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The Association of Late-Life Depression, Cognitive Functioning, and Sleep Disorder in Aging

Jessica B. Aronis
University of Maine, jessica.aronis@maine.edu

THE ASSOCIATION OF LATE-LIFE DEPRESSION, COGNITIVE FUNCTIONING, AND SLEEP DISORDER IN AGING

By

Jessica Aronis

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Advisory Committee:

Marie J. Hayes, Professor of Psychology, Advisor

Ali Abedi, Professor of Electrical & Computer Engineering

Fayeza Ahmed, Assistant Professor of Psychology

Clifford Singer, Chief of Geriatric Mental Health and Neuropsychology Services

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Thesis Advisor: Dr. Marie J. Hayes

An Abstract of Thesis Presented
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The continuing growth in the demographic of aging individuals in the United States creates concern for diseases of aging that are chronic, notably unipolar depressive disorders. The high rates of depression in the aging population are a concern because of the strong association between late-life depression and cognitive impairment. Poor cognitive functioning is a hallmark of aging related neurological disorders, the most prevalent being Alzheimer's Disease (AD). Sleep disorder is a core symptom of depression, and is definitively associated with the development of mild cognitive impairment (MCI), the prodrome of AD. MCI is also characterized by similar types of sleep disturbance including sleep fragmentation, which consists of excessive awakenings during the night that leads to atypical suppression of night-time full awakenings and chronic sleep debt that impairs daytime attention and cognition as a consequence of poor sleep quality. The main hypothesis of this study is that current or historical depression in older adults will be associated with poor sleep quality and cognitive impairment.

Participants (N=50) from 65-85 years were assessed to determine the impact of depression status on sleep disturbance and cognitive variables. Individuals endorsing *current depression* (n=9), *history of diagnosed depression but no current depression* (n=7), or *no current depression* (n=34) were tested for 7 nights using wrist actigraphy and self-report sleep diaries to assess various sleep parameters used to identify sleep disturbance. Memory consolidation was probed surrounding one night of sleep using a simple procedural memory task and one-month follow-up assessment was used to assess a variety of neurocognitive domains including immediate and delayed recall, visuospatial abilities, etc. Results from this study revealed that individuals with current depression showed poorer sleep quality (i.e. shorter sleep time, lower mean sleep efficiency, longer sleep latency, etc.) and self-reported more sleep disturbances and greater daytime dysfunction when compared with individuals with no current depression or depressive history (p's $< .05$). Results of impairment on cognitive tasks from participants with current depression or a history of diagnosed depression were not found. These results provide evidence of an association between sleep disturbance and late-life depression. Cognitive performance of depressed older adults warrants further exploration.

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LIST OF ABBREVIATIONS AND ACRONYMS

Aβ	amyloid-beta
ACTH	adrenocorticotropic hormone
AD	Alzheimer's Disease
aMCI	amnestic mild cognitive impairment
AMNART	American National Adult Reading Test
APOE	apolipoprotein E
BMI	body mass index
BNT	Boston Naming Test
BVMT-R	Brief Visuospatial Memory Test-Revised
CSD-M	Consensus Sleep Diary-Modified
CES-D	Center for Epidemiological Studies Depression Scale
CRH	corticotropin-releasing hormone
EDS	excessive daytime sleepiness
EDS	elevated depressive symptoms
EEG	electroencephalogram
ESS	Epworth Sleepiness Scale
FLAIR	fluid attenuated inversion recovery

GLM	General Linear Modeling
HIPAA	Health Insurance Portability and Accountability Act
HPA	hypothalamic-pituitary-adrenal
HSCL	Hopkins Symptom Checklist
HVLT-R	Hopkins Verbal Learning Test-Revised
IRB	Institutional Review Board
MCI	Mild cognitive impairment
MDD	Major depressive disorder
MIRAGE	Multi-Institutional Research in Alzheimer's Genetic Epidemiology
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
naMCI	non-amnestic mild cognitive impairment
NFT	neurofibrillary tangles
NREM	non-rapid eye movement
OSA	obstructive sleep apnea
PET	positron emission tomography
PSG	polysomnography

PSQI	Pittsburgh Sleep Quality Index
REM	Rapid Eye Movement
SCID	Structured Clinical Interview for DSM-III-R
SD	sleep deprivation
SSS	Stanford Sleepiness Scale
SWA	slow-wave activity
SWS	slow-wave sleep
TBI	traumatic brain injury
TBM	tensor-based morphometry
TMT	Trail Making Test
WAIS-III	Wechsler Adult Intelligence Scale-Third Edition
WASO	wake after sleep onset
WMH	white matter hyperintensities
WML	white matter lesion

CHAPTER 1

INTRODUCTION

The continuing growth in the demographic of aging individuals in the United States creates multiple health and economic concerns. The past decade alone has shown increases in the population of aging individuals (65-85 years) of over 25% and it is projected to rise in the near future as baby boomers enter this age range at rates of ~10,000 individuals per day (Lock et al., 2017). As individuals grow older, they experience degradation of many health systems with primary concern for diseases of aging that are chronic (Cauley, 2012; McNicoll, 2012). In high-income countries such as the United States, most of the disease burden falls on chronic conditions. In a rank order of disease burden in high income countries compiled in 2001, unipolar depressive disorders were rated third highest (Cauley, 2012). The World Health Organization estimates that 7% of the general elderly population has unipolar depression (World Health Organization, 2016). The high rates of depression in the aging population are a concern for a variety of reasons with one important one being the strong association between late-life depression and cognitive impairment. Poor cognitive functioning is the hallmark of aging-related neurological diseases, the most prevalent being Alzheimer's disease (AD) (Butters et al., 2008; Kirova, Bays, & Lagalwar, 2015).

The rapidly increasing aging population produces an extensive demographic of aging individuals with Alzheimer's disease and other dementias not only in the United States, but throughout the world (Qiu, De Ronchi, & Fratiglioni, 2007). A reported 13.9% increase of aging individuals with dementia, 9.7% of which have AD, and a projected likelihood of diagnoses doubling every 5 years after the age of 65 creates an imperative need for further research into neurodegenerative disorders (Plassman et al, 2007). In particular, an increased focus on

understanding early biobehavioral markers of AD and its prodrome, mild cognitive impairment (MCI), is critical for early identification and intervention. MCI refers to decline in cognitive ability that is greater than expected for an individual's age and education level but does not interfere with activities of daily life (Petersen et al., 2014). MCI can either be amnestic (aMCI) or non-amnestic (naMCI). aMCI is a memory disorder with relative preservation of other cognitive domains and is often prodromal to AD. This type of MCI is most commonly associated with late-life depression. In naMCI, memory remains intact, but one or more other cognitive abilities (e.g. language, visuospatial skills, executive functioning) is significantly impaired and can be prodromal to other types of dementia such as: frontotemporal dementia, dementia with Lewy bodies, primary progressive aphasia, and Parkinson's disease (UCI Institute for Memory Impairments and Neurological Disorders, 2017). The prevalence of MCI in the United States ranges from 12-18% among individuals over the age of 60 years (Tampi et al., 2018). Late-life depression and memory impairment have been explored through primarily prospective studies (Ganguli, Du, Dodge, Ratcliff, & Chang., 2006; Rapp et al., 2011; Richard et al., 2013), but bear further investigation.

Late-life depression occurs in older adults ages 65 and older and is defined as "a mood disorder with symptoms of sadness, negative self-regard, loss of interest in life, and disruptions of sleep, appetite, and energy for more than 2 weeks that affects daily living" (5th ed, *DSM*, American Psychiatric Association, 2013). A strong association exists between late-life depression, cognitive impairment, and poor cognitive outcomes, including risk of MCI and dementia (Sheline et al., 2006; Saczynski et al., 2010; Liu et al., 2017). The mechanisms linking late-life depression to MCI and AD are known to be bidirectional but a definitive answer to exactly how they are associated has yet to be discovered. The two most prominent mechanisms

linking depression and poor cognitive outcomes, such as MCI, include depression being used to reveal or unmask clinical MCI or depression overlapping with clinical MCI. The idea of depression revealing or unmasking MCI posits that depression may be a risk factor or prodrome to MCI development. Conversely, the idea of depression overlapping with MCI propounds that depression may be an additional symptom of MCI. Other factors influencing the association between depression and MCI include: genetic susceptibility, environmental factors, depression as a reaction to MCI, biological bases, etc. (Barnes, Alexopoulos, Lopez, Williams, & Yaffe, 2006; Panza et al., 2009). Regardless of the specific mechanism linking late-life depression and MCI, sleep disturbance is included as another important factor to consider that influences both disorders.

Sleep quality drastically impacts overall health as individuals age, specifically brain health and associated cognition (Kryger, Monjan, Bliwise, & Ancoli-Israel, 2004). Aging individuals in the United States are at greater risk for sleep disturbance and its prevalence continues to increase as individuals grow older (Baldwin et al, 2001). A primary physiological component of sleep disturbance is sleep fragmentation, defined as the disturbance of sleep maintenance that has a negative impact on daytime cognitive ability (Stepanski, 2002). The primary self-reported sleep complaint in older adults is difficulty initiating and maintaining sleep (insomnia) which exists as a function of sleep fragmentation (Baldwin et al, 2001; Kryger, Monjan, Bliwise, & Ancoli-Israel, 2004).

Sleep disturbance or sleep disorder is a core symptom of late-life depression. Insomnia symptoms and excessive daytime sleepiness (EDS) have been shown to increase the risk of developing depressive symptoms (Jaussent et al, 2011). Sleep disturbance, including persistent insomnia, may continue even after effective treatment for other symptoms of depression and can

put an individual at greater risk for relapse (Nutt, Wilson, & Paterson, 2008; Pigeon et al, 2008). Sleep disorder also shows a definitive association with MCI development and diagnosis. Poor subjective sleep quality has been shown to be connected to incident cognitive impairment in community-dwelling older men (Potvin et al, 2012). In addition, sleep disorder in MCI has been found to be strongly connected to current or historical diagnosis of major depression (Naismith et al, 2011).

As previously noted, prospective studies have been primarily used in research to explore the relationship between late-life depression and memory impairment (Green et al., 2003; Ganguli, Du, Dodge, Ratcliff, & Chang, 2006; Rapp et al., 2011, Richard et al., 2013). Although these types of studies are influential in understanding the relationship between late-life depression and memory impairment, they are not useful in finding methods of early detection for aging-related neurological disorders. Research exploring the association between late-life depression and preclinical markers of cognitive decline, an area that currently presents as a gap in the literature, may be useful in developing such methods. This thesis project explores both current depressive symptoms and history of depressive symptoms, age-adjusted cognitive functioning, and objective and self-report sleep measures in older adults from the community with and without diagnosed MCI. A participant community sample that includes cognitively normal older adults was used for this study because of my thesis project's interest in early markers of cognitive decline associated with either current or past history of depressive symptoms, another area for which there is limited research. Participants with diagnosed MCI, collected from the same age cohort and demographics, were included to explore the strength of association between the two disorders. Cognitive functioning, measured through a variety of

paper and pencil neurocognitive tests, were assessed across a participant sample with varying presence and severity of past or present depressive symptoms.

1.1. Late-Life Depression and Cognitive Impairment are Strongly Associated.

Major depressive disorder significantly impacts the geriatric population, with 12-month prevalence rates of 2.7-5.4% and subclinical rates of 8-10% reported by community-dwelling older adults (Dotson, Beydoun, & Zonderman, 2010). Late-life depression is additionally tied to considerable cognitive complaints, with 20-50% of older adults with late-life depression displaying greater cognitive deficits than expected for their age and education level. Common cognitive deficits exhibited in late-life depression, even at a subclinical level, include worse performance in processing speed, visuospatial abilities, episodic memory, verbal fluency, and executive dysfunction, as well as poor learning and free recall on memory tests (Dotson, Beydoun, & Zonderman, 2010). Many times, the cognitive complaints in late-life depression progress to poor cognitive outcomes. Having a late-life major depressive episode has been found to increase risk of dementia 4- to 6- fold and that risk worsens with more persistent depressive symptoms (Lenze et al., 2018). Despite the strong associations found among late-life depression, cognitive impairment, and poor cognitive outcomes, the directionality and mechanisms underlying this connection are poorly understood.

Panza et al. (2009) explores various possible mechanisms that may explain this association. First, depression has specific neurobiological effects on the brain that may make the brain more susceptible to developing neurodegenerative disorders in late-life, namely Alzheimer's Disease (AD), and its precursor aMCI. This mechanism is specifically addressed in the reserve threshold hypothesis (Butters et al., 2008; Stern, 2012). Another possibility is that there may be an interaction in which depression leads to cognitive decline only in the presence of

a genetic susceptibility factor (Barnes, Alexopoulos, Lopez, Williams, & Yaffe., 2006) or other vascular or environmental determinants. Environmental determinants of neurodegenerative disorders may include diet, viral infections, and exposure to neurotoxins (Grant, Campbell, Itzhaki, & Savory, 2002). Vascular factors predisposing depression in MCI and AD are further explored in the vascular depression hypothesis (Taylor et al., 2005; Taylor, Aizenstein, & Alexopoulos, 2013). Depression may additionally be a reaction to the initial symptoms of MCI. It is common for older adults to feel a variety of negative emotions upon first encountering cognitive decline or a formal diagnosis of a memory disorder, such as MCI (Lahr, Beblo, & Hartje, 2007). Depression may be an early manifestation of clinical MCI. More specifically, depressive symptoms may reflect an underlying neuropathological condition that results in cognitive decline over time. So, depressive symptoms before clinical cognitive impairment may represent an early sign of neurodegenerative disease (Chen, Ganguli, Mulsant, & DeKasky, 1999). However, the two most common mechanisms linking late-life depression and clinical cognitive impairment in research are: 1) depression as a risk factor or a prodromal condition to MCI development (Palmer et al., 2007) and 2) depression as an additional symptom of MCI (Robert et al., 2008). The many possible mechanisms driving these conditions interrelation are not mutually exclusive and bear further investigation.

Since dementia and depression are often comorbid conditions in older adults, they share many of the same features that may make the two disorders hard to distinguish. Wright & Persad (2007) explored the neuropsychological and neuropathological correlates that make the two disorders similar and dissimilar. Impaired function of the HPA axis is a factor of both dementia and late-life depression with the explanation of how this factor connects them being further spelled out in the reserve threshold hypothesis (Stern, 2002). The reserve threshold hypothesis

will be further explained in a future section. Cognitive deficits in both AD and depression include impaired performance on tasks of recall memory, visuospatial skills, and executive functioning, however, these deficits may also be explained by decreased levels of motivation in depressed older adults. The specific behavioral profile of depressed individuals with symptoms of disinterest and apathy may in fact predict those who will eventually develop dementia (Berger, Fratiglioni, Forsell, Winblad, & Backman, 1999). For instance, depressed individuals that eventually developed dementia often presented with disinterest, lower energy, and concentration difficulties in a greater proportion than nondemented older adults (Robert et al, 2006). In addition, the cognitive deficits in depressed individuals may put non-demented depressed older adults at greater risk of developing AD (Devanand et al., 1996; Chen, Ganguli, Mulsant, & DeKosky, 1999). Both depression and dementia disorders, particularly AD, in their own way create serious economic and health concerns that may be ameliorated by research into preventative measures.

Dementia is estimated to increase to 8.2 million cases in the United States by 2030 (Lenze et al., 2018). Research into early detection and preventative measures of dementia can greatly improve these rates and their economic burden. In fact, if a preventative measure is discovered and disseminated by 2025, we could reduce costs of dementia by 30% and have a projected cost-savings of $83 billion dollars by 2030 (Lenze et al., 2018). It is important to consider that late-life depression significantly impacts the risk for dementia, particularly AD, which may further increase the number of demented individuals. Before we begin work on exploring possible preventative measures of dementia, namely AD, we must understand how late-life depression and AD area associated through a variety of ideas and theories, with the most prominent ones being: the vascular depression hypothesis and amyloid beta pathology.

1.1.1. Vascular Depression Hypothesis. The vascular depression hypothesis posits that cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes (Taylor, Aizenstein, & Alexopoulos, 2013). Vascular depression is considered a form of late-onset depression first occurring after age 50 or 60 years. The cognitive profile of this form of depression is indicative of fronto-subcortical dysfunction and has clinical features such as: psychomotor change, executive dysfunction, apathy, treatment resistance, absence of family history, and disability disproportionate to depression severity (Jain & Steffens, 2018). A "depression-related dysfunction syndrome" was conceptualized to define the clinical expression of this type of depression, characterized by frontal network impairment caused by vascular and other aging related factors and describing depressed patients with vascular disease and evidence of impairment in networks related to mood and executive function (Alexopoulos, 2001).

MRI-defined vascular depression is characterized by the presence of white matter lesions (WMLs), or white matter hyperintensities (WMH), on T2 weighted or fluid attenuated inversion recovery (FLAIR) MRI (Taylor, Aizenstein, & Alexopoulos, 2013). WMLs are defined as areas of demyelinated cells located in the white matter of the brain. The exact effect of WMLs on brain dysfunction remains unclear but it helps to define underlying pathology and greater volumes of WMLs have been found to be associated with more rapid progression of AD ("Segmentation and Quantification of White Matter Lesions", Radboud University Medical Center, 2018). Late-life depression has been found to be associated with greater WMH severity and greater measured WMH volumes which may be a potential diagnostic entity of vascular depression and associated cognitive deficits/poor cognitive outcomes (Taylor et al, 2005; Taylor, Aizenstein, & Alexopoulos, 2013).

1.1.2. Amyloid Pathology. Amyloid-β (Aβ) peptide accumulation in the brain has been observed in both sleep disorder, AD, and late-life depression. A variety of molecular and cellular changes occur in the brain of a person with AD. The characteristic neuropathological hallmarks of the brain of an individual with AD are neurofibrillary tangles and plaques of the Aβ protein (Martins et al., 2018). Neurofibrillary tangles (NFT) involve the abnormal accumulation of tau protein inside neurons that block the neuron's transport system, therefore impairing synaptic communication between neurons. Accumulation of Aβ protein is the strongest physiological correlate of AD, and occurs when there is an abnormally high production of the protein that clumps together to form plaques between neurons that disrupt cell function ("What Happens to the Brain in Alzheimer's Disease?", National Institute on Aging, 2018). Hardy & Selkoe (2002) found that individuals with AD had increased levels of Aβ plaques which were associated with more severe cognitive dysfunction. Early studies also found that a specific gene present in these Aβ plaques known as apolipoprotein E (APOE) was an important genetic risk factor for AD (Martins et al., 2018).

Accumulation of Aβ plaques are also found in the brains of individuals with late-life depression. A pilot study by Li et al. (2017) found increased Aβ accumulation in cognitively normal, depressed older adults. Particularly, elderly depressed patients that have experienced a lifetime history of depression had a high volume of Aβ accumulation in mood-related areas of the brain. This may indicate that depressive history increases the risk of developing AD and may even be a prodromal stage to the disorder. Additional research of Aβ plaques in late-life depression, lifetime history of depression, and AD/MCI help to support this hypothesis. Through the use of neuroimaging techniques such as positron emission tomography (PET) scans and MRI, Chung (2018) explored the relationship between lifetime history of depression and late-life

depressive symptoms with cortical Aβ levels. Results indicate that older adults with a history of depression, compared to those that had never experienced depression, had increased Aβ burden that was also greater than those participants that had only experienced late-life depressive symptoms. Wu et al. (2018) also sought to explore amyloid pathology and neurodegeneration in a sample of depressed adults without dementia. The sample consisted of 63 middle-aged and elderly patients with Major Depressive Disorder (MDD) (n = 24 with MCI, n = 39 with normal cognition) and 22 non-depressed, control subjects. PET imaging was used to measure cerebral amyloidosis and hippocampal volume as biomarkers of neurodegeneration. Results revealed that there were significant differences between Aβ burden in control subjects and subjects with MCI and MDD (81.8% of control subjects vs. 37.5% of MCI and MDD subjects were Aβ negative). In addition, a considerable amount of MCI and MDD subjects (12.5%) exhibited both Aβ positivity and hippocampal atrophy compared to that of control subjects (4.5%) and non-MCI subjects (5.1%). These results highlight the heterogeneity of neurodegeneration and Aβ accumulation in adults with MDD.

Aβ deposition and sleep disorder also have a significant association. Disruption of the sleep-wake cycle, including nighttime awakenings, may directly increase levels of Aβ in the brain. This has been found through much research to also be correlated with AD development (Rogers et al., 1992; Musiek et al., 2018). One may thus conclude that sleep disorder and fragmentation may lead to increased Aβ levels, accelerated cognitive decline, and greater incidence of MCI and AD (Rogers et al., 1992; Musiek et al., 2018). Mander et al. (2015) conducted a study that explored Aβ deposition and sleep patterns in aging individuals. Researchers utilized PET scans to measure Aβ levels, polysomnography to measure sleep patterns, and an episodic associative word-pair task to measure cognition. Results indicated that

Aβ pathology was associated with decreased slow wave sleep (SWS), the deepest phase of stage 3 non-rapid eye movement (NREM) sleep, and impaired memory ability. These results may provide a functional pathway by which Aβ deposition may contribute to hippocampus-dependent cognitive decline in older adults (Mander et al., 2015).

1.1.3. Depression in MCI and AD. Promising support of late-life depression and memory impairment have been found through prospective studies, most notably the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) Study. The MIRAGE study is a cross-sectional study exploring the temporal association between prior depressive symptoms and development of AD (Green et al, 2003). Genetic and historical information, including history of depression, as determined by self-report, was collected over a period of 10 years from families in which at least one member met criteria for AD (N=4046). Odds ratios, a common measure of association between exposure and outcome used in epidemiological studies, of AD were estimated in individuals with and without depressive symptoms adjusting for covariates, such as genetic susceptibility. Results indicated that there was a significant association between depressive symptoms and AD even when depressive symptoms occurred more than 25 years before the onset of AD. The strongest association were found in families in which depressive symptoms first occurred within one year of AD onset. A modest association was still maintained in families that had depressive symptoms occur more than 25 years prior to AD onset. Green et al. (2003) cite two likely sources for the depression and AD association. If AD onset develops within one year of depression onset, it is likely that depression is prodromal or an early symptom of AD. Alternatively, depression is a risk factor when depressive symptoms occur greater than one year before AD onset.

