasks. Table 5.3 displayed the results of Pearson partial correlations between objective napping parameters and baseline cognitive performance.

For both TMT and Stroop tasks, the analysis results showed no significant correlations between task reaction time and objective napping parameters.

For the Oxford VSTM task, results showed that for 1-item conditions, both identification reaction time and localization reaction time significantly related to TST (min), percentage of sleep stage 2 and SWS. Specifically, the analysis indicated that after controlling for age, BMI and MoCA score, longer TST (Pearson partial correlation $r(31) = -0.37$, $p = 0.035$) and higher percentage of sleep stage 2 (Pearson partial correlation $r(31) = -0.33$, $p = 0.059$) significantly related to faster identification reaction time for the 1 item with 4-second delay condition. After controlling for age, BMI, and MoCA score, longer TST also significantly related to faster localization reaction time for the 1 item with 4-second condition (Pearson partial correlation $r(31) = -0.36$, $p = 0.043$). In addition, the proportion of correct responses for 3-item conditions were found to be correlated with the percentage of sleep stage 1 and the percentage of SWS. In particular, the analysis indicated that after controlling for age, BMI and MoCA score, a higher percentage of sleep stage 1 significantly correlated with lower proportions of correct responses for the 3item-1second condition (Pearson partial correlation $r(31) = -0.34$, $p = 0.050$). A higher percentage of SWS significantly correlated with a higher proportion of correct responses for the 3item-1second condition (Pearson partial correlation $r(31) = 0.36$, $p = 0.040$). A higher percentage of sleep stage 1 significantly correlated with a lower proportion of correct responses for the 3item-4second condition (Pearson partial correlation $r(31) = -0.37$, $p = 0.032$). Additionally, a higher percentage of SWS significantly correlated with a higher proportion of correct responses for the 3item-4second condition (Pearson partial correlation $r(31) = 0.44$, $p = 0.010$).

Table 5.3: Partial correlations between PSG parameters and baseline cognitive performance

Variable	Condition	TST	Stage1 (%)	Stage2 (%)	SWS (%)
TMT RT	Number	-0.03	0.08	0.07	0.10
	Number-Letter	-0.13	0.07	0.26	-0.07
VSTM i-RT	1item-1sec	-0.05	-0.01	-0.22	-0.31
	1item-4sec	**-0.37***	-0.08	**-0.33***	-0.22
	3item-1sec	-0.13	-0.10	-0.07	-0.27
	3item-4sec	0.02	-0.06	-0.03	-0.30
VSTM l-RT	1item-1sec	-0.09	-0.07	0.14	-0.31
	1item-4sec	**-0.36***	-0.14	-0.30	-0.13
	3item-1sec	-0.13	-0.22	0.14	-0.30
	3item-4sec	0.03	-0.19	0.08	-0.30
VSTM PCR	1item-1sec	0.10	-0.18	0.07	-0.01
	1item-4sec	-0.02	-0.10	0.03	-0.02
	3item-1sec	0.17	**-0.34***	-0.04	**0.36***
	3item-4sec	0.06	**-0.37***	-0.20	**0.44****
Stroop RT	word-color	-0.07	0.26	-0.09	0.06

Notes: PSG: Polysomnography. TST: Total Sleep Time. SWS: Slow-Wave Sleep.
TMT: Trail Making Task. VSTM: Visual Short-Term Memory.
RT: Reaction Time. i-RT: identification Reaction Time. l-RT: localization Reaction Time. PCR: Proportion of Correct Response.
Variables that are significantly skewed (Shapiro-test) were log-transformed to normal distribution before conducting t-tests.
*p<0.05, **p<0.01, ***p<0.001.

5.4 Discussion

The main goal of the present study was to investigate whether sleep patterns, especially SWS, were different in MCI subjects and their normal-aging peers. The results demonstrated that MCI subjects experienced significantly lower percentages of SWS when compared to healthy controls. Such results were consistent with previous studies in MCI nocturnal sleep [24, 82, 85] and AD napping [113, 101] and with claims that the cognitive impairment in MCI subjects might be linked with the loss of SWS [145].

Given the importance of SWS in memory consolidation [47], a related question that has been under investigation was whether the SWS declines in older adults may account for the memory declines. Previous studies showed that the declines in SWS appear to be parallel with the cognitive declines during nocturnal sleep [146]. The current study further supported that the positive relationship between the percentage of SWS and memory in MCI samples was also maintained during

napping. In other words, the cognitive impairments in MCI subjects compared to their normal-aging peers might be partially due to the SWS declines during their naps or the inefficient sleep architecture of a nap is an accurate reflection of underlying issues in their sleep more generally. The findings of declined SWS in MCI subjects suggested that further research is needed to examine the differences in SWS between MCI subjects and the healthy controls and the underlying mechanisms.

Further exploratory analyses indicated that even in light sleep stages, MCI subjects were potentially experiencing disturbed sleep. Such sleep disturbances included higher percentage of stage1 sleep and lower number of sleep spindles per minute in stage 2 sleep. Even though such differences were not statistically significant, the results might still contribute to the discussion that disturbed sleep might be linked with cognitive impairments in MCI subjects.

The present results found that MCI subjects expressed higher percentages of stage1 sleep than the healthy controls, which agreed with previous studies that reported on MCI nocturnal sleep patterns [24, 82, 85]. Apparently, it was not the percentage of stage1 sleep that solely explained the relationship between sleep disturbances and cognitive impairment. The combination of increases in stage1 sleep and decreases in SWS was powerful in explaining the potential association between sleep disturbances and cognitive impairments.

Our data revealed a decrease in the number of sleep spindles in stage 2 sleep in MCI subjects when compared to their normal-aging peers. Researchers often correlated sleep spindles with cognitive functioning and memory [37]. Previous studies believe that when spindles occur, the brain disconnects from outside sensory input and begins the process of memory consolidation [37]. Schabus and colleagues combined EEG and functional MRI measures and further demonstrated that sleep spindles recruited various cortical areas, including the hippocampus [147]. Therefore, it is very likely that spindles play an important role in memory consolidation. This result was also particularly interesting because recent studies showed that the hippocampus is one of the earliest brain regions that is affected in AD [148, 149]. Thus, the deduction in spindles might contribute to explain the relationship between sleep disturbances and memory declines in MCI and AD subjects.

The secondary analyses focused on examining the relationship between PSG napping parameters and baseline cognitive performance. The present study found that for the VSTM 1item-4second condition, higher percentages of stage 2 sleep and longer TST were associated with faster identification reaction time. Longer TST was also related to faster localization reaction time. Furthermore, higher percentages of SWS related to a higher proportion of correct response in 3item conditions. While, higher percentages of stage1 sleep was associated with a lower proportion of correct response.

It has been known that NREM sleep, primarily SWS, was beneficial for hippocampus-dependent memory consolidation [150, 151]. Previous studies further reported SWS to be positively associated with spatial memory performance [151, 152]. Consistent with previous findings we found that higher percentages of SWS were associated with better performance in the spatial memory task. Both animal [153] and human [154] studies indicated that spatial memory would be largely impaired following hippocampal dysfunctions. Additionally, MCI subjects were found to experience similar patterns of hippocampal dysfunction like AD subjects [155]. Therefore, the present findings supported the view that SWS might play a specific role in spatial memory as well.

The present findings demonstrated that the percentage of stage 2 sleep was positively associated with reaction time on the memory task. Smith & MacNeill [156] reported that disturbed stage 2 sleep was associated with impaired cognitive processing speed in college students. Thus, the current results indicated that disturbances in sleep stage 2 might relate to impairments in cognitive processing speed for older adults as well. Important characteristics for stage 2 sleep are sleep spindle and k-complex, and the functions of stage 2 sleep were always discussed under those parameters. Due to the limitation of the sample size, the current study was not able to identify the relationship between sleep spindle or k-complex with cognitive processing speed. Therefore, further studies are needed to explore the relationship between stage 2 sleep and cognitive processing speed (i.e. for a spatial memory task) using sleep spindle and k-complexes.

There were several strengths of the present study. First, we tried to capture napping parameters and the relationship between those parameters and cognitive performance using the gold standard

PSG system. Second, we were one of the few studies comparing PSG parameters in MCI subjects with their normal-aging peers. Last but not least, we conducted a battery of neuropsychological tasks including an intensive memory task. However, several limitations should also be noted. First, although the subjects were pre-screened for sleep disorders, the screening was based on self-report and medical history but not on clinical interviews and diagnosis. Therefore, it is possible that older adults, especially the subjects with higher BMI, would potentially experience sleep disorders such as sleep apnea. Such sleep disorders were associated with SWS declines and other disturbances of sleep. Therefore, further clinical diagnosis or interviews might be helpful in categorizing the subjects and a better understanding of the relationship between sleep and cognitive decline. Another limitation is in regard to the minimal information available on PSG parameters. The present study followed the AASM scoring rules in analyzing PSG parameters and determining sleep stages. Further studies using more advanced analysis such as power analysis would contribute to examine SWS fragmentation (i.e. amplitude of SWS) in relation to cognitive impairment. Last, the interpretation of our results is limited by the small sample size of the present study, and further studies with larger sample size are needed to verify the results.

In summary, PSG parameters, and in particular measures of SWS, were consistently found to be reduced in MCI subjects. These results indicated that sleep patterns might be disrupted in parallel with cognitive impairment. Furthermore, the present findings indicated that a higher percentage of SWS resulted in better performance in the spatial memory task. In combination with prior brain imaging studies, our data further provides support that disturbed sleep, especially SWS, might be an indication for the hippocampal dysfunction in early cognitive impairment stages. We are hopeful the current findings would contribute to the early diagnosis of MCI, and will ultimately provide useful links to AD biomarkers.

6. IMPROVING COGNITIVE PERFORMANCE BEFORE AND AFTER NAPPING IN MCI & HEALTHY OLDER ADULTS

6.1 Introduction

The post-nap improvements in alertness, mood, and cognitive performance have been well established in healthy adults [90]. For instance, naps from 5 minutes to 2 hours have shown to be beneficial to cognition [157]. A short nap (10-30 minutes) showed almost immediate benefits and can last up to 3 hours for the following psychomotor tasks [158]. Moreover, other researchers also demonstrated that in addition to the improvements in reaction speed and accuracy in cognitive tasks, subjects also experienced improved subjective feelings such as increased alertness and decreased fatigue [159].

Even for older adults or adults with MCI, the majority of studies found napping has immediate benefits in improving cognitive performance. For instance, results showed that MCI subjects had improved performance in the post-nap recognition tasks compared to their pre-nap performance [10]. Schneider and colleagues measured a 90-min nap for MCI subjects and observed significant improvements in the memory and psychomotor speed tasks after their naps [105]. Nevertheless, the role of napping in cognitive improvements was still under debate. Cross and colleagues compared MCI subjects performance before and after napping, they found excessive napping (over 2 hours per day) might have negative effects on post-nap reaction speeds for MCI subjects [11].

To the best of my knowledge, no study has examined whether the immediate cognitive changes in MCI subjects and healthy older adults relate to objective napping parameters. However, previous studies reported a positive correlation between nocturnal sleep quality and cognitive improvements. For instance, Kim and colleagues [82] found that healthy older adults had greater post-sleep improvements in the visual memory task and delayed verbal recall tasks than MCI subjects. They further concluded that better sleep quality in healthy older adults might be associated with greater improvements in cognition.

There are multiple possible explanations for the role of napping in such immediate effects on cognitive performance. First, aligning with the theories about the mechanism of sleep, napping has been found to result in helping cleaning β-myloid just like nocturnal sleep. Therefore, it would be beneficial in improving cognitive functions. On the other hand, excessive daytime napping has been linked to more disturbances in nocturnal sleep and such disturbed sleep could result in more deposition of β-amyloid, which will lead to further cognitive impairments. Thus, excessive napping might be associated with impaired cognitive functioning. Second, excessive napping was found to be associated with medical conditions such as type-II diabetes [110], higher incidence of cardiovascular disease [111], and greater risk of obesity [112]. Those medical conditions were highly correlated with impaired cognitive functioning [101]. Thus, excessive napping was hypothesized to affect cognition through those medical conditions.

One of the limitations, as well as a possible explanation of the inconsistency between previous studies, was that studies typically relied on subjective reports (i.e. survey, interview) when measuring napping quality. That might limit the power of describing the characteristics of napping. The degree of benefits from a nap might be influenced by characteristics of napping such as duration of the nap and sleep stages generated by the nap. Such characteristics would only be fully captured using objective measures like a PSG system. To the best of the authors knowledge, for MCI subjects, no study has conducted a detailed examination of the relationship between changes in cognitive performance and napping quality using PSG parameters. Further investigation could help explain the effects of napping in MCI subjects, as well as provide possible intervention ideas for preventing the progression of AD.

The main purpose of this study is to compare the changes in cognitive performance between MCI subjects and their normal-aging peers. I hypothesize that ***MCI subjects would have less improvements in cognitive tasks than their normal-aging peers***. As a secondary aim, I will further examine the relationship between objective napping quality and changes in cognitive performance. In particular, I hypothesize that ***better objective napping quality would relate to larger improvements in post-nap cognitive performance***. Although the study was not designed to directly test

the effects of napping, looking at such correlations would help to explore potential links between PSG napping parameters and cognitive improvements.

6.2 Methods

This study included objective daytime sleep measurement data and both pre- and post- cognitive measurements data from a project which investigated the effects of daytime sleep in MCI subjects and their normal-aging peers. More information will be provided in the general methods section (Section 3).

6.2.1 Sample

Out of the initially measured subjects (N = 37), 36 of them had complete data that could be used for further analysis (1 subject was excluded due to incomplete data from PSG recording). All subjects (N = 36) were recruited from College Station - Bryan area, TX. Subjects were classified into either MCI or healthy older adults groups based on their MoCA scores. For those 36 subjects included in analysis, 20 were from the MCI group (average age = 73.73; SD = 6.12) and 16 were from the healthy group (average age = 68.67; SD = 6.99). The basic demographic characteristics of subjects were compared across groups.

Table 6.1 displayed demographic information for the sample. There were no significant differences between subject groups in terms of sex and BMI. There were significant differences between groups in their age ($p = 0.045$). Therefore, due to the MCI being older, age was treated as a control variable for further correlation analysis. As expected, there were significant differences between groups on their MoCA scores ($p < 0.001$). MCI subjects had significantly lower MoCA scores than their normal-aging peers, which indicated that they tended to experience more cognitive impairment.

Table 6.1: Demographic characteristics by subject group

Variable	MCI (n = 20) n(%) | mean(*SD*)	Healthy (n = 16) n(%) | mean(*SD*)	Chi-square | *t*-test	*p*	Effect Size
Sex			$x^2(1) = 3.11$	0.080	$\phi_{Cramer} = 0.50$
Female	8 (40%)	12 (75%)			
Male	12 (60%)	4 (25%)			
Age	73.73 (6.12)	68.67 (6.99)	$t(34) = -2.21$*	0.045	$d = 0.71$
BMI	27.07 (7.46)	27.64 (8.80)	$t(34) = 0.21$	0.962	$d = 0.07$
MoCA	22.70 (2.13)	26.88 (1.36)	$t(34) = 7.13$***	<0.001	$d = 2.34$

Notes: MCI: Mild Cognitive Impairment. BMI: Body Mass Index in units of kg/m^2. MoCA: Montreal Cognitive Assessment.
*p<0.05, **p<0.01, ***p<0.001.

6.2.2 Objective napping measures

PSG with 30s epochs will be recorded for subjects using the Compumedics (Victoria, Australia) system during a napping session (up to 120 min). EEG will be recorded from 11 scale sites (Fp1, Fp2, Fz, F3, F4, C3, Cz, C4, O1, Oz, and O2) being placed according to the 10-20 system. Additionally, 3 chin EMG channels, 2 EOG channels, 2 ECG/EKG channels, and 2 respiration bands will be applied to extend the stability of the measurement.