Richard et al. (2013) also evaluated the association between late-life depression and poor cognitive outcomes, such as MCI and dementia. The participant sample included 2160 community-dwelling older adults, ages 65 and older. Participants completed the Center for Epidemiological Studies Depression Scale (CES-D) and clinicians evaluated MCI and dementia diagnoses. Follow-up visits occurred 18-24 months after baseline to reevaluate MCI and dementia status. Results indicated a significant association between depression and prevalent MCI but not incident MCI. Prevalent MCI cases included individuals who had developed or been diagnosed with MCI prior to the onset of the study. Conversely, incident MCI cases included individuals that were diagnosed with MCI over the course of the study (Alexander, Lopes, Ricchetti-Masterson, & Yeatts, 2017). Individuals with comorbid depression and MCI were also at greater risk of progressing into dementia. These results suggest that depression accompanies MCI but does not precede it. This study supports the idea that late-life depression may be a comorbid condition or early symptom of MCI but not a risk factor. Along with the significant effect that late-life depression has on cognition, it is important to take into account the effect of historical depressive symptoms on cognitive decline and AD development.

Rapp et al. (2011) conducted a three-year longitudinal study that explored cognitive decline over time in a sample of older adults with and without dementia as a function of current and historical depressive symptoms. Participants included 313 older individuals, ages 55-105, from elderly nursing homes with 61.3% of the study sample suffering from dementia at baseline. Results indicated that the presence of major depression, both currently and historically, led to accelerated cognitive decline in dementia that was greater than expected for age and education level. In addition, Geerlings et al. (2008) explored whether historical and current depressive symptoms were associated with increased risk for incident MCI, and its neurobiological effects

such as smaller hippocampal and amygdalar volumes. Within the Rotterdam Scan Study, 503 nondemented older adults between 60 and 90 years of age with reported historical depressive symptoms at baseline were used as the participant sample for this study. At baseline, participants were asked whether they had experienced a history of depression and if so, the age of onset and if they sought medical treatment for their symptoms. Participants were split into three study groups: early onset depression (before the age of 60), late-onset depression (at age 60 or older), and no depressive symptoms. Volumetric assessment of the hippocampus and amygdala using three-dimensional MRI scans were also performed at baseline for all participants. All participants were then followed for an average of 6 years to assess development of AD, determined by clinicians using the Mini-Mental State Examination (MMSE). Current depressive symptoms were assessed over the course of the study using the CES-D. Results showed that a total of 134 subjects (26.6%) reported a history of depression at baseline, with 88 individuals reporting early onset and 46 individuals reporting late onset. Results also indicated that history of depression, particularly early onset depression, increased risk of AD at follow-up independent of hippocampal and amygdalar atrophy as well as presence of current depressive symptoms. Although progression of cognitive decline into MCI and dementia diagnoses as a function of depression appears bleak, one factor that may be protective against this functional pathway of declining cognition is cognitive reserve.

1.2. Cognitive and Brain Reserve.

The factors that contribute to making certain aging individuals with certain life histories resilient to onset of diseases of aging have been a topic of conversation and study over many years. Resilience refers to multiple structural and functional neurological processes that are protective of clinical displays of neurodegenerative and other aging-related diseases. Three of

these processes that hold deep importance are cognitive reserve, brain reserve, and brain maintenance (Stern et al., 2018).

Cognitive reserve refers to differences in ability to perform cognitive processes and function daily in the face of brain aging, injury, or pathology. An individual's cognitive reserve is not a fixed property and is influenced by interactions between innate biological differences and lifetime exposures (Stern, 2002; Stern et al., 2018). There are various sociobehavioral and early-life factors that may be assessed when estimating cognitive reserve capacity. These include: early-life and current general cognitive ability (e.g. IQ), education level, occupational complexity, choice in leisure activities, amount of physical exercise, and social engagement. Researchers must take residual approaches to quantify cognitive reserve and often use functional imaging, participant characteristics (e.g. IQ and educational/occupational attainment), as well as cognitive measures that remain intact throughout the lifespan (e.g. reading tests and vocabulary assessments) to accomplish this goal (Stern, 2009; Stern et al., 2018).

On the other hand, brain reserve pertains to one's neurobiology (e.g. neuronal redundancy, brain and hippocampal size, etc.) and is theoretically used to account for individual structural differences in the brain that allows certain individuals to have a delay in experiencing clinical and cognitive symptoms in the face of brain aging and pathology (Satz, 1993; Stern et al., 2018). Brain reserve is not something that can be measured directly but may still be assessed through gross whole-brain measures reflective of premorbid brain volume. These measures include intracranial brain volume, measured through MRI, as well as head circumference. Brain reserve may be additionally assessed through more specific neurobiological measures such as: specific patterns of gray matter volume, cortical surface area, and cortical thickness, as well as

PET scan measures of synaptic integrity, or functional synapses without functional damage in neuronal transmission, and white matter structural properties (Stern et al., 2018).

A related but distinct concept to both brain and cognitive reserve is brain maintenance. Brain maintenance is defined as a reduction in aging-related brain changes and pathology due to genetics or lifestyle. Brain maintenance is also assumed to be modifiable by experience and has similar life factors to cognitive reserve that influence its capacity. Brain maintenance is best measured longitudinally to assess the change and preservation of brain morphology through many of the same scanning measures used to measure brain reserve (Nyberg, Lodven, Riklundm Lindenberger, & Backman, 2012; Stern et al., 2018). Studies have been conducted to measure the concept of reserve through its proxy measures that underlie its functionality.

1.2.1. Reserve assessed in research studies. Education is often a proxy measure used to assess cognitive reserve capacity. In previous studies, dementia incidence rates are lower in individuals with higher levels of education to be delayed (Stern, 2012; Mungas et al., 2018). In a seminal study conducted by Stern et al. (1999), it was found that higher education was also associated with more rapid cognitive decline after initial AD or dementia diagnosis. The proposed explanation for this surprising finding was that education, a factor that indicates a higher cognitive reserve capacity, promotes resilience to pathological brain changes and delays clinical dementia symptoms. In turn, cognition is more greatly depleted by the time it is detected on neurocognitive measures in higher educated individuals with dementia since its clinical diagnosis is so significantly delayed.

Mungas et al. (2018) sought to further explore the effect of higher education on rates of brain atrophy and cognitive decline. Researchers utilized participants from the UC Davis Diversity Cohort, a longitudinal study population of aging individuals that was significantly

heterogeneous in race/ethnicity and educational attainment. The participant sample for this study included 460 older adults that had at least 2 cognitive evaluations to assess domains such as episodic memory, semantic memory, executive functioning, and spatial ability, as well as at least 1 MRI brain scan. For participants that were assessed through 2 or more MRI scans over the course of the study, longitudinal structural change and grey matter volume change were assessed using tensor-based morphometry (TBM). Results indicated that education alone did not have a significant effect on cognitive change over time, however global grey matter change had a large significant effect on cognitive decline, with an increased rate of atrophy associated with faster cognitive decline. There was also a strong education by grey matter interaction. Grey matter atrophy had a stronger impact on cognitive decline in participants with higher levels of education. Additionally, the rate of grey matter atrophy increased by 9% per year of education. These results indicate that both brain reserve and cognitive reserve, evaluated through proxy measures, have a more complicated effect on cognition once clinical symptoms appear than initially hypothesized.

1.2.2. The Reserve Threshold Hypothesis. One pathway proposed to explain the connection between depression and cognitive functioning in aging is the reserve threshold hypothesis. Reserve is used to account for individual differences in adapting to age-related brain pathological changes (Stern, 2012). There are two distinct types of reserve: brain reserve and cognitive reserve.

Cognitive reserve is a functional assessment that focuses on the individual differences in efficiency when performing cognitive tasks or information processed. Cognitive reserve is protective of AD and related conditions. It indicates resilience to neuropathological damage by exploring how the brain utilizes damaged resources (Stern, 2002). Higher levels of intelligence

or education are often associated with the ability to sustain greater brain damage without functional damage, or a higher cognitive reserve capacity (Stern, 2012). Brain reserve is structural and measured mainly by neuronal redundancy. Neuronal redundancy proposes that neuronal circuits likely contain more than the minimum number of neurons needed to perform an operation. Individuals with greater neuronal redundancy are proposed to be better able to tolerate substantial neuronal loss, as occurs in AD or its prodrome, MCI, than those with less redundancy before the appearance of clinical symptoms (Satz, 1993).

The etiology of cognitive decline in aging is poorly understood. One hypothesis is that depression may contribute to risk through stress-related neuronal injury and its action on the hypothalamic-pituitary-adrenal (HPA) axis (Butters et al., 2008). The HPA axis is the primary stress response system. It is activated in response to stressful events, and corticotropin-releasing hormone (CRH) is released from the hypothalamus stimulating adrenocorticotropic-releasing hormone (ACTH) release from the anterior pituitary gland, which further stimulates cortisol release from the adrenal cortex. HPA axis function works through negative feedback inhibition. When appropriate levels of ACTH and CRH are reached in the body, cortisol binds to receptor cells in the hippocampus (a structure specialized for learning and memory), hypothalamus, and anterior pituitary gland, to inhibit the stress system, including cortisol (Tsigos & Chrousos, 2002; Murri et al., 2014). In depression, hypercortisolemia or high levels of endogenous glucocorticoids are diagnostic (Lupien et al., 1999; Zunszain, Anacker, Cattaneo, Carvalho, & Pariante, 2011). Over time in a depressed state, elevated glucocorticoid levels cause lowered hippocampal formation volume, reduced metabolism, and eventual atrophy (Rapp et al., 2006; Wright & Persad, 2007). Hippocampal atrophy leads to decrease in cognitive/brain reserve and AD may ultimately develop (Butters et al., 2008).

Depression-related neuronal injury in aging is also associated with cerebrovascular disease (Alexopoulos et al, 1997). Ischemia in frontostriatal brain regions accompanies cerebrovascular disease. Brain ischemia occurs when there is insufficient blood flow to the brain to meet metabolic demand and leads to cerebral hypoxia and brain tissue death ("About Cerebral Ischemia", Columbia Doctors, 2017). Since the frontostriatal brain circuits mediate motor, cognitive, and behavioral functions, brain tissue death in these regions can help explain executive dysfunction, psychomotor slowing, and resistance to treatment exhibited in late-life depression (Alexopoulos, 2006). Brain ischemia in frontostriatal brain regions leads to decline in cognitive and brain reserve as well and AD may ultimately develop (Butters et al, 2008). Taking into account the role of HPA axis dysfunction and cerebrovascular disease, the reserve threshold hypothesis posits that depression causes neuronal injury which lowers cognitive and brain reserve and causes cognitive impairment to manifest earlier and more frequently (Butters et al, 2008).

1.3. Sleep Disorder in Aging. Individuals in the United States, particularly aging individuals, have an increased incidence of sleep disturbance (Baldwin et al., 2001). Sleep disturbance is often characterized by sleep fragmentation. Sleep fragmentation, or WASO (wake after sleep onset), consists of excessive awakenings during the night that leads to atypical suppression of night-time full awakenings and chronic sleep debt as a consequence of poor sleep quality (Durmer & Dinges, 2005; Troese et al., 2008; Smagula, Stone, Fabio, & Cauley, 2016; Mander, Winer, & Walker, 2017). In fact, the primary sleep complaint reported by aging individuals is difficulty initiating and maintaining sleep (insomnia) throughout the night (Baldwin et al., 2001; Kryger, Monjan, Bliwise, & Ancoli-Israel, 2004). Sleep architecture in aging is uniquely altered in a way that individuals experience decreases in slow wave sleep (SWS) and rapid eye

movement (REM) sleep, while there is an increase in stage 1 sleep, nighttime wakefulness, and sleep fragmentation (Van Cauter, Leproult, & Plat, 2000; Ancoli-Israel, 2009). This specific sleep architecture, namely the presence of increased sleep fragmentation, may ultimately drive older adults to experience sleep deprivation.

Sleep deprivation (SD) is a common plague to modern society, particularly in aging individuals, and is created through lack of sleep and/or chronically fragmented sleep that produces a number of negative effects on daily functioning (Kilgore et al., 2010). Sleep deprivation decreases sleep-related movements which has significant detrimental effects on cognitive functioning through deoxygenation of the brain, which is known to limit neural activity and plasticity and ultimately lead to brain atrophy (Potts, Rybak, & Paton, 2005; Segers et al, 2008; Troese et al., 2008; Feldman, Del Negro, & Gray, 2013; Hadanny & Efrati, 2015). Prolonged sleeplessness, which leads to SD, has been shown to have significant negative effects on perception, concentration, vision, reaction time, and processing speed (Kilgore et al., 2010; Orzel-Gryglewska, 2010). In addition, SD is reflected in the arousal system (Hayes, 2002) and has been shown through research to have a dose-dependent relationship with reduced daytime alertness, impaired executive function, fatigue, and mood problems. Most importantly, sleep disturbance is closely linked to a significant reduction in daytime functioning in almost all cognitive domains (Hedden, Oh, Younger, & Patel, 2013).

1.3.1. Cognition is Impaired by Sleep Deprivation. Sleep plays an imperative role in promoting higher order cognitive processes such as memory and integration of information, mainly through the consolidation of both declarative and nondeclarative memories. Memory consolidation is defined as the process of stabilizing a memory after initial acquisition so that it is encoded and stored in long-term memory (Walker, Brakefield, Morgan, Hobson, & Stickgold,

2002; Walker & Stickgold, 2004; Durmer & Dinges, 2005). Individuals with neurological and neurodegenerative disorders, such as MCI, experience higher rates of sleep disorder than healthy older adults (Beaulieu-Bonneau & Hudon, 2009) and have a unique pattern of sleep fragmentation (Tractenberg, Singer, Cummings, Thal, 2003; Crowley, 2011; McCarter, Lewis, & Boeve, 2012; Ju, Lucey, & Holtzman, 2014) that may provide insight into a better understanding of cognitive decline in the geriatric community.

Sleep and circadian disturbance is a key clinical feature of AD, and its prodrome MCI, that is typically characterized by frequent daytime napping, increased nocturnal wakefulness, and agitation ("sundowning") with these changes showing direct links to cognitive impairment and functional change (Naismith et al., 2010; Geda et al., 2013). Naismith et al. (2010) sought to explore the association between sleep-wake disturbances and neuropsychiatric/cognitive symptoms and suggested that sleep disturbance may be etiologically linked to neurodegenerative disorders as a prodromal, prognostic, or mediating factor. The study sample consisted of 15 older adults with naMCI who were administered psychiatric and neuropsychological assessments, sleep questionnaires and diaries, and 2 weeks of actigraphy (used to measure WASO and number of arousals/wake bouts). Results indicated that a greater WASO was associated with impaired attention and executive functioning and increased arousals/wake bouts were associated with poorer nonverbal learning and problem solving. These results suggest that sleep-wake disturbance, particularly in naMCI, is related to impaired cognitive functioning indicating shared neurobiological underpinnings. Subjective poor sleep quality in older adults has also been studied in connection with cognitive impairment.

Potvin et al. (2012) examined the relationship between subjective sleep quality and 1-year incident of cognitive impairment in cognitively normal men and women. This prospective

cohort study included a community sample of 1664 older adults between the ages of 65 and 96 years old. Sleep quality and cognitive functioning were assessed at baseline using the PSQI and MMSE, respectively. Incident cognitive impairment was defined as a follow-up MMSE score below the 15th percentile according to normative data and at least 2 points below the baseline score. Cognitively impaired participants were then split into amnestic and non-amnestic groups according to MMSE delayed recall performance. Results indicated that global PSQI scores were significantly associated with incident MCI in men but not in women. In women, sleep disturbance and long sleep duration were correlated with non-amnestic and amnestic cognitive impairment, respectively. In men, short sleep duration and habitual sleep efficiency were associated with amnestic and general incident cognitive impairment, respectively (Potvin et al., 2012). The results from this study show that subjective sleep quality impairs cognitive performance in a similar manner to objective sleep quality.

Research in both older and younger adults suggest that sleep disturbance is integral not only to neuropsychological function, but also to mood. Sleep deprivation and fragmentation, as well as insomnia, are associated with a variety of mood changes, as found in large community samples, and namely a risk factor for onset and recurrence of depression in older adults (Buysse, 2004; Cho et al, 2008; Naismith et al, 2010). Through these studies, one can conclude that sleep disorder presents as both a prodrome and a symptom of depression in aging individuals

1.3.2. Sleep Disorder as a Risk Factor and Symptom of Depression. Major depression changes objective sleep architecture in a variety of ways. Depressed patients experience increased wakefulness, reduced sleep efficiency, increased sleep onset latency, decreased total sleep time, decreased SWS, and fragmented sleep (Benca, Obermeyer, Thisted, & Gillin, 1992; Nutt et al, 2008). Slow-wave activity (SWA), a marker of homeostatic drive to sleep evaluated

by an electroencephalogram (EEG) during non-REM sleep, is also markedly different in depressed individuals. SWA is normally highest at the onset of sleep and through the first sleep cycle, then diminished through the subsequent sleep cycle as sleep debt is repaid and sleep drive declines. In depressed patients, the decrease in SWA throughout the subsequent sleep cycle is disrupted, with highest SWA occurring in the second non-REM period. Individuals with depression also subjectively report sleep disturbance, with this initial complaint sometimes occurring before diagnosis of depression (Argyropoulos & Wilson, 2005; Armitage, 2007). Sleep disturbances (e.g. persistent insomnia) can continue even after effective treatment of other symptoms of depression and puts an individual at greater risk for relapse (Carney, Segal, Edinger, & Krystal, 2007; Dombrovski et al., 2007). Persistent insomnia has been a topic of study as not just a symptom but also a significant risk factor for developing depression.

Sleep disturbance namely, persistent insomnia, is an established risk factor for the development of new-onset and recurrent major depressive disorder (Kennedy, Kelman, & Thomas, 1991; Brabbins et al., 1993; Mallon, Broman, & Hetta, 2000; Roberts, Shema, Kaplan, & Strawbridge, 2000). Research of persistent insomnia and whether it perpetuates MDD has not been as fully explored. Pigeon et al. (2008) conducted a longitudinal study to examine the relationship between insomnia and continuation of depression and/or dysthymia (e.g. persistent depressive disorder) in older adults. The participant sample included older adults over the age of 60 with depression. Participants were taken from a cohort that participated in Project IMPACT, a multi-site intervention study of 1801 elderly patients with MDD and/or dysthymia. Participants were assessed on insomnia status using the Hopkins Symptom Checklist (HSCL) at baseline and 3-, 6-, and 12-month time points and were sorted into study groups (persistent insomnia, intermediate insomnia, no insomnia). Depression status was also evaluated at these time points

using the 20 depression items on the HSCL and through a Structured Clinical Interview for DSM-III-R (SCID). Results indicated that participants with persistent insomnia were 1.8 to 3.5 times more likely to remain depressed when compared to their counterparts without insomnia. This pattern was more robust in participants with MDD as opposed to dysthymia. These results suggest that persistent insomnia is not only a risk factor for depression but also serves to perpetuate the illness in those that receive standard care for depression (Pigeon et al., 2008).

Depressed older adults that experience insomnia also suffer from excessive daytime sleepiness (EDS) with this association being shown in the few prospective studies that have been conducted (Dryman & Eaton, 1991; Livingston, Blizard, & Mann, 1993; Cho et al., 2008; Jaussent et al., 2011). Jaussent et al. (2011) sought to explore insomnia and EDS as predictive factors for depressive symptoms in community-dwelling older adults. 3824 older adults, ages 65 or older and free of depressive symptoms at baseline, were taken from the cohort partaking in The French Three-City Study, a longitudinal study that spanned across 4 years. Questionnaires were used to evaluate insomnia symptoms, EDS, and use of sleep medication. Depressive symptoms were assessed at 2- and 4-year follow-up visits using the CES-D. Results indicated that insomnia symptoms and EDS each independently increased risk for incident depressive symptoms. Poor sleep quality and difficulty in initiating and maintaining sleep were also found to be risk factors of incident depressive symptoms. Finally, use of sleep medication was a risk factor of incident depressive symptoms, independent of insomnia symptoms and EDS. These results indicate that insomnia symptoms, EDS, and use of sleep medication all increase the risk for incident depression and therefore may be explored clinically as early indicators of depression in older adults (Jaussent et al., 2011).

1.3.3. Sleep and Depression in MCI and AD. The link between sleep disorder, including self-reported symptoms and objective sleep architecture, and impaired cognition resulting in neurodegenerative disorders, such as MCI, is well established (Naismith et al, 2010). One factor that may influence the relationship between sleep and cognition is depression, a disorder that is also significantly affected by sleep quality. Few studies have considered the role that depression plays in the association between sleep and cognition despite evidence that poor sleep is closely related to depression (Sbarra & Allen, 2009) and sleep disorder and depressive symptoms are both independently associated with cognitive impairment (Riemann, Berger, & Voderholzer, 2001; Naismith, Norrie, Lewis, Scott, & Hickie, 2009; Koehler, Thomas, Barnett, & O'Brien, 2010; Smagula et al., 2013; Snyder, 2013).