6.2.3 Cognitive performance measures

Memory was measured by the Oxford VSTM task. Spatial working memory and item-location binding were assessed through a series of trials containing fractal objects [120]. A schematic of the task was shown in the following figure. In each trial, subjects viewed 1 or 3 fractal objects, each randomly located on the screen. They were asked to remember both objects and the locations. A blank screen was then displayed for 1 or 4 seconds, followed by a test array in which two fractals appear. Subjects were then asked to pick out the target object they remembered and drag the object to its displayed location. The VSTM task contained 4 conditions: 1-item with 1-sec delay (1item-1s), 1-item with 4-sec delay (1item-4s), 3-item with 1-sec delay (3item-1s), and 3-item with 4-sec delay (3item-4s). Subjects' ***reaction time*** in identifying and localizing the objects as well as the ***accuracy*** of the responses were recorded.

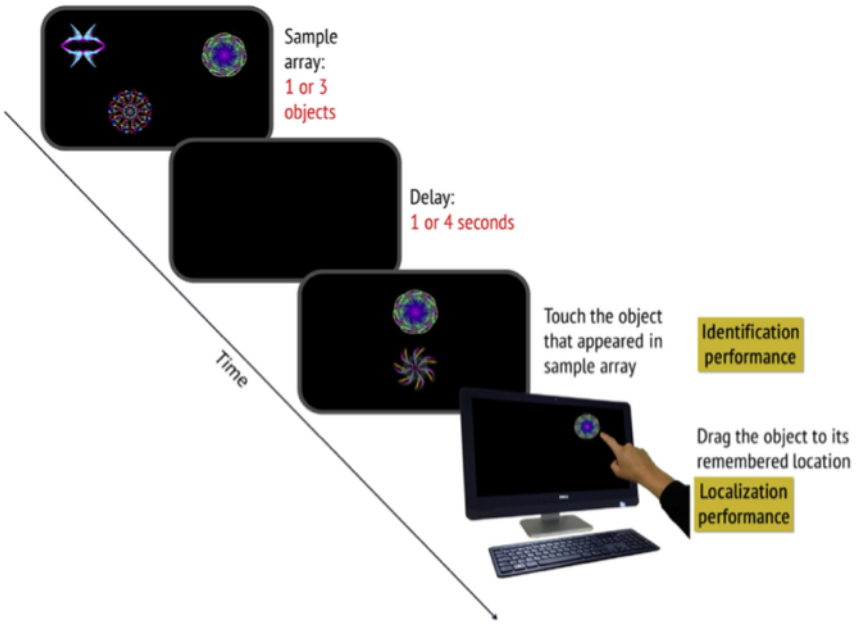

Figure 6.1: Schema of VSTM task. Adapted from [120]

Executive function was measured by the Trail Making Test (TMT) [122] and Stroop color-word test [126]. TMT assessed subjects' visual attention and task switching. The TMT task consisted of two conditions in which the subjects were instructed to connect a sequence of 25 consecutive targets as quickly as possible. One condition included targets with only numbers and the other condition included targets with numbers and letters mixed. The TMT recorded subjects' ***reaction time*** and ***error rate*** when they were instructed to trace the targets as quickly as possible. Stroop color-word test assessed subjects' ability to inhibit their automatic response (naming the colors instead of the words). The subjects were instructed to name the color of the printed words as quickly and as accurately as possible. The Stroop test also recorded subjects' ***reaction time*** and ***error rate*** when they were instructed to respond as quickly as possible.

6.2.4 Analysis plan

The main analyses focused on examining the changes in cognitive performance. For both groups, the changes of cognitive performance were tested by mixed-effect Analysis of Variance (ANOVA) for three tasks separately with the group as a between-subject variable and time and

task condition as within-subject variables. In particular, for the TMT task, I conducted a three-way mixed-effect ANOVA to compare the main and interaction effects of time, task condition, and group on reaction time. For the TMT task, time included two levels (pre-test, and post-test), condition included two levels (number condition, and number-letter condition), and group included two levels (MCI group and healthy group). For the VSTM task, I conducted a three-way mixed-effect ANOVA to compare the main and interaction effects of time, task condition, and group on reaction time and proportion of correct response. For the VSTM task, time included two levels (pre-test, and post-test), condition included four levels (1item-1sec condition, 1item-4sec condition, 3item-1sec condition, and 3item-4sec condition), and group included two levels (MCI group and healthy group). For the Stroop task, I conducted a two-way mixed effect ANOVA to compare the main and interaction effects of time and group on reaction time. For the Stroop task, time included two levels (pre-test and post-test), and group included two levels (MCI group and healthy group). Effect sizes for ANOVA will be calculated using partial η^2.

The secondary analyses examined the relationship between PSG napping parameters and changes in cognitive performance (post-test score minus pre-test score) after controlling for age, BMI and MoCA scores. The Pearson correlation tests were implemented for PSG napping parameters and changes in those three cognitive performance tasks separately. Correlation coefficients were used to evaluate the correlation coefficient to determine the strength of the relationship or the effect sizes.

6.3 Results

6.3.1 Changes of cognitive performance

A three-way mixed-effect ANOVA was used to examine the main effects and interactions of three independent variables (time, task condition, and subject group) on TMT reaction time. Table 6.2 and Table 6.3 displayed the descriptive statistics and the results of ANOVA and Figure 6.2 displayed the pre- and post-test changes of TMT reaction time for MCI subjects and their normal-aging peers. The main effect for group was significant, indicating that MCI subjects had a slower

reaction time than their normal-aging peers (p = 0.012). The main effect for time was significant, indicating that subjects had significantly faster reaction time in post-test than pre-test (p = 0.004). The main effect for condition was also significant, indicating that subjects had significantly faster reaction time in the number-only condition than the number-letter condition ($p < 0.001$). The interaction effect for group and time was significant (p = 0.031). The following Tukey post hoc analysis showed that subjects performed significantly better in the post-test than the pre-test, and this effect was stronger for MCI subjects. The interaction effect for time and condition was significant (p = 0.048). The following Tukey post hoc analysis showed that subjects performed better in the post-test than the pre-test, and this effect was stronger for the number-letter condition than the number-only condition.

Table 6.2: Descriptive statistics for TMT reaction time by condition and group

Variable	MCI (n = 20) mean(*SD*)	Healthy (n = 16) mean(*SD*)
Number-Only		
Pre-test	48.90 (23.79)	34.10 (13.83)
Post-test	34.80 (10.35)	27.80 (6.89)
Number-Letter		
Pre-test	113.70 (69.15)	64.60 (35.48)
Post-test	80.50 (47.57)	51.90 (20.06)

Notes: TMT: Trail Making Task. MCI: Mild Cognitive Impairment.

Table 6.3: Three-way ANOVA of TMT reaction time by time, condition, and group

Source	*SS*	*MS*	*F*	*p*	η_p^2
Group	3.63	3.63	$F(1, 34) = 2.02$	**0.165**	0.06
Time	2.63	2.63	$F(1, 34) = 9.26$***	**0.004**	0.21
Condition	48.82	16.27	$F(1, 34) = 37.73$***	**<0.001**	0.53
Group * Time	16.46	16.46	$F(1, 34) = 5.80$	**0.031**	0.12
Group * Condition	2.83	0.94	$F(1, 34) = 2.19$	0.094	0.06
Time * Condition	21.22	21.22	$F(1, 34) = 4.22$*	**0.048**	0.11

Notes: ANOVA: Analysis of Variance. TMT: Trial Making Task.
SS: Sum of Squares. MS: Mean Square.
*p<0.05, **p<0.01, ***p<0.001.

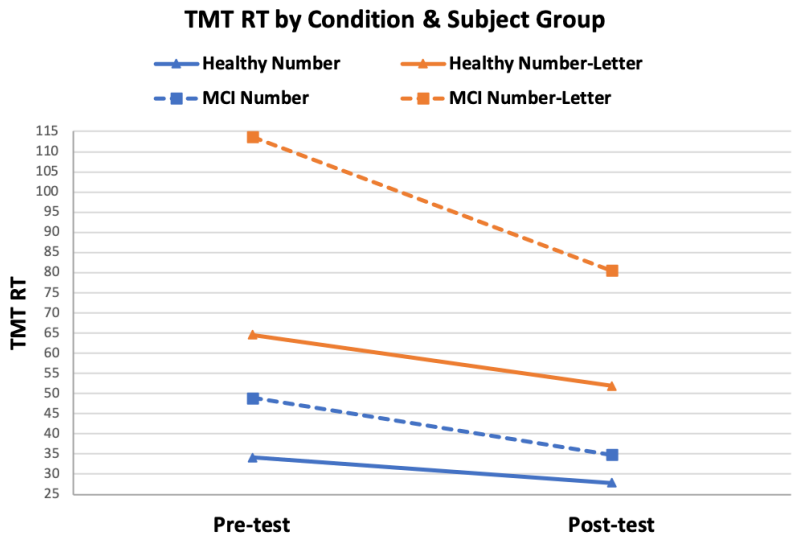

Figure 6.2: Pre- and post-test TMT reaction time by condition & subject group

A three-way mixed-effect ANOVA was used to examine the main effects and interactions of three independent variables (time, task condition, and subject group) on VSTM identification reaction time. Table 6.4 and Table 6.5 displayed the descriptive statistics and the results of ANOVA and Figure 6.3 displayed the pre- and post-test changes of VSTM identification reaction time for MCI subjects and their normal-aging peers. The main effect for time was significant, indicating that subjects had significantly faster identification reaction time in post-test than pre-test ($p = 0.004$). The main effect for condition was also significant, indicating that subjects had significantly faster identification reaction time in 1-item conditions than 3-item conditions ($p < 0.001$).

Table 6.4: Descriptive statistics for VSTM identification reaction time by condition and group

Variable	MCI (n = 20) mean(*SD*)	Healthy (n = 16) mean(*SD*)
1item-1sec		
Pre-test	1.46 (0.56)	1.16 (0.22)
Post-test	1.26 (0.46)	1.07 (0.21)
1item-4sec		
Pre-test	2.09 (1.50)	1.33 (0.34)
Post-test	1.52 (0.57)	1.19 (0.23)
3item-1sec		
Pre-test	2.10 (0.71)	2.05 (0.39)
Post-test	1.98 (0.68)	1.96 (0.40)
3item-4sec		
Pre-test	2.38 (0.83)	2.39 (0.67)
Post-test	2.33 (1.16)	2.15 (0.57)

Notes: VSTM: Visual Short-Term Memory. MCI: Mild Cognitive Impairment.

Table 6.5: Three-way ANOVA of VSTM identification reaction time by time, condition, and group

Source	*SS*	*MS*	*F*	*p*	η_p^2
Group	3.63	3.63	$F(1, 34) = 2.02$	0.165	0.06
Time	2.63	2.63	$F(1, 34) = 9.26$**	**0.004**	0.21
Condition	48.82	16.27	$F(3, 102) = 39.93$***	**<0.001**	0.53
Group * Condition	2.83	0.94	$F(3, 102) = 2.19$	0.094	0.06
Time * Condition	0.85	0.28	$F(3, 102) = 1.35$	0.261	0.04
Time * Group	0.16	0.16	$F(1, 34) = 0.58$	0.452	0.02

Notes: ANOVA: Analysis of Variance. VSTM: Visual Short-Term Memory.
SS: Sum of Squares. MS: Mean Square.
*p<0.05, **p<0.01, ***p<0.001.

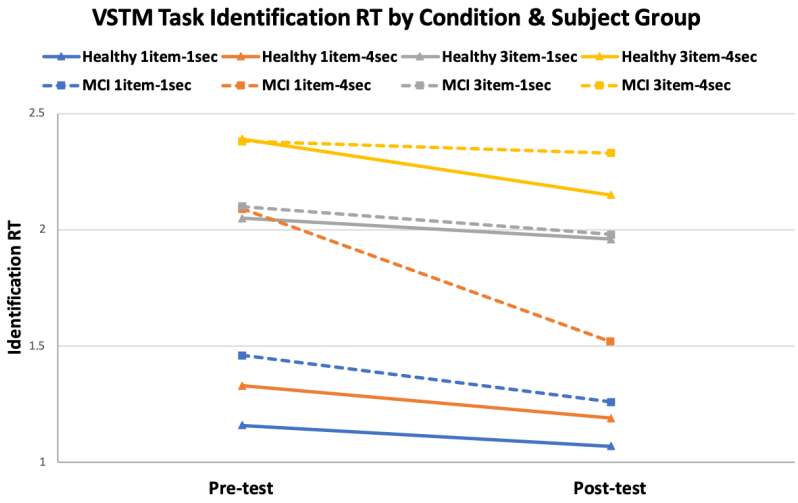

Figure 6.3: Pre- and post-test VSTM identification reaction time by condition & subject group

A three-way mixed-effect ANOVA was used to examine the main effects and interactions of three independent variables (time, task condition, and subject group) on VSTM localization reaction time. Table 6.6 and Table 6.7 displayed the descriptive statistics and the results of ANOVA and Figure 6.4 displayed the pre- and post-test changes of VSTM localization reaction time for MCI subjects and their normal-aging peers. The main effect for time was significant, indicating that subjects had significantly faster localization reaction time in post-test than pre-test ($p = 0.004$). The main effect for condition was also significant, indicating that subjects had significantly faster identification reaction time in 1-item conditions than 3-item conditions ($p < 0.001$).

Table 6.6: Descriptive statistics for VSTM localization reaction time by condition and group

Variable	MCI (n = 20) mean(*SD*)	Healthy (n = 16) mean(*SD*)
1item-1sec		
Pre-test	2.84 (0.93)	2.33 (0.43)
Post-test	2.53 (0.72)	2.20 (0.39)
1item-4sec		
Pre-test	3.53 (1.74)	2.57 (0.51)
Post-test	2.86 (0.83)	2.37 (0.41)
3item-1sec		
Pre-test	3.70 (1.39)	3.53 (0.63)
Post-test	3.38 (1.05)	3.18 (0.60)
3item-4sec		
Pre-test	3.89 (1.26)	3.72 (0.86)
Post-test	3.85 (1.70)	3.39 (0.80)

Notes: VSTM: Visual Short-Term Memory. MCI: Mild Cognitive Impairment.

Table 6.7: Three-way ANOVA of VSTM localization reaction time by time, condition, and group

Source	*SS*	*MS*	*F*	*p*	η_p^2
Group	13.44	13.44	$F(1, 34) = 2.66$	0.112	0.07
Time	5.54	5.54	$F(1, 34) = 9.27$**	**0.004**	0.21
Condition	65.55	21.85	$F(3, 102) = 36.99$***	**<0.001**	0.52
Group * Condition	2.83	0.94	$F(3, 102) = 2.19$	0.094	0.06
Time * Condition	0.87	0.29	$F(3, 102) = 1.19$	0.316	0.03
Time * Group	0.29	0.29	$F(1, 34) = 0.49$	0.489	0.01

Notes: ANOVA: Analysis of Variance. VSTM: Visual Short-Term Memory.
SS: Sum of Squares. MS: Mean Square.
*p<0.05, **p<0.01, ***p<0.001.