Mellor et al. (2018) sought to investigate the association of sleep architecture/sleep-wake patterns and daytime cognitive performance in older adults with a current diagnosis of MDD. The participant sample included 43 older adults, ages 50-78, including individuals that had a current clinical diagnosis of MDD (n=10) and those that were not currently depressed (n=33). Home polysomnography (PSG), an in-home method used to diagnose a variety of sleep disorders by recording brain waves, blood oxygenation, heart rate, breathing, and leg/eye movements, was conducted for 2 nights, with each night separated by a week. Patients also wore an actiwatch, a non-invasive monitor worn on the wrist that is used to measure sleep-wake cycles, for a total of two weeks. A standardized battery of neurocognitive assessments was given to all participants. Results revealed that sleep-wake patterns, measured by actigraphy (e.g. actiwatch), were linked to vigilance and memory across the entire sample. Specifically, greater WASO was associated with slower vigilance (speed) and poorer memory (delayed recall accuracy). There were medium to large interaction effects of depression and actigraphic sleep variables (e.g. WASO and total

sleep time) in predicting performance on cognitive variables. Significant results linking PSG data and depression status were not found. Therefore, this study shows that depression has a significant impact on the relationship between sleep-wake patterns (but not sleep architecture) and cognition (Mellor et al., 2018). The association between sleep architecture, depression, and cognition should still be further explored in future studies. The results found associating sleep-wake variables and depression with cognition provide exciting possibilities for early intervention of cognitive impairment in older adults. Early detection of sleep problems in both depressed and non-depressed older adults offers a possible window to provide behavioral or pharmacological treatments that may improve cognition (Pace-Schott & Spencer, 2011; Mellor et al., 2018)

1.4. Hypotheses.

Based on the studies and information provided regarding current and historical depressive symptoms and sleep parameters, and their effect on pathological cognitive decline in aging individuals, the following hypotheses were proposed and tested in this thesis study.

1.4.1. Hypothesis I: Impact of Age and Health. Current depressive symptoms and/or history of clinical diagnosis of depression in a community sample will be associated with age and health history.

1.4.1.1. Chronic Health is Associated with Depression Status. The presence of any history of depression in a community sample will be associated with higher incidence of chronic health problems including cerebrovascular disease, cardiovascular disease, and diabetes (Lenze et al, 2005; Moussavi et al, 2007; Taylor, Aizenstein, & Alexopoulos, 2013).

1.4.1.2. Health Deterioration in Aging. Older participants will report a greater amount of health problems than younger participants across the whole sample, as health deterioration corresponds with increased age (Cauley, 2012; McNicoll, 2012).

1.4.2. Hypothesis II: Depressive Symptoms are Connected to Poorer Sleep Quality. Participants with current depressive symptoms will show poorer sleep quality than participants without current or historical depression.

1.4.2.1. Depressive Symptoms and Poor Objective Sleep Quality. Participants with current depressive symptoms will show poorer objective sleep quality, as measured through 7 consecutive days and nights of wrist actigraphy, than participants without current or historical depression (Naismith et al., 2009, 2011).

1.4.2.2. Subjective Measures of Sleep will Reflect Objective Measures. Through subjective measures of sleep quality (e.g. Epworth Sleepiness Scale, Stanford Sleepiness Scale, Pittsburgh Sleep Quality Index), participants with current depressive symptoms will report a greater amount of sleep problems than participants without current or historical depression (Foley et a., 1995; Becker, Jesus, Joao, Viseu, & Martins, 2017).

1.4.2.3. Depressive History will Impact Sleep Quality. Participants with a *history* of diagnosed depression will show and report more sleep problems than participants without a depressive history, as persistent insomnia may continue even after effective treatment of depression (Carney, Segal, Edinger, & Krystal, 2007; Dombrovski et al, 2007).

1.4.3. Hypothesis III: Current Depressive Symptoms Impair Cognition. Aging participants who display symptoms of *current* depression will perform more poorly on neurocognitive testing (e.g. paper and pencil neurocognitive assessments and overnight memory consolidation task) than participants without current or historical depressive symptomatology (Lenze et al., 2018).

1.4.3.1. Historical Depressive Symptoms Impair Cognition. Aging participants who report a *history* of diagnosed depression will perform more poorly on neurocognitive testing than participants without depressive history (Rapp et al., 2011).

1.4.4. Hypothesis IV: Higher Incidence of MCI in Depressed Older Adults. Aging participants who display symptoms of *current* depression will have a higher incidence of aMCI, as late-life depression is associated with poor cognitive outcomes such as neurodegenerative disorders (Sheline et al., 2006; Dotson et al., 2010; Lenze et al., 2018).

1.4.5. Hypothesis V: Cognitive Reserve Moderates Levels of Cognitive Impairment. Cognitive reserve (measured through education level and IQ correlates such as the vocabulary subtest of the WAIS-III and AMNART) will have a protective or moderating effect on neurocognitive impairment in participants with or without positive current or historical depressive symptoms (Stern, 2002; Stern et al., 2018).

CHAPTER 2

METHOD

2.1 Participants.

A sample of aging individuals were recruited as part of an externally (National Institute of Health; NIH) funded sleep monitoring project (number R44AG059536-01). University of Maine's Institutional Review Board (IRB) approved this study in which participants, ages 65 to 85 years, were recruited from the greater Bangor, Maine area (within 40 minutes of Bangor). Participants diagnosed with MCI (n=12) were referred by Dr. Clifford Singer, at the Mood and Memory Clinic at Northern Lights Acadia Hospital in Bangor, Maine. HIPAA (Health Insurance Portability and Accountability Act) acceptance for this study was obtained in order to allow researchers to use clinical reports made prior to assessment to determine symptomology and diagnosis only for patients referred from the Mood and Memory Clinic. A socio-demographically similar, but undiagnosed, group of participants (n=38) were accumulated through distribution of flyers in the aging community and through area agencies. In addition, Dr. Lenard Kaye, director of the University of Maine Center on Aging, provided contact information for older adults that had expressed interest in participating in research studies. All participants were given information over the phone and at the time of consent, in person, during the study visit. Both the MCI-diagnosed and undiagnosed participant groups were matched on sociodemographic and health characteristics, with the difference being the clinical diagnosis of MCI.

2.1.1. Recruitment Sites. All participants with clinical diagnosis of MCI were recruited from the Mood and Memory Clinic at Northern Light Acadia Hospital in Bangor, Maine led by

chief geriatric psychiatrist, Dr. Singer. The Mood and Memory Clinic is a geriatric psychiatry facility catering to accurate diagnosis of common psychiatric disorders in aging.

Additional participants reached out to our participant study staff via email or phone upon seeing a study flyer. Facilities where flyers were placed include, but are not limited to, Eastern Area Agency on Aging, Dirigo Pines, Winterberry Heights Assisted Living and Memory Care, Sunbury Village, Bradford Commons, Edward Ernst Manor, and Ellen M. Leach Memorial Home. These individuals could contact us through the contact information provided on the study flyer. Brief presentations were given to communities of older adults to give additional information on this study and to answer questions, during which study flyers were distributed. Dr. Lenard Kaye, heads the University of Maine Center on Aging, a community center offering various services and programs to aging individuals while promoting research, education, and training to individuals in geriatric research and care. The center keeps a large database of names and contact information of local older adults interested in participating in research studies. Individuals on this list, that were located in the Greater Bangor area, were contacted over the phone to determine interest and eligibility for the study. Finally, aging individuals reached out to our study team via email following media coverage of our project through the Bangor Daily News newspaper and various local news stations.

2.1.2. Inclusionary and Exclusionary Criteria. Participants were prescreened for initial eligibility criteria including age and physical and mental health status. Inclusionary criteria for this study includes male or female participants who are between the ages of 65 and 85 years, live independently in the community, are English speaking, and possess adequate vision with correction to read. For the MCI group, MoCA score <26 (inclusive), with a delayed recall subtest score of 0 or 1 out of 5; Clinical Dementia Rating score of 0.5; normal circadian entrainment to

nighttime sleep hours; and decision making capacity to consent to research participation is required. For the Comparison group, normal cognition for age (MoCA ≥ 26) and no history of sleep-related disorders, periodic leg syndrome, hypnotic/psychotropic medication changes, and significant neurological, medical, or psychiatric disorder other than depression are inclusionary (drug/alcohol abuse >5 years ago is allowed). Participants in both groups have varying levels of depressive symptoms and could be taking medication for their depression, but are labeled as having current depressive symptoms and a positive history of depression. Exclusionary criteria for the MCI group include normal cognition for age (MoCA ≥ 26 or CDR=0), dementia (MoCA< 15 or CDR ≥1), non-amnestic MCI, evidence of another psychiatric or medical disorder that may be a cause for MCI (e.g. partial list: more than one cerebral infarct, poorly controlled diabetes, hypothyroidism, parkinsonism, parasomnia or REM sleep disorder, developmental disability, etc.); acute symptom onset; restless or periodic leg syndrome; hypnotic or psychotropic medication change; active bipolar disorder or other psychotic disorders (e.g. schizophrenia, delusional disorder, schizotypal personality disorder, schizoaffective disorder, etc.); drug/alcohol abuse ≤5 years ago (self-report).

2.1.3. Institutional Review Board Approval. This project achieved approval from the University of Maine's IRB, with a Business Associate Agreement (BAA) between the University of Maine and Northern Light Acadia Hospital. This study fulfills all requirements for Health Insurance Portability and Accountability Act (HIPAA) compliance.

2.1.4. Risks and Discomforts. Risk to a participant who is from a vulnerable population of cognitively impaired persons and some who are depressed has been carefully considered for this study. First, special consideration was taken if a participant presented with severe depressive symptoms (e.g. a score of ≥24 on the CES-D). To ensure these participants were able to get

appropriate help, contact information was provided on the consent form to community resources, most notably the Maine Crisis Hotline and the Geriatric Mental Health and Neuropsychiatry Program at Acadia Hospital. All depressive measures were reviewed after completion of the study on that day. Follow-up communication via email or phone encouraging participants to contact available resources and what those resources were was done that day if participants showed severe depressive symptomology or presented as a danger to themselves or others. Referrals and follow-up communication were completed according to the standards provided on the University of Maine IRB website. Contact information of the participant was collected before the onset of the study as a component of the informed consent. In order to insure the cognitively impaired person was adequately relayed information on participation, all study information was explained in layman's terms by both the cognitively impaired person's physician and the study stuff. All questions were answered and participants who wished to have a caretaker/case manager/family member/friend assist in communication with researchers were encouraged to do so. Though there were no physical risks, one issue may be the equipment of the sleep study in the bedroom. There is very little equipment that remained in the home overnight (a small box for wireless data collection placed at the foot of or underneath the bed, the mattress sheet unobtrusively below the standard bed-sheet, the tablet for testing, and the Actiwatch device) and no complaints were relayed from participants regarding discomfort or annoyance of equipment. In regards to the 60-minute neurocognitive testing, risks were limited to time, inconvenience, fatigue, and possible frustration due to the nature of the testing. Researchers provided frequent breaks and the option to discontinue testing at any point without loss of compensation if the participant showed discomfort or fatigue. Researchers rescheduled discontinued testing if desired by the participant.

2.1.5 Benefits. As a participant in this study, individuals may discover information about their sleep, mood, and cognitive performance, as tested in this research. The results of testing will be revealed and interpreted for participants in a thank-you letter after the study is completed, with the caveat that these results are for research purposes only. If additional information is requested, participants can meet with a researcher to discuss the findings of the study in general, and their individual participation. It is also a benefit to contribute to a better understanding of the association between late-life depression and neurocognitive functioning in aging and support future work toward early detection of aging-related neurological disorders and possible minimization of further cognitive decline.

2.1.6. Confidentiality. Participant data was de-identified when any data reached the laboratory and was instead linked to a study number. The link between data and identifying information (i.e. name, address, etc.) is encrypted through a double password method for information stored on internet drive, and a hard copy is maintained in a locked file cabinet in a locked lab room, ensuring named investigators are the only ones with access to the files. The key for the filing cabinet is kept in a separate, locked lab room to provide increased insurance that all information is secure. All deidentified data collected in this study will be kept indefinitely according to NIH guidelines. The identification key will be protected until March 1, 2028 allowing adequate time for data collection and potential follow-up studies.

2.1.7. Compensation. Participants had a chance to earn up to $150 total for completion of this research study. Compensation for the completion of the two-night sleep study was a $100 Visa gift card and compensation for the completion of the neurocognitive follow-up assessment was a $50 Visa gift card. If individuals withdrew before the start of the assessment,

compensation was not provided. However, if testing was discontinued due to fatigue and the participant did not want to reschedule then full compensation was provided.

2.1.8. Voluntary Participation. Participants were informed during initial communication about the study and at the time of informed consent that participation was entirely voluntary and the participant had a right to decide whether or not he/she chooses to participant in the study and may discontinue testing at any time during the course of the study. The theme of voluntary participation was repeated and emphasized to ensure participants fully understood the rights they had as a participant and that participants did not feel any pressure from the researchers to participate or complete assessments.

2.2 Materials and Measures.

All participants were assessed using multiple IRB approved measures and methods used for assessing current and historical depressive symptoms, neurocognitive status, and sleep parameters, outlined below. This study was broken into two parts, Study 1 (pilot study; N=18) and Study 2 (N=32).

Study 1 was the pilot study for our lab's mattress device (not a component of this thesis), conducted from Fall 2016-Fall 2017, and had some protocol differences. Most notably, depression was not a focus in the pilot study and participants were only asked a question about current depression (binary: yes/no) on the demographic interview with no measures assessing depression severity or history of diagnosed depression. In addition, cognitive reserve proxy measures were not included in the one-month neurocognitive follow-up for study 1 participants. All other self-report sleep, actigraphy, overnight memory consolidation, and one-month follow-up neurocognitive measures were identical between studies. The primary reason for inclusion of Study 1 participants in analyses was to have a greater n for the current depression group.

Study 2 is an NIH Phase II study on our lab's mattress device that has been ongoing since March 2019. My thesis project on depression status in older adults has been folded into this study. Depression measures (CES-D, supplemental questions on depressive history) and cognitive reserve proxy measures (vocabulary subtest of the WAIS-III, AMNART) have been added to protocol. All other self-report sleep, actigraphy, overnight memory consolidation, and one-month follow-up measures are identical between studies. To keep groups as similar as possible, current depression group for analyses were made only by endorsement of current depression. History of diagnosed depression was only assessed in Study 2.

2.2.1. Depression Measures. Depression measures were used to assess both current and historical depressive symptoms in Study 2. These measures are used to 1.) run exploratory analyses between sleep and cognitive variables across depression scores on CES-D and 2.) group participants into study groups for historical depression analyses.

2.2.1.1 Center for Epidemiological Studies Depression Scale. The Center for Epidemiological Studies Depression Scale (CES-D) is a brief self-report questionnaire on depressive symptoms. Participants were instructed to rate how often they felt a certain way during the past week by checking one of four boxes: rarely or none of the time (less than 1 day), some or little of the time (1-2 days), occasionally or a moderate amount of time (3-4 days), and most or all of the time (5-7 days) (Radloff, 1977) (see Appendix A). This measure has been successfully used to measure depression in older adults mainly due to its brief format and low levels of cognitive burden (Andresen, Malmgren, Carter, & Patrick, 1994; Lewinsohn et al, 1997).

2.2.1.2 Supplemental Questions on Depressive History. Participants were asked a number of supplemental questions assessing depressive and psychiatric history designed

specifically for use in this study (see Appendix B). The supplemental questions were utilized to establish if a participant had a history of clinical depression and to learn more about that history. All questions were delivered in a verbal interview with the participant.

2.2.2. Neurocognitive Measures. A battery of validated standardized neurocognitive assessments was used to test current cognitive functioning in various domains, including, but not limited to: visuospatial, episodic and working memory, and verbal learning. A novel procedural memory task was also utilized in testing to assess overnight memory consolidation. Participants in both Study 1 and Study 2 were assessed on all neurocognitive measures.

2.2.2.1. Montreal Cognitive Assessment. The Montreal Cognitive Assessment (MoCA) is a brief (1 page, <10 minutes) screening instrument for MCI and mild AD assessing seven areas of cognition: visuospatial and executive functioning, naming, memory (i.e. delayed recall), attention, language, abstraction, and orientation (Nasreddine et al., 2005) (see Appendix C). The MoCA is designed to provide a measure of global cognitive function. Scores ≥ 26 indicate normal cognition, scores 19-25 indicate MCI, and scores less than 19 indicate dementia (Freitas, Simoes, Alves, & Santana, 2013). Using these cut-off scores, the MoCA has 90% and 100% specificity to detect MCI and mild AD, respectively, as well as a sensitivity of 87% (Nasreddine et al., 2005).

2.2.2.2. Overnight Procedural Memory Consolidation Task. Since sleep quality impacts overnight memory consolidation, an overnight memory consolidation task was developed for use in this study and mimics the procedural protocol of Walker and Stickgold (2004). This task was developed as an application for an Android tablet. This task consists of 4 circles, labeled 1, 2, 3, and 4. Once the task starts, a participant is presented with a 5 number sequence consisting of numbers 1-4 which remains on the screen. The participant was told to

remember this sequence and asked to tap the sequence "as quickly and as accurately as possible" for 30 seconds followed by a 30 second rest period. This protocol was repeated for 12 trials with the same sequence. Participants were instructed to complete this task once in the evening on the first visit (following a full completion of the protocol with the research team as training) and once the next morning after awakening. A variety of information was taken from this task including number of correct sequences, % improvement overnight, speed of tapping, etc. (Table 1). It is shown in previous literature that procedural memory should improve by ~20% in individuals with proper sleep efficiency (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002; Stickgold & Walker, 2005).

Table 1
Overnight Memory Consolidation Variables

Variable Name	**Definition**
Total Taps	Total sum of taps for the 12 trial assessment
Total Correct Taps	Total sum of correct taps for the 12 trial assessment
Total Correct Sequences	Total sum of correct sequences for the 12 trial assessment
Average Correct Taps per Trial	The number of correct taps divided by number of trials (12)
Efficiency	Number of correct sequences divided by number of trials (12)
Average Speed	(Number of taps per trial) How fast a participant is tapping
Percent Correct Taps	Percentage of total correct taps

Table 1 Continued

Percent Improvement	Percentage improvement of correct taps between night and morning assessments
Difference in Total Number of Taps between Night and Morning	Difference between morning and night of total taps
Difference in Total Correct Taps between Night and Morning	Difference between morning and night of correct taps
Difference in Number of Correct Sequences between Night and Morning	Difference between morning and night of correct sequences
Average Error Rate per Trial	Number of incorrect taps divided by number of trials (12)
Average Number of Taps for Last 3 Trials (Morning and Night)	Average number of total taps for the last 3 trials for both morning and night assessments
Average Correct Sequences for Last 3 Trials (Morning and Night)	Average number of correct sequences for the last 3 trials for both morning and night assessments
Difference in Number of Taps in Last 3 Trials between Night and Morning	Difference between morning and night of total taps in the last 3 trials
Difference in Number of Correct Sequences in Last 3 Trials between Night and Morning	Difference between morning and night of correct sequences in last 3 trials
Percent Difference in Number of Taps (Last 3 Trials)	Percentage of difference between morning and night of total taps for the last 3 trials
Percent Difference in Number of Correct Sequences (Last 3 Trials)	Percentage of difference between morning and night of correct sequences for the last 3 trials

Table 1 Continued

Average Number of Taps for Last 6 Trials (Morning and Night)	Average Number of Total Taps for the Last 6 Trials for both morning and night assessments
Average Correct Sequences for Last 6 Trials (Morning and Night)	Average number of correct sequences for the last 6 trials for both morning and night assessments
Difference in Number of Taps in Last 6 Trials between Night and Morning	Difference between morning and night of total taps in the last 6 trials
Difference in Number of Correct Sequences in Last 6 Trials between Night and Morning	Difference between morning and night of correct sequences in last 6 trials
Percent Difference in Number of Taps (Last 6 Trials)	Percentage of difference between morning and night of total taps for the last 6 trials
Percent Difference in Number of Correct Sequences (Last 6 Trials)	Difference between morning and night of correct sequences in last 6 trials

Note. All output variables assess overnight memory consolidation using a sequence tapping application adapted from Walker and Stickgold literature.

2.2.2.3. Trail Making Test Parts A and B. The Trail Making Test (TMT) is comprised of two parts; Trails A and Trails B (see Appendix D). Both parts consist of 25 circles scattered across a page. For Trails A, participants were instructed to keep their pen on the paper while connecting circles containing numbers 1-25 in ascending order (e.g. 1 → 2 → 3 → 4 …). For Trails B, the circles contain both numbers (1-13) and letters (A-L) and participants have the added task of connecting the circles alternating between numbers and letters in ascending order (e.g. 1 → A → 2 → B …) (Tombaugh, 2004). Shorter sample versions of Trails A and Trails B were given before each assessment to ensure participants understand the instructions. If an error

was made by a participant during the assessment, researchers immediately corrected the mistake before allowing the assessment to continue. Both assessments were timed by researchers. The TMT assesses visual scanning, sequencing, and task switching abilities which primarily activates the prefrontal regions of the frontal lobe (Ashendorf et al., 2008; Salthouse, 2011). TMT shows good psychometric properties, including construct validity and test-retest reliability (Giovagnoli et al., 1996; Amodio et al., 2002).

2.2.2.4. Hopkins Verbal Learning Test-Revised. Form 1 of the Hopkins Verbal Learning Test-Revised (HVLT-R) was used for all participants (Benedict, Schretlen, Groninger, & Brandt, 1998). This assessment involves 12 target words, four words from each of three semantic categories, to be learned over the course of three learning trials. After a 20-25 minute delay, a delayed free recall trial and recognition trial was administered. The delayed free recall trial allowed the participant to list all words from the original list that they remember. The recognition trial allowed participants to indicate whether each word on a list of 24 words was or was not on the original list. This list of words contains the 12 target words, as well as six semantically related and six semantically unrelated words that were not on the original list. This assessment is used to measure verbal learning, episodic verbal memory, and confrontational word retrieval through activation of the hippocampal region, temporal lobe, and subsequent connections to the cortex (Xu, Xiao, Rahardjo, & Hogervorst, 2015). The HVLT-R has acceptable reliability and good validity, and is best suited for use in an elderly population with suspected dementia (Benedict, Schretlen, Groninger, & Brandt, 1998; Sharpito, Benedict, Schretlen, & Brandt, 1999).

2.2.2.5. Boston Naming Test. The Boston Naming Test (BNT) short form contains 15 images of different objects (e.g. hammock, Sphinx, etc.) of varied difficulty (Mack, Freed,

Williams, & Henderson, 1992). Participants were asked to identify the object in the picture as quickly as possible. If a participant could not identify the object within 10 seconds or gave an incorrect response, he or she was given a semantic cue. If the participant was still unable to identify the object, he or she was given a phonemic cue (e.g. the first letter of the object). If the participant was again not able to identify the object, researchers provided the object name as a multiple choice option among four words. The BNT assesses confrontational word retrieval and semantic memory focused in the posterior section of the left temporal lobe (Trebuchon-Da Fonseca et al, 2009). The BNT short form showed good psychometric properties (Fastenau, Denburg, & Mauer, 1998).

2.2.2.6. Brief Visuospatial Memory Test-Revised. The Brief Visuospatial Memory Test-Revised (BVMT-R) Form 1 was used on all participants (Benedict, Schretlen, Groninger, Dobraski, & Schpritz, 1996). For this assessment, participants were instructed to study an array of 6 simple, 2-dimensional figures for 10 seconds and draw as many figures as they can remember in the proper places after the display is removed from sight. There are three trials of drawing, followed by a delayed recall trial 25 minutes after the last sighting of the display. Additionally, there is a recognition trial in which researchers showed a series of figures one at a time and participants were asked to identify whether each figure was or was not on the original display. This test assesses visual learning and memory, focused in the visual cortex of the occipital lobe (Tam & Schmitter-Edgecombe, 2013). The BVMT-R shows excellent interform reliability and construct and criterion validity (Benedict, Schretlen, Groninger, Dobraski, & Schpritz, 1996).

2.2.3. Cognitive Reserve Measures. Proxy measures of cognitive reserve such as intelligence, reading ability, and vocabulary were assessed in order to quantify if a participant

had low or high levels of cognitive reserve. Aging research has shown that premorbid intelligence, as assessed with word-reading tests, can help determine cognitive reserve capacity when combined with assessing vocabulary since these measures of cognition tend to remain stable over time (Stern, 2009). Cognitive reserve proxy measures were only administered to Study 2 participants.

2.2.3.1. American National Adult Reading Test. The American National Adult Reading Test (AMNART) is a neuropsychological assessment used to provide a measure of premorbid intelligence before onset of illness or injury (Blair & Spreen, 1989; Uttl, 2002). Participants were presented with 45 irregularly spelled words one at a time and prompted for a single pronunciation of each word (see Appendix E).

2.2.3.2. Vocabulary subtest of the Wechsler Adult Intelligence Scale-Third Edition. The vocabulary subtest of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) is a component of an in-depth adult intelligence scale that measures semantic knowledge. Participants were asked to define words presented to them (Tulsky, Saklofske, Wilkins, & Weiss, 2001).

2.2.4. Sleep Measures. The purpose of completing various sleep measures was to get a more comprehensive understanding of a participant's sleep patterns and to compare sleep quality to depression and neurocognitive status. Objective (*Sleep*Move, Actiwatch) and self-report (PSQI, Stanford Sleepiness Scale, Consensus Sleep Diary, and Epworth Sleepiness Scale) indices were used to identify sleep fragmentation by measuring sleep quality, as well as sleep deprivation through daytime sleepiness. *Sleep*Move device measures were not analyzed as part of this thesis and are only included here to identify it as part of the protocol for the study. Sleep measures were a main component of both Study 1 and Study 2.

2.2.4.1. SleepMove. The *Sleep*Move system is a patented (US Patent 13/106,451) mattress device developed by our team at Activas Diagnostics (Activas-Diagnostics.com). The novel sleep monitoring device consists of 32 small pressure sensors embedded into a noninvasive sheet and used to collect data on movement and respiration throughout the night. 16 are 50-pound sensors located at the head and torso areas. The remaining 16 sensors are 1-pound sensors located at the chest, abdomen, and pelvis regions. With algorithms developed by our team, the *Sleep*Move device is designed to identify movement and sleep-wake parameters, as well as respiration throughout the night. Using a noninvasive design, a waterproof-type sheet with embedded flat sensors is placed directly under a standard bed sheet with the goal of becoming an alternative to current sleep monitoring techniques.

2.2.4.2. Philips Respironics Actiwatch™ The Actiwatch 2 is a small (43mm x 23mm x 10mm, 16g), waterproof, unobtrusive device worn on a participant's wrist and used to measure overnight movement and sleep/wake parameters with accelerometer-type sensors (Philips Respironics, 2013). This device is worn on the non-dominant wrist of the participant for 7 consecutive days and nights as a standard measure of sleep/wake. The device has been shown to be sufficient in assessing movement in older adults through empirical research (Hurelbrink, Lewis, & Barker, 2005). In addition, it is the gold standard for assessing sleep parameters (for output measures see Table 2).

Table 2
Philips Respironics Actigraphic Output Measures

Output Variable	Definition of Output Variable
Bed Time	Time participant got into bed for the night (24 hour clock)

Table 2 Continued

Get Up Time	Time participant got out of bed after sleep period (24 hour clock)
Time in Bed	Difference between “Bed Time” and “Get Up Time” (hr:min)
Sleep Start	Time participant fell asleep (24 hour clock)
Sleep End	Time participant had their final awakening (24 hour clock)
Assumed Sleep	Time between “Sleep Start” and “Sleep End” (hr:min)
Actual Sleep Time	Amount of sleep determined by the Actiwatch algorithm (Assumed Sleep – Wake time) (hr:min)
Actual Sleep (%)	Percentage of actual sleep throughout the night
Actual Wake Time	Amount of time awake determined by the Actiwatch algorithm (hr:min)
Actual Wake (%)	Percentage of time spent awake throughout the night
Sleep Efficiency	“Actual Sleep Time” / “Time in Bed (%)
Sleep Latency	Latency before sleep onset following bed time (hr:min)
Sleep Bouts	The actual number of episodes of sleep
Wake Bouts	The actual number of episodes of wakefulness

Table 2 Continued

Mean Sleep Bout Time	Total duration of sleep / sleep bouts (hr:min)
Mean Wake Bout Time	Total duration of sleep / wake bouts (hr:min)
Immobile Mins	Total number of minutes during "Assumed Sleep" where the counts per minute are below a predetermined "immobility" threshold
Immobile Time (%)	"Immobile Mins" / "Assumed Sleep" (%)
Moving Mins	Total number of minutes during "Assumed Sleep" where the counts per minute are above a predetermined "immobility" threshold
Moving Time (%)	"Moving Mins" / "Assumed Sleep" (%)
No of Immobile Phases	The number continuous periods made up of consecutive epochs where the counts are < than the "immobility" threshold. E.g. suppose a score of <4 was recorded in 4 consecutive epochs. This is classified as one Immobile Phase.
Mean Length Immobility	Average length of the immobile bouts
One Minute Immobility	The number of immobile phases where the duration is no more than 1 minute.
One Min Immobility (%)	The number of immobile phases of 1 minute as a proportion of the number of immobile phases (%).
Fragmentation Index	The addition of Percentage Minutes Moving and Percentage Immobility. This is used as an indicator of restlessness.

Table 2 Continued

Avg. Wake Movement	Average activity score per epoch of the wake period before the previous night's sleep. Calculated by activity counts between sleep end in the morning and sleep start at night.

Note. All output variables from participant Actiwatch data, obtained using *Philips Actiware 6*, version 6.0.9.

2.2.4.3. Pittsburgh Sleep Quality Index. The Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) is a self-report measure that assesses sleep quality over a one-month time interval. Sleep quality is determined through assessment of seven components of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime functioning (see Appendix F)

2.2.4.4. Stanford Sleepiness Scale. The Stanford Sleepiness Scale (SSS; Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973) is a self-report measure of alertness for each hour throughout the day, over a period of 7 consecutive days (see Appendix G). This subjective measure is scored using a 7-point scale to indicate degree of sleepiness (e.g. 1= feeling active, vital, alert, or wide awake; 2= functioning at high levels but not fully alert, etc.; and X = asleep). This measure allows for self-report parameters of sleep deprivation. Participants completed this scale starting on the first day of the sleep study and continuing for the 7 days they wore the Actiwatch (above; 2.2.4.2.).

2.2.4.5. Consensus Sleep Diary. Participants were asked to complete a standardized sleep diary (see Appendix H) for seven consecutive days while wearing the Actiwatch (above;

2.2.4.2.). The Consensus Sleep Diary is a validated subjective measure used to assess parameters of sleep quality such as sleep/wake times, self-reported sleep fragmentation, sleep quality, nap measures, etc. (Carney et al., 2012).

2.2.4.6. Epworth Sleepiness Scale. The Epworth Sleepiness Scale (ESS; Johns, 1992) is a self-report measure of dozing likelihood in various situations throughout the day. The participant rated his or her probability of falling asleep on a scale from 0 (no chance of dozing) to 3 (high chance of dozing) for eight different situations that most people engage in during their daily life (e.g. watching TV, sitting as a passenger in a car for an hour without a break, etc.) (see Appendix I). Responses were used to analyze overall daytime sleepiness and to assess sleep deprivation.

2.3. Study Design and Procedure.

Participants from either the MCI group or the group of undiagnosed community controls who endorsed current depression in intake interview were considered positive for current depression (G1, Current Dep). Group 1 includes participants from Study 1 and Study 2. Participants from either the MCI group or the group of undiagnosed community controls who endorsed a history of diagnosed depression but no current depression were considered positive for history of diagnosed depression (G2, History of Dep). Group 2 includes participants from Study 2 only. Those who did not endorse current depression or history of diagnosed depression were considered negative for depression (G3, Non-Dep). Group 3 includes participants from Study 2 only, as we do not have information on history of diagnosed depression from participants in Study 1 that did not endorse current depression.

2.3.1 Participant Recruitment Protocol. Participants with previous diagnosis of MCI were screened by clinical staff at the Mood and Memory Clinic at Northern Light Acadia

Hospital for study eligibility based on inclusionary and exclusionary criteria, and then referred to the study staff for scheduling. Undiagnosed comparison participants were a community sample who contacted research assistants via phone or email. Those who expressed interest in the study were screened for eligibility using a recruitment script for the study, based on inclusionary and exclusionary criteria, by research assistants over the phone. The University of Maine Center on Aging also provided access to their large database of names and contact information of local older adults interested in participating in research studies. Appropriately aged individuals located in the Greater Bangor area from this database were contacted by a research assistant over the phone to determine interest and eligibility using a recruitment script for the study based on inclusionary and exclusionary criteria.

2.3.2. Sleep Study Visit. Once individuals met eligibility criteria and agreed to participate in the study over the phone, a study visit was scheduled to complete informed consent and set up the 2 night sleep study at the participant's home. The study visit was conducted at the participant's home and lasted 60-90 minutes. Study protocol is described below and outlined in Figure 1.

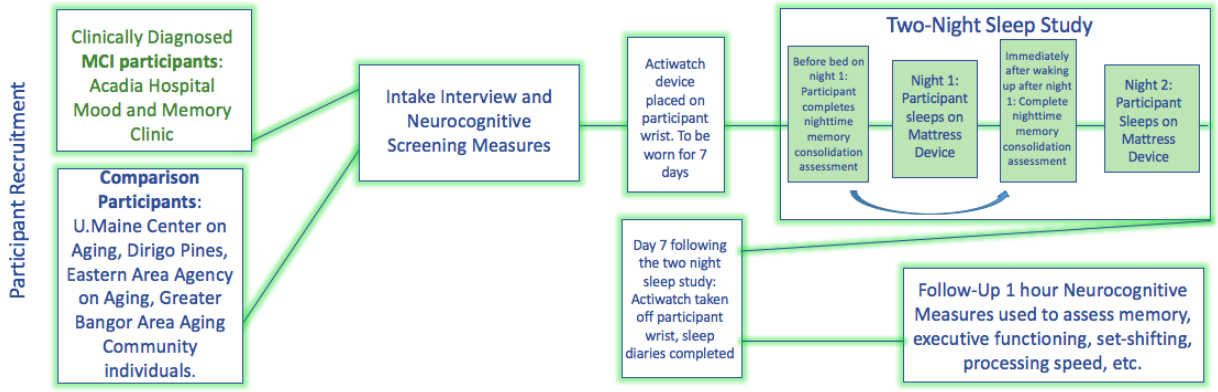


Figure 1. Study Protocol Timeline. A timeline of the participant experience in this study. Participants were recruited from Northern Light Acadia Hospital or community areas and completed a sleep study visit and a follow-up neurocognitive visit.

2.3.2.1. Informed Consent. Upon arrival to each participant's home, the trained undergraduate or graduate research assistant explained the study and reviewed all aspects of the informed consent with the participant. Participants were encouraged to ask questions or for additional information at any time. After participants signed the informed consent, they were given their own copy of the informed consent to keep for their records.

2.3.2.2. MoCA Administration. Following review and signing of informed consent, the MoCA (Appendix C) was administered by a trained research assistant, following protocol according to Nasreddine (2005) that included standardized scripts for proper administration.

2.3.2.3. Demographics. Questions regarding participant demographic information and health history were delivered orally and recorded by a trained research assistant (see Appendix J). Demographic questions were split into three categories: 1.) patient characteristics (i.e. age, dominant hand, marital status, living situation), 2.) medical history (i.e. cardiovascular disease, cerebrovascular disease, diabetes, traumatic brain injury, etc.), and 3.) substance use (current and historical). Everything a participant answered to the questions were written down. It should be noted that, in Study 1, demographic questions were compiled by patients' self-report through a questionnaire on a tablet. We moved towards collecting demographic questions orally to ensure that all questions were answered and that participants fully understood what they were being asked.

2.3.2.4. Depression Measures. The research assistant explained and orally delivered all depression measures in Study 2. Participants were instructed on how to respond to the

supplemental questions (Appendix B) and the CES-D (Appendix A). For the supplemental questions, the research assistant recorded all responses given by the participant. The participant was seated next to the research assistant and was able to look at the CES-D in order to reference the ranking scale for each response. The research assistant recorded all responses for this measure as well.

2.3.2.5. Sleep Measures. The graduate or undergraduate research assistant verbally gave directions on how to fill out the Epworth Sleepiness Scale (Appendix I) and the PSQI (Appendix F) and recorded all responses. If participants requested, research assistants would further explain questions. Research assistants then explained how to complete the SSS (Appendix G). Participants were instructed to place a scale rating for the degree of sleepiness they were feeling for each hour of the day. Participants completed all hours until the current moment for the present day and research assistants answered any questions. In addition, research assistants explained how to complete the Consensus Sleep Diary (Appendix H), and read an explained questions as necessary. Participants were asked to complete both the SSS and the Consensus Sleep Diary for 7 consecutive days. Finally, research assistants explained the use of the Actiwatch and placed it on the non-dominant wrist of the participant. Participants were instructed to leave the watch on 24 hours a day for 7 days, with the exception of being in water (e.g. swimming, bathing, washing dishes). Participants were additionally instructed to press and hold the event marker button on the side of the Actiwatch for 3 seconds when they felt sleep onset was coming soon at night. Upon completion of these assessments and Actiwatch placement, research assistants scheduled a time to return to the participant's home in 7 days for <10 minutes to retrieve the Actiwatch, Consensus Sleep Diary, and SSS. Eventually, the study team began

utilizing UPS for these pick-ups by giving participants an envelope with shipping label and setting up a pickup time for these materials after 7 days of use.

2.3.2.6. SleepMove Placement. Following completion of paperwork, participants were asked to show research assistants to their bedroom and to instruct research assistants where they normally lay on their bed on a typical night. The bed was stripped of all bed sheets and blankets and research assistants placed a new, clinical fitted sheet on top of the participant's mattress. Then, research assistants place the sensor sheet on top of the clinical fitted sheet. After placing the sensor sheet, research assistants ensured that the end with three sensors is located at the head/top and the end with two sensors is located at the feet/bottom of the mattress. Research assistants also ensured that all sensors are flat with the small circular sensor on top of the large square sensor and that wires were as flat as possible underneath the sensor pad and traveling out from the sides of the mattress (two connectors per side). Research assistants then ran the connector ribbon cables along the side of the mattress to the foot of the bed and place the second clinical fitted sheet on top of the sensor pad. Research assistants ensured wires were not a fall hazard and that no sensors were bent or sticking up.

In order to start recording data, research assistants plugged connector ribbon cables into the wireless transmitting device (cable "A" attaches to input "A", cable "B" attaches to input "B", etc.). A tool was used to press the "Start" button on the box to begin mattress recording. Research assistants looked in the hole on the opposite side of the "Start" button to ensure the LED is flashing and thus the mattress device had begun recording. Research assistants tucked the box and cables underneath the participant's bed so that no materials were exposed and finally, remade the participant's bed with the participant's blankets and pillows.

2.3.2.7. Overnight Memory Consolidation Task Training. Participants were given the opportunity to complete the overnight memory consolidation task in full as training. Research assistants gave participants a printed copy of instructions explaining the use of the tablet beginning at "turning on the tablet" and going through which application to click on and how to begin the task. Research assistants then ran through the task protocol completing the steps for 1 trial before handing the tablet to the participant to complete the remaining 11 trials. Participants were encouraged to ask questions and research assistants looked on to the training to ensure participants understood the task. Research assistants reminded the participants that they need to tap the sequence as many times and as accurately as possible in each 30 second test phase using their non-dominant hand. Following completion of the training and after a brief break if needed, participants were asked to complete "Night 1" of the procedural memory task. Research assistants were still present when the participant completed this task but they did not prompt or correct how the participant was performing. After the participant completed the full 12 trials of this task, they were asked what time would be best for a research assistant to call in the morning to remind them to complete their morning 12 trials. The sheet with tablet instructions was left with the participant and they were told to call if there were any questions or concerns regarding the task. Participants were further asked not to touch the tablet following completion of the task in the morning and that research assistants would pick up the tablet in 2 days. It should be noted that participants in Study 1 completed ONMC task on night 2 and the morning following night 2. ONMC task completion was moved to night 1 and the morning following night 1 so testing could be completed as close to training as possible, which was especially important for MCI participants. The task and output measures were identical between Study 1 and Study 2. A procedural memory consolidation task protocol is explained in Figure 2.

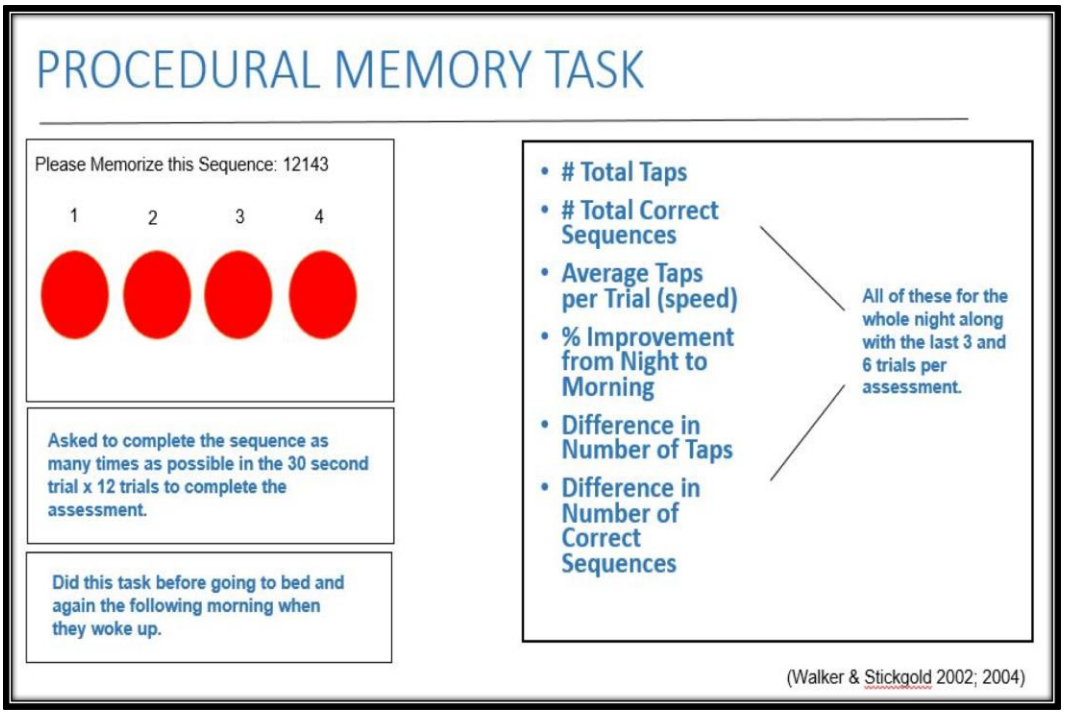


Figure 2. Overnight Memory Consolidation Task Protocol. The overnight memory consolidation task is displayed above. A view of the testing screen is shown in the top left corner, in which participants were asked to tap the red circles in the order of the sequence provided.

2.3.3. Neurocognitive Assessment Visit. Participants were contacted via phone to schedule a follow-up neurocognitive assessment for approximately one month following completion of the sleep study. Upon arrival to the participant's home at the scheduled time, research assistants reminded participants that the study is both voluntary and confidential. Participants were also reminded what they were to be completing at the visit and about the risks and benefits of participation. To begin the neurocognitive assessment, the graduate research assistant presented participants with scripted directions and an orally delivered word list to complete the direct recall portion of the HVLT-R. Then, the graduate research assistant followed scripted directions for the TMT. Participants completed Trail Making Test Part A and Trail Making Test Part B (Appendix D). An undergraduate research assistant timed the Trails A

assessment and the Trails B assessment and recorded the time upon completion. After completion of the TMT, the graduate research assistant gave instructions for completion of the BNT while an undergraduate research assistant recorded responses. Participants were then given directions for the BVMT-R and completed the direct recall portion of this assessment. The TMT, BNT, and direct recall portion of the BVMT-R were used as the delay time for the HVLT-R as these assessments together last about 10-20 minutes. If additional delay time was needed, the graduate research assistant gave the participant a break from testing. Following completion of these tasks/break, participants were asked to recall the word list from the HVLT-R and to complete a recognition memory task. Upon completion of the HVLT-R, the graduate research assistant then presented participants with scripted directions and a paper word list to complete the AMNART (see Appendix E). Each word was individually shown to the participant and, after the participant provided a single pronunciation of the word, the research assistant instructed the participant to move on to the next word after about a one second delay. Then, the vocabulary subtest of the WAIS-III was administered by a trained graduate research assistant, following standardized scripts for proper administration. The AMNART and WAIS-III Vocabulary subtest served as the delay for the BVMT-R, as they together took approximately 25 minutes. Following completion of these tasks, participants were asked to draw what they could remember from the display given earlier on the BVMT-R, and complete a recognition memory task. Throughout the assessment, that lasted no longer than 90 minutes, participants were encouraged to take breaks as needed, and were reminded that they were entitled to discontinue at any point without loss of compensation.