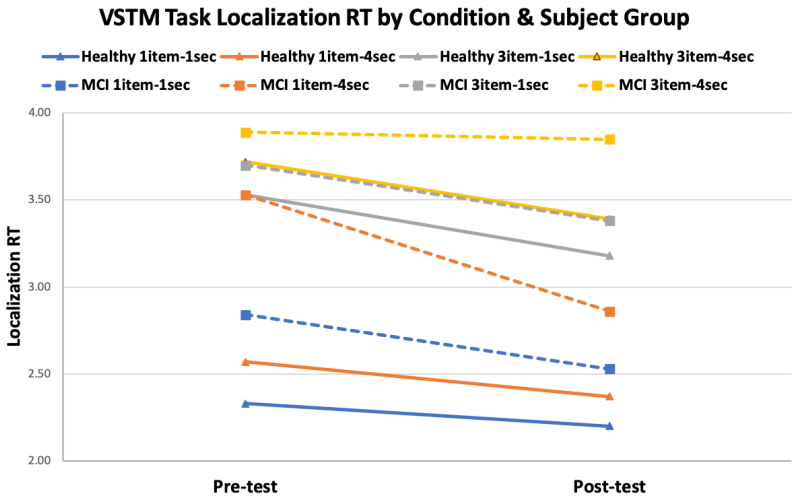

Figure 6.4: Pre- and post-test VSTM localization reaction time by condition & subject group

A three-way mixed-effect ANOVA was used to examine the main effects and interactions of three independent variables (time, task condition, and subject group) on the VSTM proportion of correct response. Table 6.8 and Table 6.9 displayed the descriptive statistics and the results of ANOVA and Figure 6.5 displayed the pre- and post-test changes of TMT reaction time for MCI subjects and their normal-aging peers. The main effect for group was significant, indicating that MCI subjects had a significantly lower proportion of correct response than their normal-aging peers (p = 0.009). The main effect for time was significant, indicating that subjects had significantly improved proportion of correct response in post-test than pre-test (p = 0.019). The main effect for condition was also significant, indicating that subjects had significantly higher proportion of correct response in 1-item conditions than 3-item conditions ($p < 0.001$). The interaction effect for time and condition was significant ($p = 0.050$). The following Tukey post hoc analysis showed that subjects performed better in the post-test than the pre-test, and this effect was stronger for the 3-item conditions than the 1-item conditions.

Table 6.8: Descriptive statistics for VSTM proportion of correct response by condition and group

Variable	MCI (n = 20) mean(*SD*)	Healthy (n = 16) mean(*SD*)
1item-1sec		
Pre-test	97.94% (0.04)	99.38% (0.02)
Post-test	97.14% (0.04)	99.38% (0.02)
1item-4sec		
Pre-test	91.59% (0.09)	97.08% (0.05)
Post-test	92.70% (0.09)	97.08% (0.03)
3item-1sec		
Pre-test	80.79% (0.11)	87.08% (0.06)
Post-test	83.33% (0.12)	90.42% (0.07)
3item-4sec		
Pre-test	74.29% (0.09)	82.29% (0.09)
Post-test	77.14% (0.09)	84.79% (0.08)

Notes: VSTM: Visual Short-Term Memory. MCI: Mild Cognitive Impairment.

Table 6.9: Three-way ANOVA of VSTM proportion of correct response by time, condition, and group

Source	*SS*	*MS*	*F*	*p*	η_p^2
Group	0.17	0.17	$F(1, 34) = 7.80$	**0.009**	0.19
Time	0.02	0.02	$F(1, 34) = 6.04$**	**0.019**	0.15
Condition	1.58	0.53	$F(3, 102) = 117.77$***	**<0.001**	0.78
Group * Condition	0.03	0.00	$F(3, 102) = 2.22$	0.090	0.06
Time * Condition	0.02	0.01	$F(3, 102) = 2.69$*	**0.050**	0.07
Time * Group	0.00	0.00	$F(1, 34) = 0.01$	0.921	0.00

Notes: ANOVA: Analysis of Variance. VSTM: Visual Short-Term Memory.
SS: Sum of Squares. MS: Mean Square.
*p<0.05, **p<0.01, ***p<0.001.

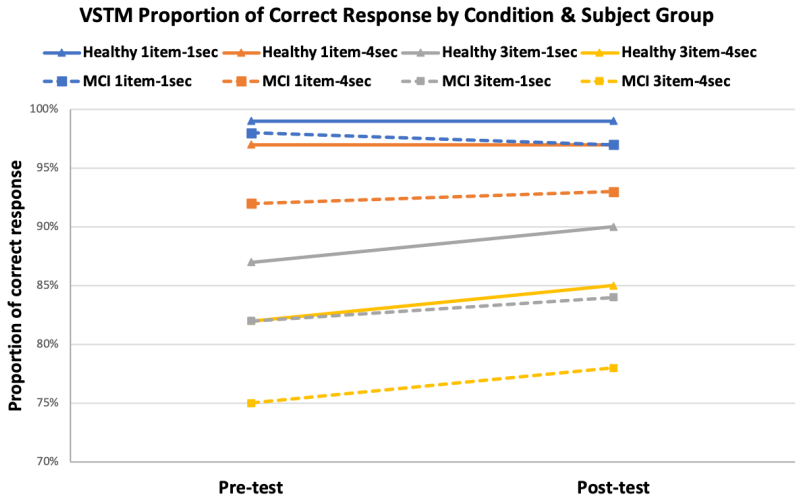

Figure 6.5: Pre- and post-test VSTM proportion of correct response by condition & subject group

A two-way mixed-effect ANOVA was used to examine the main effects and interactions of two independent variables (time, and subject group) on Stroop reaction time. Table 6.10 and Table 6.11 displayed the descriptive statistics and the results of ANOVA and Figure 6.6 displayed the pre- and post-test changes of TMT reaction time for MCI subjects and their normal-aging peers. The main effect for group was significant, indicating that MCI subjects had significantly slower reaction time than their normal-aging peers (p = 0.017). The main effect for time was marginally significant, indicating that subjects had faster reaction time in post-test than pre-test (p = 0.080).

Table 6.10: Descriptive statistics for Stroop reaction time by group

Variable	MCI (n = 20) mean(*SD*)	Healthy (n = 16) mean(*SD*)
Stroop		
Pre-test	118.10 (37.55)	96.40 (23.57)
Post-test	112.40 (20.59)	91.50 (21.09)

Notes: MCI: Mild Cognitive Impairment.

Table 6.11: Two-way ANOVA of Stroop reaction time by time, and group

Source	*SS*	*MS*	*F*	*p*	η_p^2
Group	8086.28	8086.28	$F(1, 34) = 6.30$*	**0.017**	0.16
Time	521.97	521.97	$F(1, 34) = 3.25$	0.080	0.09
Time * Group	2.60	2.60	$F(1, 34) = 0.02$	0.899	0.00

Notes: ANOVA: Analysis of Variance.
SS: Sum of Squares. MS: Mean Square.
*p<0.05, **p<0.01, ***p<0.001.

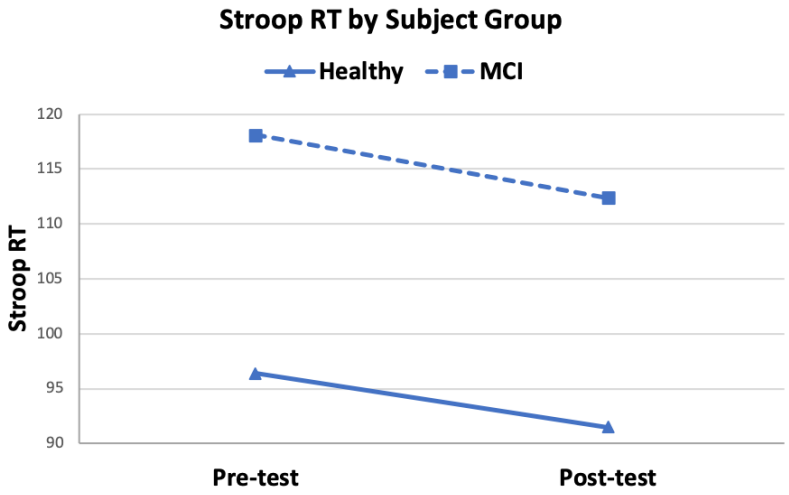

Figure 6.6: Pre- and post-test Stroop reaction time by subject group

6.3.2 Correlation between objective napping quality and changes in cognitive performance

To explore the relationship between objective napping quality and improvements of cognitive performance, Pearson partial correlations were calculated for the entire sample. The relationship between objective napping quality and improvements of cognitive performance varied between tasks.

For the TMT task, the analysis results showed there was a marginally significant correlation between the number of k-complex per minute and TMT reaction time with number targets (Pearson partial correlation $r(31) = 0.30$, $p = 0.089$).