2.3.4. Scoring Protocol. All packets were scored by the graduate research assistant or scored by a trained undergraduate research assistant and double scored by the graduate research

assistant to ensure accurate scores were reported. All standardized assessments conducted were scored according to original protocol. All original files were de-identified and stored in a double-locked cabinet in a separate lab room.

2.3.4.1. Philips Respironics Actiwatch Data Processing. Data from the Philips Respironics Actiwatch, "Actiwatch 2" were collected for a total of 7 consecutive days and nights. Data were processed using Version 6.0.9 of "Philips Actiware 6" software developed by Philips Respironics. Actiwatch 2 devices were placed on the Actiwatch 2 Communications Dock (SN:A2D10139) and processed using a Windows 10 Home, 64-bit, version 1809 computer. Philips Actiware 2 allowed various output parameters for sleep wake and sleep movement (table 2) to be used for analysis.

2.3.4.2. Memory Consolidation Application Data Processing. The software for this protocol was developed for our sleep study and adapted from the work of Stickgold and colleagues (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002; Walker & Stickgold, 2004). Data from the memory application were downloaded in command prompt (cmd). Data collected included: dates and times of completion for the memory consolidation task in the evening and morning, sequence given, correct sequences tapped, and number of total taps. From this data, a separate coded excel file was used to calculate output variables of interest (see table 2).

2.4. Data Analysis

2.4.1. Statistical Analysis. Data were analyzed using IBM Statistical Package for the Social Sciences - Version 26 (IBM-SPSS-26) for OS-X. Demographic and reported health history characteristics were analyzed for group differences between currently depressed (n=9), history of diagnosed depression (n=7), and non-depressed from study 2 (n=22) groups using one-

way ANOVA for continuous variables, and Kruskal-Wallis Test for categorical variables. Overnight procedural memory consolidation speed and percent improvement were calculated and analyzed using parametric tests. Composite scores for neurocognitive assessments and subjective sleep measures were calculated according to protocol. Parametric variables were analyzed using General Linear Modeling (GLM) and regression analyses while nonparametric variables were analyzed using Kruskal Wallis and other methods.

For CURRENT DEPRESSION, separate multivariate GLMs with current depression status (binary: yes/no) as a factor and covariate MCI status (clinically diagnosed positive or negative) was examined. Categories of dependent variables were examined separately and dependent variables included 1.) self-report sleep measures (SSS, ESS, PSQI), 2.) wrist actigraphy, 3.) overnight memory consolidation task variables, 4.) 30-day neurocognitive follow-up measures, and 5.) cognitive reserve measures (WAIS-III Vocabulary Subtest, AMNART). These analyses used groups current depression vs. no current depression.

Current depression group (n=9) included participants who answered "yes" for current depression from study 1 (query: yes/no choice; n=6) and participants who answered "yes" for current depression from study 2 (query: yes/no choice for current; n=3). No current depression group (n=41) included participants that answered "no" for current depression from study 2 (n=22). For exploratory analyses for no current depression, I also examined those with a positive *history of diagnosed depression* but *no current depression* from study 2 (n=7) as well as those that answered "no" for current depression from study 1 (n=12).

For CURRENT DEPRESSION, multivariate GLM with current depression status (binary: yes/no) as a factor and covariate MCI status (clinically diagnosed positive or negative) was examined. Categories of dependent variables were examined separately and included 1.) self-

report sleep measures (SSS, ESS, PSQI), 2.) wrist actigraphy, 3.) overnight memory consolidation task variables, 4.) 30-day neurocognitive follow-up measures, and 5.) cognitive reserve measures (WAIS-III Vocabulary Subtest, AMNART). These analyses used groups current depression vs. no depression.

In the next analysis, I was able to analyze current depression group (n=9) excluding those with a history of depression (n=7, Study 2). Please recall that in Study 1, history of depression was not queried. No depression group (n=22) included participants that answered "no" for current depression from study 2.

For HISTORICAL DEPRESSION, multivariate GLMs with history of diagnosed depression status (binary: yes/no) as a factor and covariate MCI status (clinically diagnosed positive or negative) was examined. Categories of dependent variables were examined separately and dependent variables included 1.) self-report sleep measures (SSS, ESS, PSQI), 2.) wrist actigraphy, 3.) overnight memory consolidation task variables, 4.) 30-day neurocognitive follow-up measures, and 5.) cognitive reserve measures (WAIS-III Vocabulary Subtest, AMNART).

History of diagnosed depression group includes participants that answered "yes" for history of diagnosed depression from study 2 (query: yes/no choice for history; n=9). No depression group includes participants that answered "no" for history of diagnosed depression from study 2 (n=22). One participant endorsed current depression but did not report a history of diagnosed depression and was excluded from analyses.

For ANY DEPRESSION, multivariate GLMs with current and/or historical depression status (binary: yes/no for history and current) as a factor and covariate MCI status (clinically diagnosed positive or negative) was examined. Categories of dependent variables were run separately and dependent variables included 1.) self-report sleep measures (SSS, ESS, PSQI), 2.)

wrist actigraphy, 3.) overnight memory consolidation task variables, 4.) 30-day neurocognitive follow-up measures, and 5.) cognitive reserve measures (WAIS-III Vocabulary Subtest, AMNART).

Any depression group includes: participants that answered "yes" for current depression from study 1 (query: yes/no choice; n=6), participants that answered "yes" for current depression from study 2 (query: yes/no choice for current; n=3), and participants that answered "yes" for history of diagnosed depression from study 2 (query: yes/no choice for history; n=7). No depression group includes participants that answered "no" for current depression from study 2 (n=22). This group EXCLUDED participants that indicated *no current depression* in study 1 (n=12) due to lack of information on history of diagnosed depression.

Simple linear regression was run to assess variables that impacted CES-D total scores in Study 2. In one model, MCI status (clinically diagnosed positive or negative), *Stanford Sleepiness Scale (SSS)* average score, and PSQI Component 7: *daytime dysfunction* are factors. A second model assesses MCI status (clinically diagnosed positive or negative) and self-reported sleep quality and uses MCI status (clinically diagnosed positive or negative) and PSQI composite score as factors. A third model assesses cognition and uses MCI status (clinically diagnosed positive or negative), BVMT-R total recall raw score, and BVMT-R percent retained from final learning trial to delayed recall as factors. The dependent variable for all models is CES-D total score for participants in Study 2. Possible factors that influenced CES-D total score were found through exploratory statistics.

Regression analysis was used to investigate whether MCI status based on MoCA score mediates the effect of current depression status on mean sleep efficiency. A second regression analysis was conducted to assess whether MCI status based on MoCA score mediates the effect

of current depression status on MoCA attention scores. Mediational models were built based on regression results. For all regression analyses, current depression and no depression groups were assessed. Current depression group includes participants who answered "yes" for current depression from study 1 (query: yes/no choice; n=6) and participants who answered "yes" for current depression from study 2 (query: yes/no choice for current; n=3). No depression group includes participants that answered "no" for current depression from study 2 (n=22). This group EXCLUDED participants that have a *history of diagnosed depression* but *no current depression* (n=7 for study 2) and participants that indicated *no current depression* in study 1 (n=12) due to lack of information on history of diagnosed depression. Significance for indirect effects (a*b) in mediational models was tested using a percentile bootstrap estimation approach with 1000 samples.

Sample size constrained model building. Because a general linear model was applied with group as the between subjects factor, MCI status, which was significantly different between groups, was used as a covariate in the analyses. Main effects were calculated with 95% confidence intervals and were adjusted to LSD at a 5% significance level. Levene's test was used to calculate homogeneity of variance.

CHAPTER 3

RESULTS

3.1. Demographic Characteristics.

Hypothesis I proposed that groups with current and/or history of diagnosed depression would show more chronic health conditions than the non-depressed comparison group. Thirty eight recruited participants were included in demographic analyses, resulting in current depression (DepCur) group from study 1 and study 2 (n=9), history of diagnosed depression but *no current depression* (DepHx) group from study 2 (n=7), and a sociodemographically similar group without current or historical depression from study 2 (Control 2; n=22). Participants from study 1 who endorsed no current depression (n=12) were excluded from demographic analyses due to lack of information on historical depression status.

Table 3
Participant Demographics and Health Characteristics

Variable (m±SD or % (n))		**Control Study 2 (n=22)**	**History of Dep (n=7)**	**Current Dep (n=9)**	**Totals (n=38)**	**p-value**
Age		71.09 (±4.25)	68.86 (±2.85)	72.51 (±6.35)		n.s.
MoCA Score		25.23 (±2.76)	25.86 (±2.73)	21.89 (4.34)		n.s.
MCI	No	91% (20)	100% (7)	33% (3)	79% (30)	**0.001**
	Yes	9% (2)	0% (0)	67% (6)	21% (8)	
Sex	Male	18% (4)	43% (3)	33% (3)	26% (10)	n.s.
	Female	82% (18)	57% (4)	67% (6)	74% (28)	

Table 3 Continued

Marital Status	Never Married	9% (2)	0% (0)	22% (2)	11% (4)	n.s.
	Divorced	41% (9)	0% (0)	11% (1)	26% (10)	
	Widowed	14% (3)	14% (1)	0% (0)	11% (4)	
	Has a partner but not married	0% (0)	14% (1)	0% (0)	3% (1)	
	Married	36% (8)	72% (5)	67% (6)	50% (19)	
Living Situation	Lives alone	64% (14)	14% (1)	33% (3)	47% (18)	**0.026**
	Cohabiting with partner/spouse	36% (8)	86% (6)	67% (6)	53% (20)	
Education	None or minimal schooling (any grade before 5th grade)	0% (0)	0% (0)	11% (1)	3% (1)	n.s.
	Completed elementary school (grade 5)	0% (0)	0% (0)	0% (0)	0% (0)	
	Completed middle school (grade 8)	5% (1)	0% (0)	11% (1)	5% (2)	
	Completed high school (grades 9-12)	18% (4)	29% (2)	11% (1)	18% (7)	

Table 3 Continued

	Diploma/Associate's degree (2 years of college)	32% (7)	29% (2)	11% (1)	26% (10)	
	Bachelor's degree (~4 years of college)	23% (5)	0% (0)	33% (3)	21% (8)	
	Master's degree (~2 years of graduate school)	14% (3)	43% (3)	11% (1)	18% (7)	
	Doctoral degree (PhD, medicine)	9% (2)	0% (0)	11% (1)	8% (3)	
OSA	No	91% (20)	57% (4)	89% (8)	84% (32)	n.s.
	Yes	9% (2)	43% (3)	11% (1)	16% (6)	
Cerebrovascular Disease	No	95% (21)	71% (5)	78% (7)	87% (33)	n.s.
	Yes	5% (1)	29% (2)	22% (2)	13% (5)	
Other Psychiatric Disorders	No	86% (19)	71% (5)	78% (7)	82% (31)	n.s.
	Yes	14% (3)	29% (2)	22% (2)	18% (7)	
Alcohol Intake	Never	23% (5)	14% (1)	44% (4)	26% (10)	n.s.

Table 3 Continued

Less than once a month	0% (0)	0% (0)	22% (2)	5% (2)
About once a month	23% (5)	29% (2)	11% (1)	21% (8)
About once a week	23% (5)	29% (2)	0% (0)	18% (7)
A few times a week	18% (4)	29% (2)	22% (2)	21% (8)
Daily or almost daily	14% (3)	0% (0)	0% (0)	8% (3)

Note. Results reveal that participants were matched on demographics and health variables in the three groups with the exception of MCI status (χ^2=14.62, p = 0.001) and living situation (χ^2=7.28, p = 0.026). Additional demographic variables that were found to be not significant across groups: *dominant hand, cardiovascular disease, arthritis, diabetes, heart attack/cardiac arrest, body mass index, traumatic brain injury, hypercholesterolemia, hypertension, thyroid disease, and current smoking status.*

Table 3 shows group differences in demographic and health variables assessed using a parametric measure (one-way ANOVA) for continuous variables, and a non-parametric measure (Kruskal Wallis Test) for categorical variables. Demographic variables including age, sex, race, marital status, living situation, education level, body mass index (BMI), and dominant hand were collected. Living situation was the only demographic variable that was significantly different between DepCur, DepHx, and Control 2 groups (χ^2=7.28, p = 0.026). All other demographics were not significant. Health variables were also collected to ensure groups were well matched. Health characteristics collected include presence or absence of the following: mild cognitive impairment (MCI), obstructive sleep apnea (OSA), arthritis, cardiovascular disease, smoking,

alcohol use, diabetes, heart attack or cardiac arrest, traumatic brain injury (TBI), hypercholesterolemia, hypertension, seizures, thyroid disease, and other psychiatric disorders. All participants were matched on health variables, with the exception of MCI status (χ^2=14.62, p= 0.001). Lastly, MoCA scores are included in the table to assess differences in global cognitive screening measure scores between depression groups. All participants were matched on MoCA scores, as no significant differences were found between groups.

3.1.1. Hypothesis I: Impact of Age and Health. It was expected in hypothesis I that chronic health deterioration is associated with both increasing age and depression status. It was expected that individuals with chronic health problems would be more likely to have current depressive symptoms or a history of diagnosed depression, and would be the older individuals in the study (Lenze et al, 2005; Moussavi et al, 2007; Cauley, 2012; McNicoll, 2012; Taylor, Aizenstein, & Alexopoulos, 2013).

3.1.1.1. Chronic Health is Associated with Depression Status. No significant associations were found using Kruskal Wallis analyses to assess the relationship between current and historical depression status and health deterioration, with the exception of MCI status (χ^2=14.62, p = 0.001). Participants with current depression were more likely to also have clinically diagnosed MCI than participants with history of diagnosed depression but no current depression and those with no current or historical depression.

3.1.1.2. Health Deterioration in Aging. To identify the relationship between age and health, Pearson's correlations were utilized. Individuals in this study range from 65-83 years of age. As individuals get older in the study sample, prevalence of MCI was more common (r=0.495, p < 0.001). No other significant associations were found between age and health variables (all p's > 0.05).

3.2. Sleep Study.

Sleep measures include 7-day wrist actigraphy and self-report measures (SSS, PSQI, and ESS) for this study. 43 participants wore an actiwatch, all complete with 7 day actiwatch data. 50 participants completed the ESS and PSQI. 37 participants completed the SSS.

3.2.1. Hypothesis II: Depressive Symptoms are Connected to Poorer Sleep Quality.

Two multivariate GLM with covariate MCI status (clinically diagnosed positive or negative) and wrist actigraphy measures as dependent variables. Factors in different analyses included: current depression status from study 1 and study 2 and any depression from study 1 and study 2.

For current depression, the *current depression group* (n=9) included participants that said "yes" for current depression from study 1 (query: yes/no choice; n=6) and participants that said "yes" for current depression from study 2 (query: yes/no choice for current; n=3). The *control study 2 group* included participants that said "no" for current depression from study 2 (n=22). This group EXCLUDED participants that have a *history of diagnosed depression* but *no current depression* (n=7 for study 2; unknown for study 1 binary query) and participants that indicated *no current depression* in study 1 (n=12) due to lack of information on history of diagnosed depression.

For actigraphic sleep measures, a significant main effect of group showed that the current depression group had lower mean assumed sleep ($F(1, 23) = 4.68$, $p = 0.041$), lower mean actual sleep time ($F(1, 23) = 4.34$, $p = 0.049$), lower mean sleep efficiency ($F(1, 23) = 11.62$, $p = 0.002$), higher mean sleep latency ($F(1, 23) = 8.77$, $p = 0.007$), and lower mean number of minutes immobile ($F(1, 23) = 4.32$, $p = 0.049$) than the control study 2 group. Table 4 shows estimated marginal means between the current depression group and the control study 2 group ± the standard error of the mean for each actigraphy variable. Figures 4 and 5 display mean

differences between the current depression and non-depressed (control study 2) groups in actigraphic measures of sleep efficiency and sleep latency, respectively.

Table 4
Actigraphy Variables for Current Depression vs. Control Study 2 Groups

Variable	**Current Dep (n=7)**	**Control Study 2* (n=19)**	***p*-value**
Mean Time in Bed	8.72 ± 0.61	8.84 ± 0.34	0.874
Mean Assumed Sleep	6.89 ± 0.55	8.35 ± 0.31	**0.041**
Mean Actual Sleep Time	5.90 ± 0.55	7.30 ± 0.30	**0.049**
Mean Actual Sleep %	86.42 ± 3.12	87.92 ± 1.72	0.698
Mean Actual Wake Time	0.55 ± 0.27	0.82 ± 0.15	0.413
Mean Actual Wake %	13.59 ± 3.12	12.08 ± 1.72	0.698
Mean Sleep Efficiency	68.12 ± 3.66	83.42 ± 2.02	**0.002**
Mean Sleep Latency	1.20 ± 0.27	0.21 ± 0.15	**0.007**
Mean Sleep Bouts	25.29 ± 2.95	22.96 ± 1.63	0.526
Mean Wake Bouts	25.29 ± 2.96	22.46 ± 1.63	0.444
Mean Sleep Bout Time	0.17 ± 0.04	0.24 ± 0.02	0.192
Mean Wake Bout Time	0.02 ± 0.006	0.03 ± 0.003	0.323
Mean Number of Minutes Immobile	350.83 ± 32.30	433.20 ± 17.83	**0.049**
Mean Immobile % Time	81.64 ± 3.53	84.79 ± 1.95	0.476
Mean Number of Minutes Moving	69.90 ± 18.64	80.97 ± 10.29	0.633
Mean Moving % Time	18.36 ± 3.53	15.23 ± 1.95	0.477
Mean Number of Immobile Phases	45.79 ± 4.78	38.91 ± 2.64	0.253
Mean Length Immobility	8.49 ± 2.45	12.64 ± 1.35	0.181

Table 4 Continued

Mean One Minute Immobility	14.32 ± 2.72	8.33 ± 1.50	0.087
Mean One Minute Immobility %	29.58 ± 4.35	18.92 ± 2.40	0.058
Mean Fragmentation Index	47.93 ± 7.55	34.15 ± 4.17	0.150
Number of Days Actiwatch Worn	6.35 ± 0.37	6.82 ± 0.20	0.313

Note. x ± y represents estimated marginal mean (EMM) ± standard error of the mean (SEM), (n) = sample size. Table adjusted for covariate MCI status.
*Control Study 2 group includes participants that indicated no current or historical depression in Study 2

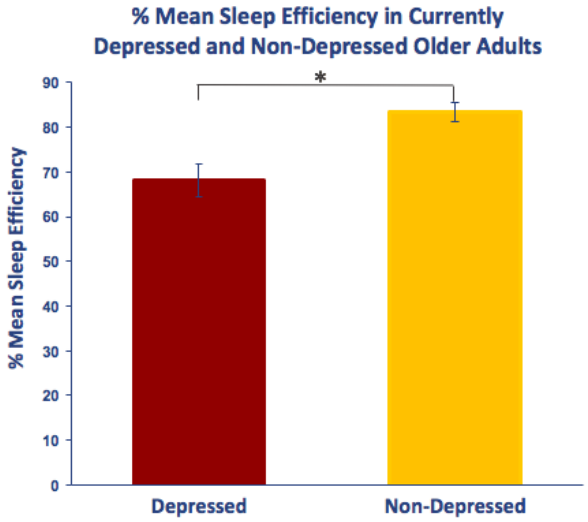


Figure 3. Actigraphy Measure of % Mean Sleep Efficiency in Currently Depressed and Non-Depressed (Control Study 2) Groups.

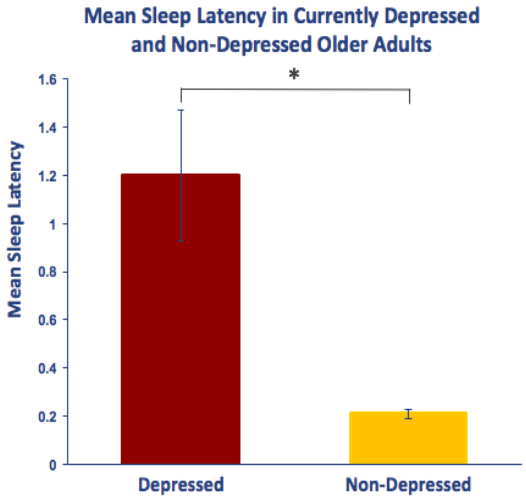


Figure 4. Actigraphy Measure of Mean Sleep Latency in Currently Depressed and Non-Depressed (Control Study 2) Groups.

Regression analysis was used to investigate whether MCI status based on MoCA total score mediates the effect of current depression status on mean sleep efficiency (see Figure 3). In Step 1 of the mediation model, the regression of mean sleep efficiency on current depression status, ignoring the mediator, was significant, b = -18.26, $t(30)$ = -5.19, $p < 0.001$. Step 2 showed that regression of the mean sleep efficiency on the mediator, MCI status based on MoCA score,

was not significant, $b = 0.379$, $t(30) = 0.074$, $p = 0.942$. Step 3 of the mediation process showed that the mediator, MCI status based on MoCA score, controlling for current depression status was significant, $b = -2.52$, $t(31) = -2.21$, $p = 0.035$. Step 4 of the analyses revealed that, controlling for the mediator MCI status based on MoCA score, current depression status was still a significant predictor of mean sleep efficiency, $b = 18.36$, $t(31) = -5.71$, $p < 0.001$. Approximately 51% of the variance in mean sleep efficiency was accounted for by the predictors ($R^2 = 0.51$). The indirect effect was tested using a percentile bootstrap estimation approach with 1000 samples.