For the Oxford VSTM task, results showed that for the 1item-4sec condition, both identification reaction time and localization reaction time were marginally significantly associated with

the percentage of sleep stage 2. Specifically, the analysis indicated that after controlling for age, BMI and MoCA score, faster identification reaction time for the 1item-4sec condition significantly correlated with higher percentages of sleep stage 2 (Pearson partial correlation $r(31) = 0.29$, $p = 0.099$). After controlling for age, BMI, and MoCA score, faster localization reaction time for the 1item-4sec condition marginally significantly correlated with higher percentages of sleep stage 2 (Pearson partial correlation $r(31) = 0.32$, $p = 0.065$).

For the Stroop task, the analysis results showed there were no significant correlations between objective napping quality and the improvements in reaction time.

Table 6.12: Partial correlations between PSG parameters and changes in cognitive performance

Variable	Condition	Stage1 (%)	Stage2 (%)	SWS (%)	k-complex/min
TMT RT	Number	0.20	-0.09	0.03	**0.30**
VSTM i-RT	1item-1sec	0.01	0.22	0.27	-0.14
	1item-4sec	-0.05	**0.29**	-0.23	0.02
VSTM l-RT	1item-1sec	0.04	0.06	0.28	-0.07
	1item-4sec	-0.12	**0.32**	-0.22	0.04
VSTM PCR	1item-1sec	-0.03	0.06	0.03	-0.04
	1item-4sec	-0.23	-0.07	0.09	0.23

Notes: PSG: Polysomnography. SWS: Slow-Wave Sleep.
TMT: Trail Making Task. VSTM: Visual Short-Term Memory.
RT: Reaction Time. i-RT: identification Reaction Time. l-RT: localization Reaction Time. PCR: Proportion of Correct Response.
Variables that are significantly skewed (Shapiro-test) were log-transformed to normal distribution before conducting t-tests.
*p<0.05, **p<0.01, ***p<0.001.

6.4 Discussion

In the present study, the results demonstrated that both MCI subjects and healthy older adults had better performance in the post-nap tests than the pre-nap tests. Furthermore, our findings showed that both groups showed improved vigilance levels after their naps in the following TMT and Stroop tasks, as well as improvements in higher cognitively demanding tasks like the spatial working memory task. However, in contrast with our hypothesis, our findings suggested that MCI subjects did not express less improvements than the healthy older adults.

In the TMT task, both groups had faster reaction time in the post-test than the pre-test, while no differences were found in the error rate. This is not surprising since accuracy was heavily emphasized in the task instruction and errors were normally rare in the TMT task [113]. The improvements might relate to napping as previous studies demonstrated reaction time for attention or visual searching tasks like TMT were positively affected by napping [113]. However, as the current study was not specifically designed to test the direct effects of napping, further examination is needed to make such interpretations. On the other hand, the improvements in reaction time might be due to practice effects [122]. Thus, repeated measurements might explain the subjects improvements. Furthermore, in contrast with our hypothesis, results showed that the improvements were stronger in MCI subjects than healthy older adults. It is possible that there is a potential ceiling effect for some healthy older adults as TMT is an easily learned task. Some healthy older adults already had a relatively short reaction time at the pre-nap test. Therefore, there was not a large degree of improvement in their post-nap performance when compared to the MCI subjects.

In the VSTM task, both groups had faster identification and localization reaction time, as well as a higher proportion of correct response in the post-test than the pre-test. Our study aligned with previous studies demonstrating that subjects had improved performance in the post-nap spatial memory task. The present study found enhanced performance in the post-test, while other studies suggesting not all performance components were equally improved. For instance, Nguyen and colleagues found that subjects had improved accuracy in the post-test, but no differences in reaction time [160]. Such discrepancies might be explained by the methodological differences. Particularly, it might be because of the different study samples we used. As we had MCI subjects, they might have different cognitive performance as well as different patterns of improvements. Moreover, it might be due to the application of an fMRI paradigm in the other studies, which limited the test trial difficulty and the task duration. In contrast, participants in our test were engaged in some high-demanding trials as well as a relatively long task duration. Thus, the current VSTM task may be more sensitive and reliable in detecting performance changes. Since we had a relatively complicated memory task, it is less likely that the improvements were due to practice effects. In

addition, previous nocturnal sleep studies found that spatial memory was really sensitive to changes in sleep [161]. For instance, the previous study reported that subjects had significantly improved post-sleep spatial memory performance and such improvements were positively associated with sleep quality [160, 162]. Thus, it is likely that improvements in the spatial memory task were due to napping. But because of the limitation of the current design, we cannot conclude that. Further examinations are needed to examine whether it is the effect of napping.

The present data showed that both groups had a faster reaction time in their post-nap Stroop task than their pre-nap test, while the error rate was not changed. This was similar to previous sleep studies which suggested that there were post-sleep improvements in the Stroop task [96]. Similar to our findings, they found that reaction time was improved but not the error rate. Cain et al. [137] further suggested that the improvements might not be on all components of the task. The Stroop task consists of both executive components (i.e. resistance to proactive interference) and non-executive components (i.e. reaction time). One or more components might improve, while others might not. That might be the reason that the reaction time was improved, but the error rate was not changed in the post-nap test. Thus, when we examine post-nap cognitive improvements, it might be important to view the task components separately.

Since the study was not designed to directly test the effects of napping, the group comparison cannot really conclude the cognitive improvements were because of napping instead of differences in practice effects due to the repeated administration of the task. However, further exploratory analyses on the relationship between PSG parameters and cognitive improvements might provide support for the hypothesis that those post-nap improvements might be associated with napping parameters and better napping quality might relate to larger improvements.

The present results showed that stage 2 activities were marginally significantly associated with the improvements in both TMT task and VSTM task. This was consistent with previous studies that reported relationships between changes in memory performance and the amount of percentage in NREM sleep [163]. Lau et al. [163] further demonstrated that the amount of stage 2 sleep during napping and performance improvements showed a positive trend but no significant relationship.

Additionally, nocturnal sleep studies reported the amount of stage 2 sleep positively correlated with improvements in following memory performance [164]. Our findings suggested there was a positive trend in the amount of stage 2 sleep during napping and spatial memory improvements. Our results also added to the previous findings and suggested that k-complexes might be another important parameter which would affect the improvements.

Multiple sleep stages have been linked to encoding and retrieval performance on memory tasks. While, different sleep stages were proposed to be more associated with different types of memory. For instance, SWS was consistently linked to episodic memory [165, 166]. REM sleep was found to play an important role in emotional memory [167, 168]. Both Stage 2 sleep and REM sleep have been linked to procedural memory [169]. The mechanisms of how sleep contributes to the following memory performance was still unclear. Based on our findings in this preliminary study, we found that Stage 2 sleep might relate to the improvements in the post-nap spatial memory task. Since we were using subjects with cognitive impairments and healthy older adults, their PSG parameters as well as their napping quality (e.g. quality of SWS) might be largely different from other samples. Therefore, even though it demonstrated a positive trend, the results were not conclusive evidence about Stage 2 sleep and the performance improvements. Together, it suggested that further research is needed on how specific sleep parameters relate to cognitive improvements.

In addition to the correlational analyses, previous studies provided more evidence that cognitive performance could be positively affected by the napping. For instance, the majority of studies found that napping was associated with improved performance in the working memory task [105], reaction time [100], and Stroop performance [150] tasks in MCI subjects. The results of the correlational analyses together with the previous studies suggested that it might be possible that napping might have a restorative function on cognition and better napping quality might be associated with greater improvements. Further examination with PSG measures is needed to compare the effects of napping between MCI subjects and healthy older adults.

There were several strengths of the present study. First, we investigated napping parameters using the gold standard PSG system in MCI subjects. Second, we were one of the few studies

that compared post-nap cognitive improvements between MCI subjects and healthy older adults. Last but not least, to the best of my knowledge, we were the first study to specifically examine the post-nap improvements using a spatial memory task in MCI subjects and relate such improvements to PSG parameters.