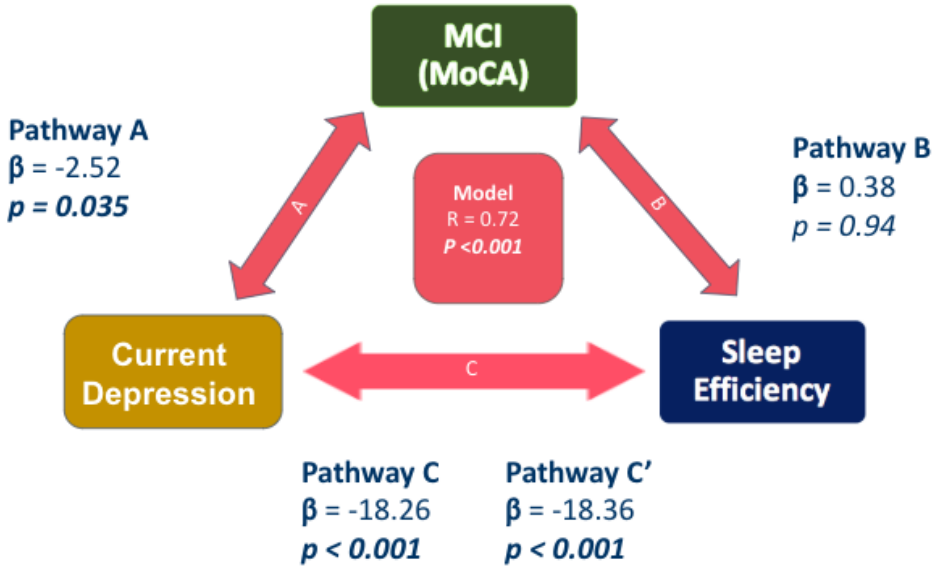


Figure 5. Standardized regression coefficients for the relationship between current depression status and mean sleep efficiency as mediated by MCI status based on MoCA total score.

For <u>any depression</u>, the *any depression group* included participants that said "yes" for current depression from study 1 (query: yes/no choice; n=6), participants that said "yes" for current depression from study 2 (query: yes/no choice for current; n=3), and participants that answered "yes" for history of diagnosed depression from study 2 (query: yes/no choice for

history; n=7). The *control study 2 group* included participants that said "no" for current depression from study 2 (n=22). This group EXCLUDED participants that indicated *no current depression* in study 1 (n=12) due to lack of information on history of diagnosed depression. Results showed that the any depression group and the control study 2 group showed no significant differences in objective sleep as measured by wrist actigraphy over a 7 day period.

3.2.1.1. Subjective Measures of Sleep will Reflect Objective Measures. Correlational analyses were used to assess the relationship between subjective and objective sleep measures between the current depression group and the control study 2 group. Results showed a negative correlation between PSQI Component 7: *daytime dysfunction* and mean assumed sleep (r = -0.57, $p < 0.001$), mean actual sleep time (r = 0.53, $p < 0.001$), mean sleep efficiency (r = -0.49, p = 0.001), and mean number of minutes immobile (r = -0.54, $p < 0.001$). This means that participants that reported more daytime dysfunction on the PSQI had lower mean assumed sleep, lower mean actual sleep time, lower mean sleep efficiency, and lower mean number of minutes immobile as measured by wrist actigraphy. Results also showed that the actigraphic measure of mean sleep latency was positively correlated with *Stanford Sleepiness Scale (SSS)* average score (r = 0.39, p = 0.018), PSQI Component 2: *sleep latency* (r = 0.40, p = 0.007), PSQI Component 6: *use of sleeping medication* (r = 0.40, p = 0.007), and PSQI composite score (r = 0.39, p = 0.009). This means that participants that showed longer sleep latency through actigraphy also reported more daytime sleepiness, longer sleep latency, greater use of sleeping medication, and an overall greater amount of sleep problems. Finally, results showed that the actigraphic measure of mean sleep efficiency negatively correlated with PSQI Component 5: *sleep disturbances* (r = -0.33, p = 0.028) and PSQI composite score (r = -0.33, p = 0.034). This means that participants

that showed lower sleep efficiency through actigraphy also reported more sleep disturbances and an overall greater amount of sleep problems.

Following correlational analyses, a multivariate GLM with covariate MCI status (clinically diagnosed positive or negative) and self-report sleep measures (SSS, ESS, PSQI) as dependent variables was run to assess differences in self-reported sleep between current depression group and control study 2 group. Results showed that the current depression group reported more sleep problems and sleepiness than the no depression group. The current depression group reported a trend toward higher average scores on the *Stanford Sleepiness Scale (SSS)* (M=1.84, SE=0.16) than the control study 2 group (M=1.45, SE=0.093; p = 0.059). The current depression group reported higher scores on PSQI Component 5: *sleep disturbances* (M=1.89, SE=0.21) than the control study 2 group (M=0.95, SE=0.12; p = 0.001). The current depression group reported higher scores on PSQI Component 7: *daytime dysfunction* (M=1.55, SE=0.26) than the control study 2 group (M=0.23, SE=0.15; p > 0.001). Table 5 shows the estimated marginal means between the current depression group and the control study 2 group ± the standard error of the mean for each self-report sleep variable.

Table 5
Self-Report Sleep Variables in Current Depression vs. Control Study 2 Groups

Variable	**Current Dep (n=9)**	**No Dep* (n=22)**	***p*-value**
SSS Average Score	1.84 ± 0.16	1.45 ± 0.09	0.059
ESS Total Score	4.12 ± 1.22	4.27 ± 0.71	0.922
ESS Average Score	0.52 ± 0.15	0.54 ± 0.09	0.923
PSQI Component 1: Subjective Sleep Quality	0.88 ± 0.25	0.50 ± 0.15	0.231
PSQI Component 2: Sleep Latency	1.47 ± 0.37	1.17 ± 0.22	0.523
PSQI Component 3: Sleep Duration	0.34 ± 0.24	0.72 ± 0.14	0.220

Table 5 Continued

PSQI Component 4: Habitual Sleep Efficiency	0.83 ± 0.32	0.57 ± 0.19	0.525
PSQI Component 5: Sleep Disturbances	1.89 ± 0.21	0.95 ± 0.12	**0.001**
PSQI Component 6: Use of Sleeping Medication	0.74 ± 0.34	1.06 ± 0.20	0.466
PSQI Component 7: Daytime Dysfunction	1.55 ± 0.26	0.23 ± 0.15	**<0.001**
PSQI Composite Score	7.71 ± 1.11	5.21 ± 0.65	0.084

Note. x ± y represents estimated marginal mean (EMM) ± standard error of the mean (SEM), (n) = sample size. Table adjusted for covariate MCI status.
SSS=Stanford Sleepiness Scale; ESS=Epworth Sleepiness Scale; PSQI=Pittsburgh Sleep Quality Index
*Control Study 2 group includes participants that indicated no current or historical depression in Study 2

Finally, linear regression was run to assess possible objective and self-report sleep variables that impacted CES-D total scores in Study 2. A simple linear regression was calculated to predict CES-D total score based on MCI status (clinically diagnosed positive or negative), *Stanford Sleepiness Scale (SSS)* average score, and PSQI Component 7: *daytime dysfunction* score. A significant regression equation was found (F (3, 18) = 12.26, $p < 0.001$), with an R^2 of 0.67. It was found that SSS average score significantly predicted CES-D total score ($\beta = 6.18$, $p = 0.017$), as did PSQI Component 7: *daytime dysfunction* ($\beta = 1.05$, $p = 0.002$) and a trend toward MCI status ($\beta = 5.37$, $p = 0.056$). A simple linear regression was calculated to predict CES-D total score based on MCI status (clinically diagnosed positive or negative) and PSQI composite score. A significant regression equation was found (F (2, 29) = 4.47, $p = 0.020$), with

an R^2 of 0.24. It was found that PSQI composite score significantly predicted CES-D total score ($\beta = 0.75$, $p = 0.010$).

3.2.1.2. Depressive History will Impact Sleep Quality. Multivariate GLM with covariate MCI status (clinically diagnosed positive or negative) was examined using self-report sleep measures (SSS, ESS, PSQI) and wrist actigraphy as dependent variables and historical diagnosed depression status (binary; yes/no) as factor. History of diagnosed depression group (n=9) includes participants that answered "yes" for history of diagnosed depression from study 2 (query: yes/no choice for history). This group includes two participants that also endorsed current depression. Control study 2 group includes participants that answered "no" for history of diagnosed depression from study 2 (n=22). One participant endorsed current depression but did not report a history of diagnosed depression and was excluded from analyses. For actigraphic sleep measures, a significant main effect of group showed that the history of diagnosed depression group had higher mean actual sleep time ($F(1, 24) = 6.08$, $p = 0.021$), higher mean sleep bout time ($F(1, 24) = 5.96$, $p = 0.022$), higher mean number of minutes immobile ($F(1, 24) = 5.65$, $p = 0.026$), and higher mean length immobility ($F(1, 24) = 5.40$, $p = 0.029$). Table 6 shows the estimated marginal means between the history of diagnosed depression group and the control study 2 group ± the standard error of the mean for each actigraphy variable.

Table 6
Actigraphy Variables for History of Diagnosed Depression vs. Control Study 2 Groups

Variable	**History of Dep (n=8)**	**Control Study 2* (n=19)**	***p*-value**
Mean Time in Bed	9.55 ± 0.37	8.74 ± 0.24	0.076
Mean Assumed Sleep	9.16 ± 0.38	8.31 ± 0.24	0.071
Mean Actual Sleep Time	8.39 ± 0.37	7.31 ± 0.24	**0.021**
Mean Actual Sleep %	91.45 ± 1.70	88.41 ± 1.10	0.148

Table 6 Continued

Mean Actual Wake Time	0.57 ± 0.18	0.76 ± 0.12	0.407
Mean Actual Wake %	8.55 ± 1.70	11.59 ± 1.10	0.148
Mean Sleep Efficiency	87.70 ± 1.80	83.96 ± 1.17	0.095
Mean Sleep Latency	0.15 ± 0.03	0.15 ± 0.02	0.897
Mean Sleep Bouts	20.35 ± 2.53	23.00 ± 1.64	0.389
Mean Wake Bouts	19.70 ± 2.52	22.48 ± 1.63	0.365
Mean Sleep Bout Time	0.90 ± 0.23	0.23 ± 0.15	**0.022**
Mean Wake Bout Time	0.03 ± 0.004	0.03 ± 0.002	0.721
Mean Number of Minutes Immobile	497.17 ± 22.50	433.23 ± 14.56	**0.026**
Mean Immobile % Time	88.22 ± 2.13	85.15 ± 1.38	0.238
Mean Number of Minutes Moving	65.97 ± 13.66	78.16 ± 8.83	0.463
Mean Moving % Time	11.78 ± 2.13	14.87 ± 1.38	0.236
Mean Number of Immobile Phases	37.84 ± 4.45	38.53 ± 2.88	0.896
Mean Length Immobility	43.15 ± 11.08	12.38 ± 7.17	**0.029**
Mean One Minute Immobility	7.04 ± 1.46	7.93 ± 0.94	0.614
Mean One Minute Immobility %	15.58 ± 1.98	18.47 ± 1.28	0.234
Mean Fragmentation Index	27.36 ± 3.97	33.34 ± 2.57	0.219
Number of Days Actiwatch Worn	7.00 ± 0.14	6.90 ± 0.09	0.555

Note. x ± y represents estimated marginal mean (EMM) ± standard error of the mean (SEM), (n) = sample size. Table adjusted for covariate MCI status.
*Control Study 2 group includes participants that indicated no current or historical depression in Study 2

For self-report sleep measures (SSS, ESS, PSQI), results revealed that the history of diagnosed depression group reported more sleep problems than the no depression group. The history of diagnosed depression group reported higher scores on PSQI Component 1: *subjective sleep quality* (*M*=1.09, *SE*=0.20) than the control study 2 group (*M*=0.46, *SE*=0.13; *p* = 0.016). The history of diagnosed depression group reported higher scores on PSQI Component 5: *sleep disturbances* (*M*=1.44, *SE*=0.11) than the control study 2 group (*M*=1.05, *SE*=0.07; *p* = 0.007). Table 7 shows the estimated marginal means between the history of diagnosed depression group and the control study 2 group ± the standard error of the mean for each self-report sleep variable.

Table 7
Self-Report Sleep Variables in Current Depression vs. Control Study 2 Groups

Variable	**Current Dep (n=9)**	**No Dep* (n=22)**	***p*-value**
SSS Average Score	1.84 ± 0.16	1.45 ± 0.09	0.059
ESS Total Score	4.12 ± 1.22	4.27 ± 0.71	0.922
ESS Average Score	0.52 ± 0.15	0.54 ± 0.09	0.923
PSQI Component 1: Subjective Sleep Quality	0.88 ± 0.25	0.50 ± 0.15	0.231
PSQI Component 2: Sleep Latency	1.47 ± 0.37	1.17 ± 0.22	0.523
PSQI Component 3: Sleep Duration	0.34 ± 0.24	0.72 ± 0.14	0.220
PSQI Component 4: Habitual Sleep Efficiency	0.83 ± 0.32	0.57 ± 0.19	0.525
PSQI Component 5: Sleep Disturbances	1.89 ± 0.21	0.95 ± 0.12	**0.001**
PSQI Component 6: Use of Sleeping Medication	0.74 ± 0.34	1.06 ± 0.20	0.466
PSQI Component 7: Daytime Dysfunction	1.55 ± 0.26	0.23 ± 0.15	**<0.001**
PSQI Composite Score	7.71 ± 1.11	5.21 ± 0.65	0.084

Note. x ± y represents estimated marginal mean (EMM) ± standard error of the mean (SEM), (n) = sample size. Table adjusted for covariate MCI status.

SSS=Stanford Sleepiness Scale; ESS=Epworth Sleepiness Scale; PSQI=Pittsburgh Sleep Quality Index
*Control Study 2 group includes participants that indicated no current or historical depression in Study 2

3.3. Neurocognitive Output Measures.

The 1-month neurocognitive assessment was used to assess the status of various cognitive domains (including, but not limited to: *immediate and delayed visuospatial and verbal memory, working memory, episodic memory, and psychomotor speed*) in all participants. Both raw scores and age-adjusted scores on neurocognitive assessments were used in analyses and produced identical results. In addition, memory was tested using a unique testing procedure during pre- and post-sleep period called overnight memory consolidation (Walker, 2002) during night 1 of the sleep study.

3.3.1. Hypothesis III: Current Depressive Symptoms Impair Cognition. As depression is associated with cognitive impairment particularly in processing speed, visuospatial abilities, episodic memory, verbal fluency, executive functioning, and learning/free recall on memory tests (Dotson, Beydoun, & Zonderman, 2010; Lenze et al., 2018), this hypothesis predicts that participants with current depression will perform significantly worse on tasks assessing these cognitive domains.

Neurocognitive status analyses between the current depression group (n=9) and the control study 2 group (n=22) revealed significant findings for overnight procedural memory, verbal learning/recall, and visuospatial abilities but in the opposite direction than expected. On the overnight memory consolidation task, the current depression group performed better than the no depression group. The current depression group had a greater speed for correct sequences per trial at night (M=16.10, SE=5.90) than the control study 2 group (M=34.45, SE=3.47; $F(1, 22)$ =

6.50, p = 0.018). The current depression group showed a trend toward higher total taps through 12 trials in the morning (M=536.92, SE=61.41) than the control study 2 group (M=382.64, SE=36.12; F (1, 22) = 4.25, p = 0.051). The current depression group had higher average correct taps per trial in the morning (M=41.80, SE=5.36) than the control study 2 group (M=27.54, SE=3.15; F(1, 22) = 4.76, p = 0.040). The current depression group had higher average taps per trial in the last 3 trials in the morning (M=47.99, SE=5.70) than the control study 2 group (M=32.32, SE=3.35; F(1, 22) = 5.09, p = 0.034). The current depression group had a trend toward higher average correct sequences in the last 3 trials in the morning (M=8.30, SE=1.09) than the control study 2 group (M=5.65, SE=0.64; F(1, 22) = 3.95, p = 0.059). The current depression group had higher average taps per trial in the last 6 trials in the morning (M=47.93, SE=5.46) than the control study 2 group (M=32.89, SE=3.21; F(1, 22) = 5.10, p = 0.034). The current depression group had a greater percent improvement of correct taps between night and morning (M=131.45, SE=101.21) than the control study 2 group (M= -138.74, SE=59.53; F(1, 22) = 4.80, p =0.039).

On the one-month follow-up neurocognitive measures, the current depression group also performed significantly better than the no depression group. The current depression group had higher raw scores for total recall on the HVLT-R (M=23.68, SE=2.00) than the control study 2 group (M=17.90, SE=1.42; F(1, 19) = 4.64, p = 0.44). Also, the current depression group had higher raw scores on Trial 1 of the BVMT-R (M=5.98, SE=0.71) than the control study 2 group (M=2.78, SE=0.41; F(1, 15) = 25.04, p = 0.002). However, the current depression group did perform significantly worse on the MoCA *Attention* component (M=4.75, SE=0.28) than the control study 2 group (M=5.65, SE=0.16; F(1, 28) = 6.81, p=0.014). No other neurocognitive

measures produced significant group differences between the current depression group and the control study 2 group (p's > 0.05).

Regression analysis was used to investigate whether MCI status based on MoCA score mediates the effect of current depression status on MoCA *Attention* score (see Figure 6). In Step 1 of the mediation model, the regression of MoCA *Attention* score on current depression status, ignoring the mediator, was significant, b = -0.67, $t(36)$ = -2.38, p = 0.023. Step 2 showed that regression of MocA *Attention* score on the mediator, MCI status based on MoCA score, was significant, b = 0.12, $t(35)$ = 3.55, p = 0.001. Step 3 of the mediation process showed that the mediator, MCI status based on MoCA score, controlling for current depression status was significant, b = -3.49, $t(36)$ = -2.90, p = 0.006. Step 4 of the analyses revealed that, controlling for the mediator MCI status based on MoCA score, current depression status was still a significant predictor of MoCA *Attention* score, b = -1.10, $t(36)$ = -3.79, $p < 0.001$. Approximately 29% of the variance in mean sleep efficiency was accounted for by the predictors (R^2 = 0.29). The indirect effect was tested using a percentile bootstrap estimation approach with 1000 samples.

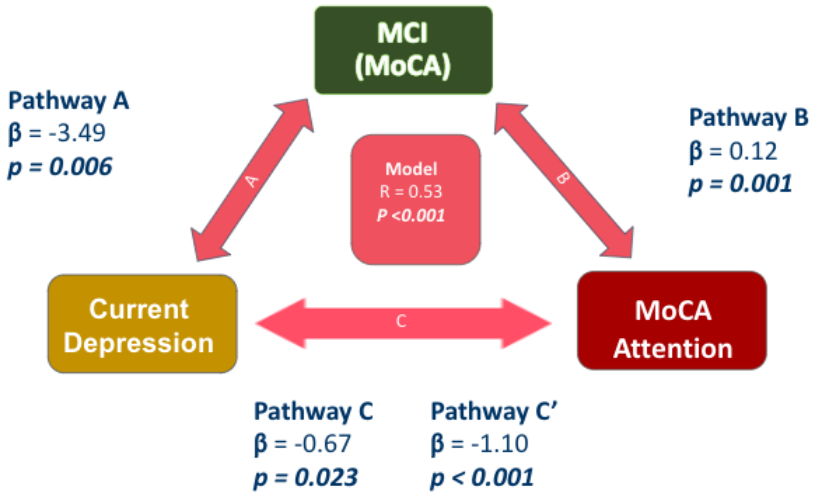


Figure 6. Standardized regression coefficients for the relationship between current depression status and MoCA *Attention* score as mediated by MCI status based on MoCA total score

Finally, linear regression was run to assess possible neurocognitive variables that impacted CES-D total scores in Study 2. A simple linear regression was calculated to predict CES-D total score based on MCI status (clinically diagnosed positive or negative), BVMT-R total recall raw score, and BVMT-R delayed recall raw score. A significant regression equation was found (F (3, 15) = 4.45, p = 0.020), with an R^2 of 0.47. It was found that MCI status significantly predicted CES-D total score (β = 15.64, p = 0.034).

3.3.1.1. Historical Depressive Symptoms Impair Cognition. Neurocognitive status analyses were also conducted between the history of diagnosed depression group (n=9) and the control study 2 group (n=22). These analyses revealed significant findings for verbal learning and episodic memory but in the opposite direction than expected. On the overnight memory consolidation task, the history of diagnosed depression group and the control study 2 group showed no significant differences on any task variable (all p's > 0.05). For the neurocognitive follow-up, the history of diagnosed depression group performed better on HVLT-R for total recall and delayed recall than the no depression group. The history of diagnosed depression

group had higher raw scores for total recall on the HVLT-R (*M*=26.00, *SE*=2.26) than the control study 2 group (*M*=20.07, *SE*=1.34; $F(1, 16) = 5.01$, $p = 0.040$). The history of diagnosed depression group also had higher raw scores for delayed recall on the HVLT-R (*M*=9.79, *SE*=1.32) than the control study 2 group (*M*=6.29, *SE*=0.78; $F(1, 16) = 5.11$, $p = 0.038$). No other neurocognitive measure produced significant group differences between the history of diagnosed depression group and the control study 2 group (*p*'s > 0.05).

3.4. MCI Diagnosis

Hypothesis IV posited that aging participants who display symptoms of *current* depression will have a higher incidence of aMCI. Thirty-eight recruited participants were assessed for MCI status, resulting in current depression group from study 1 and study 2 (n=9), history of diagnosed depression but *no current depression* group from study 2 (n=7), and a sociodemographically similar group without current or historical depression from study 2 (Control 2; n=22). Participants from study 1 who endorsed no current depression (n=12) were excluded from analyses due to lack of information on historical depression status.

3.4.1. Hypothesis IV: Higher Incidence of MCI in Depressed Older Adults.

Correlational analyses were used to assess the percentage of participants in each of three groups that have clinically diagnosed MCI. In the history of diagnosed depression but *no current depression* group, 0 participants of 7 (0%) were diagnosed with MCI. In Control Study 2 group, 2 participants of 22 (9%) were diagnosed with MCI. In the current depression group, 6 participants of 9 (67%) were diagnosed with MCI. Post-hoc tests reveal significant differences in MCI status between the current depression group vs. control study 2 group (p=0.003) and the current depression group vs. the history of diagnosed depression but *no current depression* group

(p=0.003). There were not significant differences between the control study 2 and the history of diagnosed depression but *no current depression* groups (p>0.05).

3.5. Cognitive Reserve.

Hypothesis V proposed that cognitive reserve (assessed based on IQ correlates such as the WAIS-III vocabulary subtest and AMNART) would be associated with higher cognitive performance regardless of current or historical depression status. Cognitive reserve measures were only employed in Study 2 so participants from Study 1 were not evaluated. Twenty participants were included in analyses including participants with current depression (n=2), history of diagnosed depression but *no current depression* (n=4), and control study 2 (n=16).

3.5.1. Hypothesis IV: Cognitive Reserve Moderates Levels of Cognitive Impairment.

Correlational analyses were used to assess if education was significantly correlated with depression status (current depression and history of diagnosed depression). No significant correlations were found between education level and current or historical depression status (*p*'s > 0.05). Correlational analyses were then used to assess the relationship between cognitive reserve proxy measures (WAIS-III vocabulary subtest and AMNART) and other neurocognitive measures. Results showed significant positive correlations between AMNART performance and HVLT-R delayed recall raw score ($r = 0.50$, $p = 0.026$), BVMT-R total recall raw score ($r = 0.49$, $p = 0.035$), and BVMT-R delayed recall raw score ($r = 0.48$, $p = 0.038$). This means that participants that performed better on the AMNART also performed better on HVLT-R delayed recall and BVMT-R total and delayed recall. Results also showed significant positive correlations between WAIS-III vocabulary subtest performance and HVLT-R total recall raw score ($r = 0.63$, $p = 0.03$), HVLT-R delayed recall raw score ($r = 0.66$, $p = 0.002$), HVLT-R retention percentage from learning trials to delayed recall ($r = 0.55$, $p = 0.012$), Boston Naming

Test total score ($r = 0.53$, $p = 0.017$), BVMT-R total recall raw score ($r = 0.77$, $p < 0.001$), BVMT-R learning raw score ($r = 0.60$, $p = 0.007$), and BVMT-R delayed recall raw score ($r = 0.72$, $p < 0.001$). This means that participants that performed better on the WAIS-III vocabulary subtest also performed better on HVLT-R total, delayed recall, and retention percentage, Boston Naming total score, and BVMT-R total, learning, and delayed recall. No significant correlations were found between cognitive reserve proxy measures and overnight memory consolidation performance (p's > 0.05).

Three multivariate GLM with covariate MCI status (clinically diagnosed positive or negative) was examined using cognitive reserve proxy measures (WAIS-III vocabulary subtest and AMNART) as dependent variables and depression status as a factor. The groups for each analysis are as follows: 1) current depression vs. no depression, 2) history of diagnosed depression vs. no depression, and 3) any depression (current or historical) vs. no depression. For all analyses, results revealed that there were no significant differences between groups on cognitive reserve proxy measure performance (all p's > 0.05).

CHAPTER 4

DISCUSSION

Sleep quality and depression status are closely associated in aging, with sleep disturbance or sleep disorder being a primary symptom of late-life depression (5th ed, *DSM*, American Psychiatric Association, 2013). Sleep disturbance, including persistent insomnia, may even continue after effective treatment for other symptoms of depression (Nutt, Wilson, & Paterson, 2008; Pigeon et al, 2008). In addition, a strong association exists between late-life depression, cognitive impairment, and poor cognitive outcomes, including risk of MCI and dementia (Sheline et al, 2006; Saczynski et al, 2010; Liu et al, 2017). The directionality and mechanisms underlying this association are, however, poorly understood.

The purpose of this thesis was to explore associations between current and historical depression status, sleep quality, and cognitive ability in a sample of older adults with normal cognition or MCI diagnosis. It was hypothesized that positive current or historical depression status is significantly related to cognitive impairment and sleep disturbance. Sleep disturbance as subjectively interpreted from participants' self-report and objectively from actigraphy were shown to be significantly associated with depression status in this study. Relationships between current depression and MCI status were shown, however depressed participants did not display impairment on cognitive measures, such as verbal and visuospatial memory, and overnight memory consolidation as expected.

4.1. Depression & Sleep Parameters.

Predictions were made regarding the relationship between depression status and self-report and objective sleep measures. Various measures were collected to assess sleep fragmentation (PSQI, actigraphy) and sleep deprivation (ESS, SSS). It was hypothesized that

participants with current depressive symptoms and/or a history of diagnosed depression would show and self-report poorer sleep quality. Results showed that participants that had current depression had poorer sleep than participants with no depression with lower mean assumed sleep, lower mean actual sleep time, lower sleep efficiency, longer sleep latency, and lower mean number of minutes immobile (as measured by wrist actigraphy). Participants with current depression also reported more sleep disturbances and greater daytime dysfunction on the PSQI and a trend toward greater average sleepiness on the SSS, when compared with participants with no depression. These results are in line with previous literature (Benca, Obermeyer, Thisted, & Gillin, 1992; Carney, Segal, Edinger, & Krystal, 2007; Dombrovski et al, 2007; Nutt et al, 2008).

Participants with a history of diagnosed depression but *no current depression* did not show sleep disturbance in actigraphy. The history of diagnosed depression group actually had higher mean actual sleep time, longer mean sleep bout time, higher mean number of minutes immobile, and longer mean length immobility than the no depression group. However, the history of diagnosed depression group did report poorer subjective sleep quality and more sleep disturbances on the PSQI than the no depression group. Some evidence exists in previous literature of older adults with a history of diagnosed depression in remission showing greater incidence of sleep disturbance through self-report and diagnostic interview (Motivala, Levin, Oxman, & Irwin, 2006). In actigraphy, the history of diagnosed depression group may have been displaying recurrent symptoms of hypersomnia, or excessive time spent sleeping, which is a less common symptom of major depression but may also continue after effective treatment (Franzen & Buysse, 2008).

It should also be noted that most literature on historical depression in older adults focuses on participants that have relapsed in their depression, with a major focus on persistent insomnia

(Mallon, Broman, & Hetta, 2000; Carney, Segal, Edinger, & Krystal, 2007; Dombrovski et al., 2007). Lack of expected actigraphy results may alternatively be explained by the fact that participants in the history of diagnosed depression group for this study were not currently experiencing depression symptoms and did not display or report significant insomnia. There is a gap in the literature exploring older adults with history of diagnosed depression but no current symptoms.

4.2. Cognitive Status and Health in Aging.

Health parameters and cognitive performance reflecting pathological cognitive decline in aging were explored in this study. As shown in previous literature, chronic health problems were expected to be associated with increased age and comorbidity with depression. In addition, individuals with current depression or history of diagnosed depression were hypothesized to have impairment in various cognitive domains including processing speed, episodic memory and language, verbal and visuospatial memory, and memory consolidation, all probed in neurocognitive assessment during the study. Results are explained and explored below.

4.2.1. Health & Depression. Individuals with current or historical depression often have comorbid common health conditions including cerebrovascular disease, cardiovascular disease, and diabetes (Lenze et al, 2005; Moussavi et al, 2007; Taylor, Aizenstein, & Alexopoulos, 2013). Health conditions were compared between groups with current depression, and history of diagnosed depression but no current depression, and no depression. Results showed no significant differences between groups on health variables, with the exception of MCI. Participants with current depression were more likely to also have clinically diagnosed MCI than participants with a history of diagnosed depression but *no current depression* and those with no depression history. As this study was designed to assess the relationship between sleep and

cognitive status in depression, a protocol was made to attempt to create similar participant groups so as to limit variance from other sources. It may therefore be beneficial to have no significant findings on other health variables, indicating groups were matched on health status. The comorbidity of current depression and poor cognitive outcomes such as MCI diagnosis was expected and supported by the literature (Green et al, 2003; Lenze et al, 2018).

In general, chronic health conditions become more of a commonality as individuals grow older (Cauley, 2012; McNicoll, 2012). It was predicted that in our sample of 65-83 year old individuals, increased age would be associated with a greater number of health complications. The only health decline parameter associated with increased age in this participant sample was MCI diagnosis. Analyses showed that individuals with diagnosed MCI are older than non-diagnosed comparison participants. Depression groups were matched on health status with the exception of MCI, which was more prevalent in the current depression group. Therefore, a potential explanation for the absence of increased health complications in older individuals is that the older individuals are concentrated in the current depression group, and the younger in the other two groups. As these three groups are matched, health complications may have been matched between "older" (i.e. current depression group) and "younger" (i.e. history of diagnosed depression and no depression groups).

4.2.2. Paradoxical Cognitive Findings. Common cognitive deficits exhibited in late-life depression include worse performance in processing speed, visuospatial abilities, episodic memory, verbal fluency, and executive dysfunction, as well as poor learning and free recall on memory tests (Dotson, Beydoun, & Zonderman, 2010). The presence of major depression, both currently and historically, shows accelerated cognitive decline in dementia that is greater than expected for age and education level (Rapp et al, 2011). It was expected that individuals who

endorsed current depression or a history of diagnosed depression would perform more poorly on neurocognitive tests that assessed these domains. These results were not found.

Participants with current depression actually performed better on various overnight memory consolidation task variables (i.e. speed for correct sequences per trial at night, total taps through 12 trials in morning, average correct taps per trial in morning, average taps per trial in the last 3 trials in morning, average correct sequences in the last 3 trials in morning, average taps per trial in the last 6 trials in the morning, percent improvement of correct taps between night and morning) than participants with no depression. There may be several reasons for the lack of impairment on the overnight memory consolidation task by the current depression group. This task has not been explored in depression before since the paradigm is novel. In addition, procedural memory has not been explored as a cognitive deficit in previous literature. Surprisingly, the current depression group also performed better on some neurocognitive follow-up measures, including HVLT-R total recall and Trial 1 of the BVMT-R, than the no depression group. Participants with current depression may not have displayed cognitive impairment on the verbal and visuospatial tasks as expected because their depression was at a subclinical level and had not yet affected cognition. Current depression was assessed through endorsement (positive or negative) in study 1 and study 2. This was not a clinical grade diagnosis and assessment. In addition, the majority of literature on depression and cognitive impairment in older adults assesses depression at a clinical level.

Participants with a history of diagnosed depression performed better on neurocognitive follow-up measures, including HVLT-R total recall and HVLT-R delayed recall, than participants with no depression. History of diagnosed depression and its effect on cognitive performance has seldom been explored in the literature. The hypothesis on the connection

between history of diagnosed depression and cognitive impairment was primarily made based on prospective studies in the literature that explored rates of cognitive decline in older adults that had dementia as a function of historical major depression (Geerlings et al, 2008; Rapp et al, 2011). No participant in this study had dementia and this study was not prospective.

One area of cognition that the current depression group did show impairment on, when compared with the no depression group, was attention. The current depression group performed significantly worse on the MoCA *Attention* component than the no depression group. This result is supported by literature showing that individuals with major depression are likely to have an attention deficit (Veiel, 1997; Paelecke-Habermann, Pohl, & Leplow, 2005; Rock, Roiser, Riedel, & Blackwell, 2014). It is interesting that the relationship between depression and attention was picked up on a subclinical level.

4.3. Cognitive Reserve.

Cognitive reserve is a functional assessment that focuses on individual differences in efficiency when performing cognitive tasks or information processed and is known to be protective of AD and related conditions (Stern, 2002). It was expected that cognitive reserve (measured through education level and IQ correlates such as the vocabulary subtest of the WAIS-III and AMNART) would be correlated with higher scores on neurocognitive assessments, regardless of current or historical depression status. Results showed no significant relationship between cognitive reserve measures and current or historical depression or education level and current or historical depression, as expected. In addition, results showed that participants that scored higher on cognitive reserve proxy measures also scored higher on various neurocognitive follow-up measures including: HVLT-R total recall, HVLT-R delayed recall, HVLT-R retention percentage from learning trials to delayed recall, BVMT-R total recall,

BVMT-R delayed recall, BVMT-R learning, and Boston Naming total score. These results were in line with what was hypothesized.

4.4. Mediational Models.

Mediational models were constructed to assess whether MCI status mediated the relationship between current depression status and different sleep variables and cognitive variables. Two significant models were made. For Model 1, it was found that MCI status partially mediated the relationship between current depression status and the actigraphic measure of mean sleep efficiency. Few studies have looked at depression, sleep, and cognition together despite evidence that poor sleep is closely related to depression (Sbarra & Allen, 2009) and sleep disorder and depressive symptoms are both independently associated with cognitive impairment (Riemann, Berger, & Voderholzer, 2001; Naismith, Norrie, Lewis, Scott, & Hickie, 2009; Koehler, Thomas, Barnett, & O'Brien, 2010; Smagula et al., 2013; Snyder, 2013). Previous literature has shown that depression has a significant impact on the relationship between sleep-wake patterns and cognition (Mellor et al, 2018). There is a gap in the literature exploring the impact cognitive status has on the relationship between depression and sleep, shown in this model.

For Model 2, it was found that MCI status partially mediated the relationship between current depression status and MoCA *Attention* scores. MCI status in this model was based on total MoCA score so it stands to reason that total score on the MoCA would be related to a score on a component of the test. And, as previously mentioned, the literature supports the relationship between attention and depression with individuals positive for depression being more likely to have an attention deficit (Veiel, 1997; Paelecke-Habermann, Pohl, & Leplow, 2005; Rock, Roiser, Riedel, & Blackwell, 2014).

4.5. Methodological Strengths and Limitations.

A major strength of this study is that it addresses several gaps in the literature including assessment of both current and historical depression status in older adults, as well as exploration of preclinical markers of cognitive decline in participants that predominantly have normal cognition. With most studies ignoring the presence of historically diagnosed depression, this study can provide new insight into how current vs. historical depression impacts sleep and cognition. In addition, literature exploring cognition and depression typically looks at a demented sample or are prospective for dementia onset in a depressed sample. This study is novel in its assessment of older adults with normal cognition, who make up the majority of the study sample (n=38). In order to minimize confounding influences, recruitment sites and strategies and careful interview were used to match the current depression, history of diagnosed depression but no current depression, and no depression groups on demographic and health characteristics. As a result, this study was able to reduce the impact of important demographic factors such as education, race, and marital status, as well as health factors including OSA, cardiovascular disease, cerebrovascular disease, etc. on variance in the findings. MCI status was, however, found to be significantly different between groups and was therefore used as a covariate in statistical analyses.

This study is both complicated and time consuming, including home visits and sleep equipment, which may have played a part in our total number of accrued patients. In addition, a number of interested older adults were too young to participate or living at a distance not feasible for the 3-4 visits required per participant. The exclusion of these individuals severely depleted the total N for this study. As there is a relatively low N, all results should be deemed preliminary.

There was also a very low n for depression groups with the majority of participants not endorsing current depression.

A major limitation of this study was the fact that it was not designed to study depression. This study was designed to explore sleep parameters in older adults with and without clinically diagnosed MCI. The factor of depression was explored as a secondary study. It should be clarified that in Study 1 (pilot study), depression was probed only through a yes/no question on the demographic interview regarding if the participant felt that he/she was currently depressed. The assessment of depression was expanded in Study 2 to include measures of depression severity (i.e. CES-D), depression medication use, and history of diagnosed depression (i.e. supplemental questions). Since different depression measures were used in Study 1 and Study 2, this made post-hoc groups complex and problematic. Analyses excluded participants from Study 1 that did not endorse current depression as history of diagnosed depression and depression medication use was unknown for these participants. I plan to continue exploring depression in this study and when my N grows to a more reasonable size, I can exclude Study 1 data from analyses to simplify analyses.

4.6. Conclusion.

This thesis study investigated the hypothesis that depression status may have an important negative impact on sleep quality and cognitive function. Overall, current depression was significantly associated with poorer objective and self-reported sleep quality. History of diagnosed depression was also associated with poorer self-reported sleep quality. Findings were not consistent with the hypothesis that depression status (current or historical) would be associated with impairment on neurocognitive measures. In fact, participants with current or historical depression performed better on neurocognitive tasks assessing verbal learning and

memory and visuospatial abilities. The only cognitive impairment associated with depression status was in attention. Due to the low N and discrepancy in depression measures, these results can only be considered preliminary and warrant further exploration. Continuation of this study and future research into the connection between depression status, cognition, and sleep quality may be useful in early detection of individuals at risk for developing aging-related neurological disorders.

REFERENCES

Alexander, L., Lopes, B., Ricchetti-Masterson, K, & Yeatts, K. (2017). Incident vs prevalent cases and measures of occurrence.

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). 'Vascular depression' hypothesis. *Archives of general psychiatry, 54*(10), 915-922.

Alexopoulos, G. S. (2001). The depression-executive dysfunction syndrome of late life: a specific target for DR agonists?. The *American Journal of Geriatric Psychiatry, 9*(1): 22-29.

Alexopoulos, G. S. (2006). The vascular depression hypothesis: 10 years later. *Biological psychiatry, 60*(12), 1304-1305.

Alonso, R., Groebe;, G., Pavone, G., Stemmelin, J., Le Fur, G., Soubie, P. (2004). Blockade of CRF (1) or V (1b) receptors reverses stress-induced suppression of neurogenesis in a mouse model of depression. *Molecular Psychiatry, 9*, 278-286.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5).* American Psychiatric Pub.

Amodio, P., Wenin, H., Del Piccolo, F., Mapelli, D., Montagnese, S., Pellegrini, A., ... & Umiltà, C. (2002). Variability of trail making test, symbol digit test and line trait test in normal people. A normative study taking into account age-dependent decline and sociobiological variables. *Aging clinical and experimental research*, *14*(2), 117-131.

Ancoli-Israel, S. (2009). Sleep and its disorders in aging populations. *Sleep medicine, 10,* S7-S11.

Andresen, E. M., Malmgren, J. A., Carter, W. B., & Patrick, D. L. (1994). Screening for Depression in Well Older Adults: Evaluation of *Prev Med, 10,* 77-84.

Argyropoulos, S. V. & Wilson, S. J. (2005). Sleep disturbances in depression and the effects of antidepressants. *International Review of Psychiatry, 17*(4), 237-245.

Armitage, R. (2007). Sleep and circadian rhythms in mood disorders. *Acta Psychiatrica Scandinavica*, *115,* 104-115.

Ashendorf, L., Jefferson, A. L., O'Connor, M. K., Chaisson, C., Green, R. C., & Stern, R. A. (2008). Trail Making Test errors in normal aging, mild cognitive impairment, and dementia. *Archives of Clinical Neuropsychology, 23*(2), 129-137.

Axelson, D., Doraiswamy, P. M., McDonald, W. M., Boyko, O. B. Tupler, L. A., Patterson, L. J., et al. (1993). Hypercortisolemia and hippocampal changes in depression. *Psychiatry Research, 47*(2), 163-173.

Baldwin, C. M., Griffith, K. A., Nieto, F. J., O'Connor, G. T., Walsleben, J. A., & Redline, S. (2001). The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. *Sleep, 24*(1), 96-105.

Barnes, D. R., Alexopoulos, G. S., Lopez, O. L., Williamson, J. D., & Yaffe, K. (2006). Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. *Archives of general psychiatry, 63*(3), 273-279.

Batty, G. D., Wennerstad, K. M., Smith, G. D., Gunnell, D., Deary, I. J., Tynelius, P., & Rasmussen, F. (2009). IQ in early adulthood and mortality by middle age: Cohort study of 1 million Swedish men. *Epidemiology, 20*, 100-109.

Beaulieu-Bonneau, S. & Hudon, C. (2009). Sleep disturbances in older adults with mild cognitive impairment. *International Psychogeriatrics, 21*(4), 654-666.

Becker, N. B., Jesus, S. N., Joao, K. A., Viseu, J. N., & Martins, R. I. (2017). Depression and sleep quality in older adults: a meta-analysis. *Psychology, health & medicine*, *22*(8), 889-895.

Benca, R. M., Obermeyer, W. H., Thisted, R. A., & Gillin, J. C. (1992). Sleep and psychiatric disorders: a meta-analysis. *Archives of general psychiatry, 49*(8), 651-668.

Benedict, R. H., Schretlen, D., Groninger, L., Dobraski, M., & Shpritz, B. (1996). Revision of the Brief Visuospatial Memory Test: Studies of normal performance, reliability, and validity. *Psychological Assessment*, *8*(2), 145.

Benedict, R. H., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins Verbal Learning Test-Revised: Normative data and analysis of inter-form and test-retest reliability. *The Clinical Neuropsychologist, 12*(1), 43-55.

Berger, A. K., Fratiglioni, L., Forsell, Y., Winblad, B., & Bäckman, L. (1999). The occurrence of depressive symptoms in the preclinical phase of AD: a population-based study. *Neurology*, *53*(9), 1998-1998.

Blair, J. R. & Spreen, O. (1989). Predicting premorbid IQ: a revision of the National Adult Reading Test. *The Clinical Neuropsychologist, 3*(2), 129-136.

Brabbins, C. J., Dewey, M. E., Copeland, J. R. M., Davidson, I. A., McWilliam, C., Saunders, P., … & Sullivan, C. (1993). Insomnia in the elderly: prevalence, gender differences, and relationships with morbidity and mortality. *International Journal of Geriatric Psychiatry, 8*(6), 473-380.

Bremner, J., Narayan, M., Anderson, E. R., Staib, L. H., Miller, H. L., Charney, D. S. (2000). Hippocampal volume reduction in major depression. *American Journal of Psychiatry, 157*, 115-118.

Brown, J., Cooper-Kuhn, C.M., Kempermann, G., Van Praag, H., Winkler, J., Gage, F. H., & Kuhn H.G. (2003). Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. *European Journal of Neuroscience, 17*, 2042-2046.

Butters, M. A., Young, J. B., Lopez, O., Aizenstein, H. J., Mulsant, B. H., Reynolds III, C. F., … & Becker, J. T. (2008). Pathways linking late-life depression to persistent cognitive impairment and dementia. *Dialogues in clinical neuroscience*, *10*(3), 345-354.

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research*, *28*(2), 193-213.

Buysse, D. J. (2004). Insomnia, depression and aging. Assessing sleep and mood interactions in older adults. *Geriatrics (Basel, Switzerland)*, *59*(2), 47-51.