However, there were some limitations of the present study that should be noted. First, a primary limitation of the current study is the small sample size. Hence, although the findings suggested interesting correlations between PSG parameters and cognitive improvements, we must be very cautious when interpreting the results. Second, since the main aim of the study was to compare post-nap improvements in MCI subjects and their normal-aging peers, we did not test a control sample of subjects without any napping sessions or an active control condition. The correlation analyses, however, tended to suggest there was a potential association between specific PSG parameters and the improvements in cognition. Therefore, further investigation is needed to further determine the features of different parameters with more subjects and study groups. Third, the present study was correlational, thus, it was unable to evaluate potential causation of the reported relationships. Last but not least, tasks like TMT might be sensitive to practice. Especially for healthy older adults, they might be able to learn the task immediately. Further studies with less prior practice might be a more accurate reflection of the improvements.

Taken together, the present study contributed to a growing body of literature on exploring post-nap cognitive improvements in MCI subjects and their normal-aging peers. The results demonstrated that both groups had improved performance after their napping and those improvements varied between tasks as well as task components. Further correlational exploration indicated that such improvements might be potentially related to the amount of stage 2 sleep and k-complex during napping. Such cognitive improvements, together with the observed relationship between PSG parameters and the improvements, may lead to contributions in intervention studies or even treatment plans in the future.

7. GENERAL DISCUSSION

The present thesis found no differences in subjective sleep quality, but significant differences of objective daytime sleep quality in subjects with Mild Cognitive Impairment (MCI) when compared to healthy older adults. Both subjective sleep quality and objective napping quality were positively associated with baseline cognitive performance. MCI subjects showed lower percentages of slow-wave sleep (SWS), less sleep spindles during stage 2 sleep, and higher percentages of stage 1 sleep than the healthy controls. Further exploratory analysis of the relationship between daytime sleep quality and cognitive functioning indicated that the amount of SWS positively correlated with baseline cognitive performance, while the amount of stage 1 and stage 2 sleep negatively related to baseline cognitive performance for MCI subjects and their normal-aging peers. In addition, there were significant cognitive improvements for both MCI subjects and healthy controls after their napping. Such improvements were correlated with stage 2 activities.

7.1 Group differences: subjective and objective measures

When compared MCI subjects to the healthy controls, there was no significant difference between subjective sleep measures. Additionally, it was confirmed that MCI subjects and healthy controls differed in objective daytime sleep parameters. Specifically, MCI subjects expressed less SWS, less sleep spindles, but more stage 1 sleep. Consistent with other clinical studies, MCI subjects showed more disturbed daytime sleep than their normal-aging peers [145]. The present findings further supported that subjective reports may be less reliable than objective measures, especially for subjects with cognitive impairments. In addition, the results indicated that disturbed daytime sleep might be another important indicator for cognitive impairment.

7.2 Baseline cognitive performance & (daytime) sleep: correlation findings

Further, the results showed that both subjective sleep quality and objective daytime sleep quality positively related to baseline cognitive performance in MCI subjects and healthy older adults. From the subjective sleep quality aspect, subjects with better sleep quality tend to have better per-

formance. From the objective daytime sleep quality aspect, PSG parameters specifically related to the performance of the VSTM spatial memory task. Subjects with more stage 1 sleep had poor performance, while subjects with more SWS had better performance. This aligned with the sleep-dependent memory consolidation, which stated the importance of SWS in memory [47]. In sum, these data provided subjective and objective evidence that disturbed sleep and daytime sleep may be related to cognitive impairments.

7.3 The role of daytime sleep in cognition

An important observation of the present study was that both MCI subjects and the healthy older adults had significantly improved cognitive performance after their napping. Additionally, those improvements were related to stage 2 activities. The relationships between improved cognitive performance and the amount of NREM sleep were reported previously [163]. Previous findings found the improvements were significantly correlated with SWS and they also reported a positive trend in the amount of stage 2 sleep and cognitive changes [163]. The waste-clearance theory offered a framework that may potentially explain the improved cognitive performance after napping in MCI subjects and healthy older adults. The waste-clearance stated that the convective exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF) was largely increased during sleep. The present results further supported that napping might play the same role as nocturnal sleep since they are generating similar PSG parameters. In other words, cognitive improvements might be due to the cleaning function of daytime sleep. Moreover, subjects with better napping quality might be able to clean more waste products, therefore, expressed larger improvements. Further identification of the PSG parameters indicated that stage 2 activities might be important when performing the cleaning function during napping.

7.4 Limitations

First, the interpretation of the present findings is limited by the small sample size, and further studies with larger sample size are needed to verify the results. Second, the present study lacks clinical diagnoses and interview assessments of MCI subjects. This was a limitation that was hard

to resolve for practical reasons. To ensure that our results were relevant to real clinical practice, the study was conducted in partnership with the Center for Translational Research in Aging and Longevity (CTRAL), where we could ensure more standard clinical operations and measures with older adults. In addition, we applied one of the most commonly used clinical assessments (i.e. MoCA) for MCI, which was also well-validated by other clinical studies. Third, as the subjects were older adults, even the healthy older adults might have some comorbidities related to cognitive performance. Thus, further research on comorbidities of older adults, especially MCI subjects, would be helpful in order to control the possible effects of comorbidities might have on cognition. Last but not least, as the primary interest was to look at the cognitive improvements in response to daytime sleep rather than using daytime sleep as a treatment. Thus, the pre-tests of subjects functioned as their own control to compare with the post-tests and implications with respect to cognitive improvement should be taken more as suggestive rather than conclusive.

7.5 Significance, implications, and future directions

The present thesis may be valuable in several ways. First, research attempting to examine the relationship between daytime sleep and cognition with MCI samples is challenging and therefore rarely conducted. For practical reasons, research often measured daytime sleep with only subjective reports. Daytime sleep patterns with brain activities were largely understudied. However, subjective measures themselves may require a lot more validation, especially for subjects with cognitive impairments. Second, examining correlations between PSG parameters and cognition may lead to unique insights. As daytime sleep was found to be a complex concept to capture, behavioral research or subjective reports cannot measure the underlying mechanisms. Research with nocturnal sleep had made progress linking nocturnal PSG parameters to cognitive functioning, however, daytime sleep parameters were still at the beginning stage. Third, studying the underlying neural activities would lead to a better understanding of potential mechanisms and contribute to future intervention studies.

Although knowledge of the relationship of daytime sleep and cognitive functioning is still limited, further identification of PSG parameters and understanding underlying mechanisms can

provide significant advantages in the long run. Daytime sleep PSG parameters, in relation to cognitive impairment, can guide future research in new directions as well as lay the groundwork for effective interventions by clinicians and health professionals.

8. CONCLUSIONS

To the best of my knowledge, this is one of the few studies to date that investigated the objective daytime sleep parameters in MCI subjects and healthy older adults, and further examined the relationship between such parameters and cognitive functioning. The study supported the idea that cognitive impairments in MCI subjects might relate to disturbed daytime sleep quality. The objective PSG parameters found in the present study (i.e. SWS, stage 2 sleep) may provide neural indicators related to cognitive impairment. Therefore, it may further help provide a more comprehensive understanding of daytime sleep behaviors in MCI subjects and contribute to future treatment programs.

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APPENDIX A

SAMPLE FOR PITTSBURGH SLEEP QUALITY INDEX (PSQI)

Name_____ Date_____

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. A. How many hours of actual sleep did you get at night? _____
   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

Scoring

Component 1	#9 Score	C1 _____
Component 2	#2 Score (<15min (0), 16-30min (1), 31-60 min (2), >60min (3)) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2 _____
Component 3	#4 Score (>7(0), 6-7 (1), 5-6 (2), <5 (3)	C3 _____
Component 4	(total # of hours asleep) / (total # of hours in bed) x 100 >85%=0, 75%-84%=!, 65%-74%=2, <65%=3	C4 _____
Component 5	# sum of scores 5b to 5j (0=0; 1-9=1; 10-18=2; 19-27=3)	C5 _____
Component 6	#6 Score	C6 _____
Component 7	#7 Score + #8 score (0=0; 1-2=1; 3-4=2; 5-6=3)	C7 _____

Add the seven component scores together _____ ***Global PSQI*** _____

A total score of "5" or greater is indicative of poor sleep quality.
If you scored "5" or more it is suggested that you discuss your sleep habits with a healthcare provider

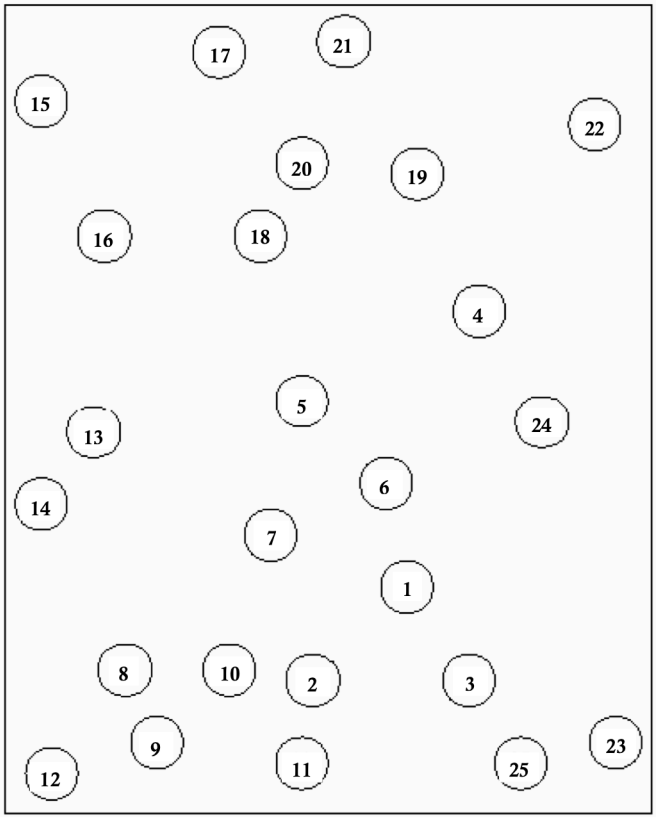
APPENDIX B

SAMPLE FOR TRIAL MAKING TASK (TMT)

Subject ID: _____
Date: _____

Trail Making Test

Part A – Vs1



Time: _____ Errors: _____

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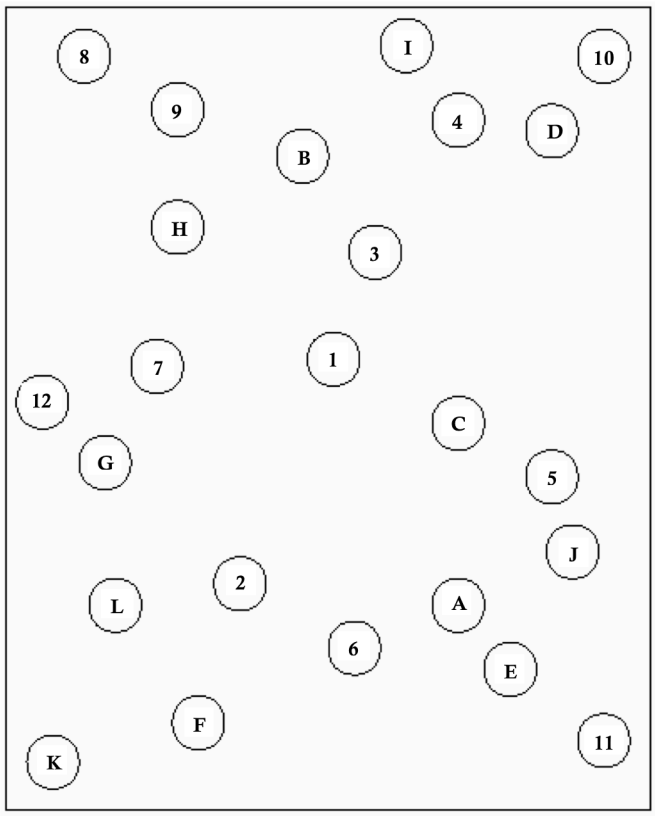
IRB APPROVAL DATE: 05/07/2018

Subject ID: _____
Date: _____

Trail Making Test

Part B – Vs1



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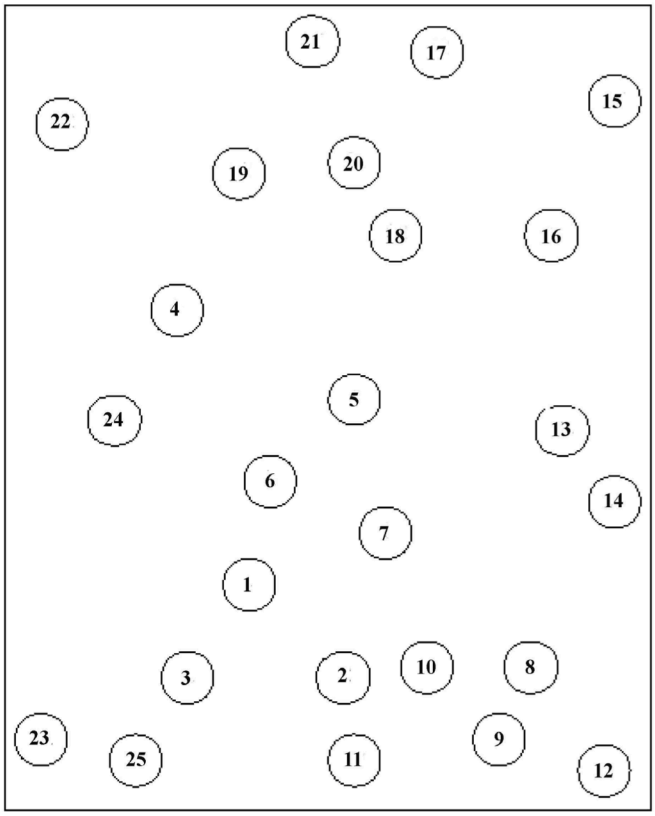
IRB APPROVAL DATE: 05/07/2018

Subject ID: _____
Date: _____

Trail Making Test

Part A – Vs2



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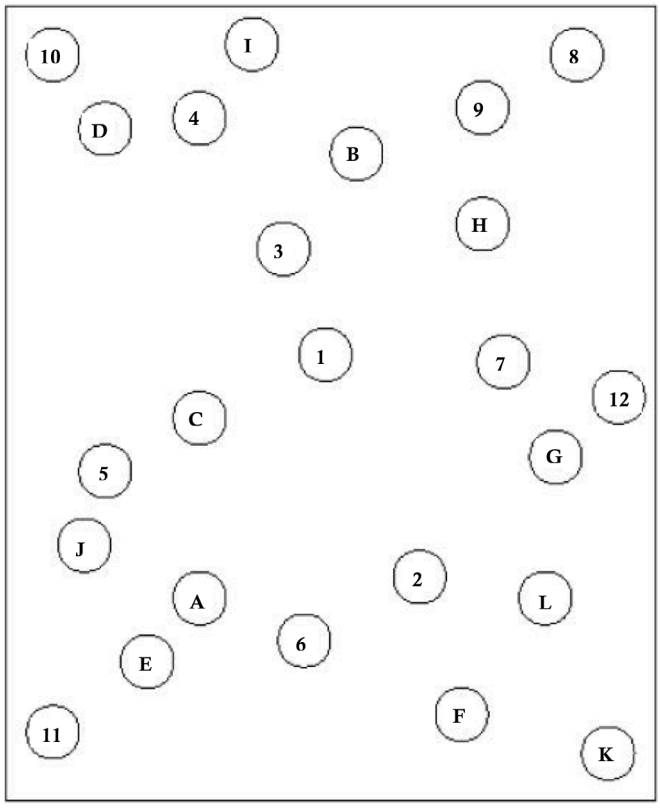
Subject ID: _____
Date: _____

Trail Making Test

Part B – Vs2



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IRB NUMBER: IRB2018-0169
IRB APPROVAL DATE: 05/07/2018