Cameron, H. & McKay, R.D.G. (2001). Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. *Journal of Comparative Neurology, 435*, 406-417.

Carney, C. E., Segal, Z. V., Edinger, J. D., & Krystal, A. D. (2007). A comparison of rates of residual insomnia symptoms following pharmacotherapy or cognitive-behavioral therapy for major depressive disorder. *The Journal of clinical psychiatry*, *68*(2), 254-260.

Carney, C. E., Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Krystal, A. D., Lichstein, K. L., & Morin, C. M. (2012). The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep*, *35*(2), 287-302.

Cauley, J. A. (2012). The Demography of Aging. In *The Epidemiology of Aging* (pp. 3-14). Springer Netherlands

Chen, P., Ganguli, M., Mulsant, B. H., & DeKosky, S. T. (1999). The temporal association between depressive symptoms and dementia: a community-based prospective study. *Archives of general psychiatry*, *56*(3), 261-266.

Cho, H. J., Lavretsky, H., Olmstead, R., Levin, M. J., Oxman, M. N., & Irwin, M. R. (2008). Sleep disturbance and depression recurrence in community-dwelling older adults: a prospective study. *American Journal of Psychiatry*, *165*(12), 1543-1550.

Chung, J. K. (2018). Using Multimodal Imaging to Examine Clinical and Cognitive Correlates of Mild Cognitive Impairment and Alzheimer's Disease (Doctoral dissertation).

Coe, C., Kramer, M., Czeh, B., Gould, E., Reeves, A.J., Kirschbaum, C., & Fuchs, E. (2003). Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. *Biological Psychiatry, 54*, 1025-1034.

Columbia Doctors. (2017). "About Cerebral Ischemia". Retrieved from https://www.columbianeurosurgery.org/conditions/cerebral-ischemia/

Cotter, D., Mackay, D., Landau, S., Kerwin, R., & Everall, I. (2001). Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Archives of General Psychiatry, 58*, 545-553.

Crowley, K. (2011). Sleep and sleep disorders in older adults. *Neuropsychology review, 21*(1), 41-53.

Czeh, B., Michaelis, T., Watanabe, T., Frahm, J., de Biurrun, G., van Kampen, M., et al (2001). Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. *Proceedings of the National Academy of Sciences, 98*(22), 12796-12801.

Deary, I. J., Whalley, L. J., Lemmon, H., Crawford, J. R., & Starr, J. M. (2000). The stability of individual differences in mental ability from childhood to old age: Follow-up of the 1932 Scottish Mental Survey. *Intelligence, 28*, 49-55.

Deary, I. J., Strand, S., Smith, P., & Fernandes, C. (2007). Intelligence and educational achievement. *Intelligence, 35*, 13-21.

Devanand, D. P., Sano, M., Tang, M. X., Taylor, S., Gurland, B. J., Wilder, D., ... & Mayeux, R. (1996). Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Archives of general psychiatry, 53*(2), 175-182.

Dombrovski, A. Y., Mulsant, B. H., Houck, P. R., Mazumdar, S., Lenze, E. J., Andreescu, C., … & Reynolds III, C. F. (2007). Residual symptoms and recurrence during maintenance treatment of late-life depression. *Journal of affective disorders, 103*(1-3), 77-82.

Dotson, V. M., Beydoun, M. A., & Zonderman, A. B. (2010). Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology, 75*(1), 27-34.

Drevets, W. C., Price, J. L., Simpson Jr., J. R., Todd, R. D., Reich, T., Vannier, M., Raichle, M. E. (1997). Subgenual prefrontal cortex abnormalities in mood disorders. *Nature, 386*, 824-827.

Drevets, W. (2001). Neuroimaging and neuropathological studies of depression: Implications for the cognitive-emotional features of mood disorders. *Current Opinions in Neurobiology, 11*,240-249.

Dryman, A. & Eaton, W. W. (1991). Affective symptoms associated with the onset of major depression in the community: findings from the US National Institute of Mental Health Epidemiologic Catchment Area Program. *Acta Psychiatrica Scandinavica, 84*(1), 1-5.

Duman, R., Malberg, J., & Nakagawa, S. (2001). Regulation of adult neurogenesis by psychotropic drugs and stress. *Journal of Pharmacology and Experimental Therapeutics, 299*(2), 401-407.

Duman, R. S. (2004). Depression: a case of neuronal life and death?. *Biological psychiatry, 56*(3), 140-145.

Durmer, J. S. & Dinges, D. F. (2005, March). Neurocognitive consequences of sleep deprivation. In *Seminars in neurology* (Vol. 25, No. 01, pp. 117-129). New York, NY: Thieme Medical.

Fastenau, P. S., Denburg, N. L., & Mauer, B. A. (1998). Parallel short forms for the Boston Naming Test: psychometric properties and norms for older adults. *Journal of Clinical and Experimental Neuropsychology, 20*(6), 828-834.

Feldman, J. L., Del Negro, C. A., & Gray, P. A. (2013). Understanding the rhythm of breathing: so near, yet so far. *Annual review of physiology, 75,* 423-452.

Foley, D. J., Monjan, A. A., Brown, S. L., Simonsick, E. M., Wallace, R. B., & Blazer, D. G. (1995). Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep, 18*(6), 425-432.

Franzen, P. L. & Buysse, D. J. (2008). Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications. *Dialogues in clinical neuroscience, 10*(4), 473.

Freitas, S., Simoes, M. R., Alves, L., & Santana, I. (2013). Montreal cognitive assessment: validation study for mild cognitive impairment and Alzheimer disease. *Alzheimer Disease & Associated Disorders, 27*(1), 37-43.

Frodl, T., Meisenzahl, E. M., Zetzsche, T., Born, C., Groll, C., Jager, M., et al (2002). Hippocampal changes in patients with a first episode of major depression. *American Journal of Psychiatry, 159,* 1112-1118.

Galton, F. (1889). On head growth in students at the University of Cambridge. *The Journal of the Anthropological Institute of Great Britain and Ireland, 64,* 18-29.

Ganguli, M., Du, Y., Dodge, H. H., Ratcliff, G. G. & Chang, C. C. H. (2006). Depressive symptoms and cognitive decline in late life: a prospective epidemiological study. *Archives of general psychiatry, 63*(2), 153-160.

Geda, Y. E., Schneider, L. S., Gitlin, L. N., Miller, D. S., Smith, G. S., Bell, J., … & Rosenberg, P. B. (2013). Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future. *Alzheimer's & dementia, 9*(5), 602-608.

Geerlings, M. I., den Heijer, T., Koudstaal, P. J., Hofman, A., & Breteler, M. M. B. (2008). History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. *Neurology, 70*(15), 1258-1264.

Giovagnoli, A. R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., & Capitani, E. (1996). Trail making test: normative values from 287 normal adult controls. *The Italian journal of neurological sciences, 17*(4), 305-309.

Gold, P. & Chrousos, G.P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs. low CRH/NE states. *Molecular Psychiatry, 7,* 254-275.

Gould, E., McEwen, B.S, Tanapat, P., Galea, L.A.M., & Fuchs, E. (1997). Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *Journal of Neuroscience, 17,* 2492-2498.

Gould, E., Tanapat P., McEwen, B.S., Flugge, G., & Fuchs., E. (1998). Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. *Proceedings of the National Academy of Sciences, 95*(6), 316-3171.

Gould, E., Reeves, A.J., Fallah, M., Tanapat, P., Gross, C.G., Fuchs, E. (1999). Hippocampal neurogenesis in adult world primates. *Proceedings of the National Academy of Sciences, 96,* 5263-5267.

Grant, W. B., Campbell, A., Izhaki, R. F., & Savory, J. (2002). The significance of environmental factors in the etiology of Alzheimer's disease. *Journal of Alzheimer's Disease, 4*(3), 179-189.

Green, R. C., Cupples, L. A., Kurz, A., Auerbach, S., Go, R., Sadovnick, D., … & Griffith, P. A. (2003). Depression as a risk factor for Alzheimer disease: the MIRAGE Study. *Archives of neurology, 60*(5), 753-759.

Hadanny, A. & Efrati, S. (2015). Oxygen - a limiting factor for brain recovery. *Critical Care, 19*(1). Doi: 10.1186/s13054-015-1034-2.

Hardy, J. & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science, 297*(5580), 353-356.

Hayes, M. J. (2002). Methodological issues in the study of arousals and awakenings during sleep. *Awakening and sleep-wake cycle across decelovement, 38,* 23.

Hedden, T., Oh, H., Younger, A. P., & Patel, T. A. (2013). Meta-analysis of amyloid-cognition relations in cognitively normal older adults. *Neurology*, *80*(14), 1341-1348.

Hoddes, E., Zarcone, V., Smythe, H., Phillips, R., & Dement, W. C. (1973). Quantification of sleepiness: a new approach. *Psychophysiology*, *10*(4), 431-436.

Hurelbrink, C. B., Lewis, S. J., & Barker, R. A. (2005). The use of the Actiwatch–Neurologica® system to objectively assess the involuntary movements and sleep–wake activity in patients with mild–moderate Huntington's disease. *Journal of neurology*, *252*(6), 642-647.

Irwin, M., Artin, K. H., & Oxman, M. N. (1999). Screening for depression in the older adult: criterion validity of the 10-item Center for Epidemiological Studies Depression Scale (CES-D). *Archives of internal medicine*, *159*(15), 1701-1704.

Jain, N. & Steffens, D. C. (2018). Neurobiology and Risk Factors of Late-Life Depression. In Kim, Y. K. (ed.), *Understanding depression. Volume 1, Biomedical and neurobiological background* (pp. 279-295). Singapore: Springer.

Jaussent, I., Bouyer, J., Ancelin, M. L., Akbarlay, T., Peres, K., Ritchie, K., … & Dauvilliers, Y. (2011). Insomnia and daytime sleepiness are risk factors for depressive symptoms in the elderly. *Sleep*, *34*(8), 1103-1110.

Johns, M. W. (1992). Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep*, *15*(4), 376-381.

Ju, Y. E. S., Lucey, B. P., Holtzman, D. M. (2014). Sleep and Alzheimer disease pathology--a bidirectional relationship. *Nature reviews Neurology*, *10*(2), 115.

Kempermann, G. & Gage, F. H. (2002). Genetic determinants of adult hippocampal neurogenesis correlate with acquisition, but not probe trial performance in the water maze task. *European Journal of Neuroscience*, *16*, 129-136.

Kennedy, G. J., Kelman, H. R., & Thomas, C. (1991). Persistence and remission of depressive symptoms in late life. *The American journal of psychiatry*, *148*(2), 174.

Kilgore, M., Miller, C. A., Fass, D. M., Hennig, K. M., Haggarty, S. J., Sweatt, J. D., & Rumbaugh, G. (2010). Inhibitors of Class I Histone Deacetylases Reverse Contextual Memory Deficits in a Mouse Model of Alzheimer's Disease. *Neuropsychopharmacology*, *35*(4), 870-880.

Kirova, A. M., Bays, R. B., & Lagalwar, S. (2015). Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. *BioMed research international*, *2015*.

Koehler, S., Thomas, A. J., Barnett, N. A., & O'Brien, J. T. (2010). The pattern and course of cognitive impairment in late-life depression. *Psychological Medicine, 40*(4), 591-602.

Koketsu, D., Mikami, Y., & Hisatsune, T. (2003). Nonrenewal of neurons in the cerebral neocortex of adult macaque monkeys. *Journal of Neuroscience, 23*, 937-942.

Kornack, D. & Rakic, P. (2001). Cell proliferation without neurogenesis in adult primate neocortex. *Science, 294*(21), 2127-2129.

Kryger, M., Monjan, A., Bliwise, D., & Ancoli-Israel, S. (2004). Sleep, health, and aging. Bridging the gap between science and clinical practice. *Geriatrics, 59*(1), 24-26.

Lahr, D., Beblo, T., Hartje, W. (2007). Cognitive performance and subjective complaints before and after remission of major depression. *Cognitive neuropsychiatry, 12*(1), 25-45.

Lemaire, V., Koehl, M., Moal, M., Abrous, D.N. (2000). Prenatal stress produces learning deficits associated with inhibition of neurogenesis in the hippocampus. *Proceedings of the National Academy of Sciences, 97*, 11032-11037.

Lenze, E. J., Schulz, R., Martire, L. M., Zdaniuk, B., Glass, T., Kop, W. J., … & Reynolds III, C. F. (2005). The course of functional decline in older people with persistently elevated depressive symptoms: longitudinal findings from the Cardiovascular Health Study. *Journal of American Geriatrics Society, 53*(4), 569-575.

Lenze, E. J., Voineskos, A. N., Butters, M. A., Karp, J. F., & of the OPTIMUM, O.B. (2018). Stopping cognitive decline in patients with late-life depression: a new front in the fight against dementia. *The American Journal of Geriatric Psychiatry, 26*(8), 828-834.

Lewinsohn, P. M., Seeley, J. R., Roberts, R. E., & Allen, N. B. (1997). Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychology and aging*, *12*(2), 277.

Li, P., Hsaio, I. T., Liu, C. Y., Chen, C. H., Huang, S. Y., Yen, T. C., … Lin, K. J. (2017). Beta-amyloid deposition in patients with major depressive disorder with differing levels of treatment resistance: a pilot study. *EJNMMI Res, 7*(1), 24. doi:10.1155/2014/927804

Liu, Y. C., Meguro, K., Nakamura, K., Akanuma, K., Nakatsuka, M., Seki, T., … & Kawakami, N. (2017). Depression and Dementia in the Old-Old Population: History of Depression May Be Associated with Dementia Onset. The Tome Project. *Frontiers in Aging Neuroscience, 9,* 335.

Livingston, G., Blizard, B., & Mann, A. (1993). Does sleep disturbance predict depression in elderly people? A study in inner London. *British Journal of General Practice, 43*(376), 445-448.

Lock, S. L., Baumgart, M., Whiting, C. G., McGuire, L. C., Iskander, J. K., Thorpe, P., & Laird, S. (2017). Healthy aging: promoting well-being in older adults.

Lupien, S. J., Nair, N. P. V., Briere, S., Maheu, F., Tu, M. T., Lemay, M., … & Meaney, M. J. (1999). Increased cortisol levels and impaired cognition in human aging: implication for depression and dementia in later life. *Reviews in the Neurosciences, 10*(2), 117-140.

Mack, W. J., Freed, D. M., Williams, B. W., & Henderson, V. W. (1992). Boston Naming Test: shortened versions for use in Alzheimer's disease. *Journal of gerontology, 47*(3), P154-P158.

MacQueen, G., Campbell, S., McEwen, B. S., Macdonald, K., Amano, S., Joffe, R. T., et al. (2003). Course of illness, hippocampal function, and hippocampal volume in major depression. *Proceedings of the National Academy of Sciences, 100*(3), 1387-1392.

Malberg, J. & Duman, R.S. (2003). Cell proliferation in adult hippocampus is decreased by inescapable stress: Reversal by fluoxetine treatment. *Neuropsychopharmacology, 28*, 1562-1571.

Mallon, L., Broman, J. E., & Hetta, J. (2000). Relationship between insomnia, depression, and mortality: a 12 year follow-up of older adults in the community. *International Psychogeriatrics, 12*(3), 295-306.

Mander, B. A., Marks, S. M., Vogel, J. W., Rao, V., Lu, B., Saletin, J. M., … Walker, M. P. (2015). □-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nature Neuroscience, 18*(7), 1051-1057. doi: 10.1038/nn.4035.

Mander, B. A., Winer, J. R., & Walker, M. P. (2017) Sleep and human aging. *Neuron, 94*(1), 19-36.

Manji, H., Drevets, W.C., & Charney, D.S. (2001). The cellular neurobiology of depression. *Nature Medicine, 7*, 541-547.

Martins, R. N., Villemagne, V., Sohrabi, H. R., Chatterjee, P., Shah, T. M., Verdile, G., … & Hone, E. (2018). Alzheimer's Disease: A Journey from Amyloid Peptides and Oxidative Stress, to Biomarker Technologies and Disease Prevention Strategies--Gains from AIBL and DIAN Cohort Studies. *Journal of Alzheimer's Disease, 62*(3), 965-992.

McCarter, S. J., Louis, E. K. S., & Boeve, B. F. (2012). REM sleep behavior disorder and REM sleep without atonia as an early manifestation of degenerative neurological disease. *Current neurology and neuroscience reports, 12*(2), 182-192.

McEwen, B. (1999). Stress and hippocampal plasticity. *Current Opinions in Neurobiology, 5*, 205-216.

McNicoll, G. (2012). The Demography and Epidemiology of Human Health and Aging, 747-748.

Mellor, A., Bucks, R. S., Maul, J., Sanders, K. A., McGowan, H., & Waters, F. (2018). Sleep and cognition in older adults: Does depression matter? An actigraphy and polysomnography study. *Archives of Psychology, 2*(1).

Mervaala, E., Fohr, J., Kononen, M., Valkonen-Korhonen, M., Vainio, P., Partanen, K., et al. (2000). Quantitative MRI of hippocampus and amygdala in severe depression. *Psychological Medicine, 30*(1), 117-125.

Motivala, S. J., Levin, M. J., Oxman, M. N., & Irwin, M. R. (2006). Impairments in health functioning and sleep quality in older adults with a history of depression. *Journal of the American Geriatrics Society, 54*(8), 1184-1191.

Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., & Ustun, B. (2007). Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *The Lancet, 370*(9590), 851-858.

Mungas, D., Gavett, B., Fletcher, E., Farias, S. T., DeCarli, C., & Reed, B. (2018). Education amplifies brain atrophy effect on cognitive decline: implications for cognitive reserve. *Neurobiology of Aging, 68,* 142-150.

Murri, M. B., Pariante, C., Mondelli, V., Masotti, M., Atti, A. R., Mellacqua, Z., … & Innamorati, M. (2014). HPA axis and aging in depression: systematic review and meta-analysis. *Psychoneuroendocrinology, 41*, 46-62.

Musiek, E. S., Bhimasani, M., Zangrilli, M. A., Morris, J. C., Holtzman, D. M., & Ju, Y. E. S. (2018). Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. *JAMA neurology, 75*(5), 582-590.

Naismith, S. L., Norrie, L., Lewis, S. J., Rogers, N. L., Scott, E. M., & Hickie, I. B. (2009). Does sleep disturbance mediate neuropsychological functioning in older people with depression? *Journal of Affective Disorders, 116*(1), 139-143.

Naismith, S. L., Rogers, N. L., Hickie, I. B., Mackenzie, J., Norrie, L. M., & Lewis, S. J. (2010). Sleep well, think well: sleep-wake disturbance in mild cognitive impairment. *Journal of Geriatric Psychiatry and Neurology, 23*(2), 123-130.

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., … & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695-699.

National Institute on Aging. (2018). "What happens to the Brain in Alzheimer's Disease?. Retrieved from https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

Nave, G., Jung, W. H., Karlsson Linner, R., Kable, J. W., & Koellinger, P. D. (2018). Are Bigger Brains Smarter? Evidence From a Large-Scale Preregistered Study. *Psychological science*, 0956797618808470.

Nutt, D., Wilson, S., & Paterson, L. (208). Sleep disorders as core symptoms of depression. *Dialogues in clinical neuroscience*, *10*(3), 329.

Nyberg, L., Lodven, M., Riklund, K., Lindenberger, U., & Backman, L. (2012). Memory aging and brain maintenance. *Trends in cognitive sciences*, *16*(5), 292-305.

Ongur, D., Drevets, W. C., & Price, J. L. (1998). Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proceedings of the National Academy of Sciences*, *95*, 13290-13295.

Orzel-Gryglewska, J. (2010). Consequences of sleep deprivation. *International journal of occupational medicine and environmental health.*

Pace-Schott, E. F. & Spencer, R. M. C. (2011). Age-related changes in the cognitive function of sleep. *Enhancing Performance for Action and Perception: Multisensory Integration, Neuroplasticity and Neuroprosthetics, Pt I*, *191*, 75-89.

Paelecke-Habermann, Y., Pohl, J., & Leplow, B. (2005). Attention and executive functions in remitted major depression patients. *Journal of affective disorders*, *89*(1-3), 125-135.

Palmer, K., Berger, A. K., Monastero, R., Winblad, B., Backman, L., & Fratiglioni, L. (2007). Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology*, *68*(19), 1596-1602.

Panza, F., Frisardi, V., Capurso, C., D'introno, A., Colacicco, A. M., Imbimbo, B. P., … & Capurso, A. (2009). Late-life depression, mild cognitive impairment, and dementia: possible continuum?. *The American Journal of Geriatric Psychiatry*, *18*(2), 98-116.

Petersen, R. C., Caracciolo, B., Brayne, C., Gauthier, S., Jelic, V., & Fratiglioni, L. (2014). Mild cognitive impairment: a concept in evolution. *Journal of internal medicine*, *275*(3), 214-228.

Pham, K., Nacher, J., Hof, P.R., McEwen, B.S. (2003). Repeated restraint stress suppresses neurogenesis and reduces biphasic PSA-NCAM expression in the adult rate dentate gyrus. *European Journal of Neuroscience*, *17*, 879-886.

Pigeon, W. R., Hegel, M., Unutzer, J., Fan, M. Y., Sateia, M. J., Lyness, J. M., … & Perlis, M.L. (2008). Is insomnia a perpetuating factor for late-life depression in the IMPACT cohort?. *Sleep*, *31*(4), 481-488.

Plassman, B. L., Langa, K. M., Fisher, G. G., Heerings, S. G., Weir, D. R., Ofstedal, M. B., … & Steffens, D. C. (2007). Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology*, *29*(1-2), 125-132.

Posener, J., Wang, L., Price, J. L., Gado, M.H., Province, M. A., Miller, M. I., et al. (2003). High-dimensional mapping of hippocampus in depression. *American Journal of Psychiatry, 160*, 83-89.

Potts, J.T., Rybak, I. A., & Paton, J. F. (2005). Respiratory rhythm entrainment by somatic afferent stimulation. *The Journal of Neuroscience, 25*(8), 1965-1978.

Potvin, O., Lorrain, D., Forget, H., Dube, M., Grenier, S., Preville, M., & Hudon, C. (2012). Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults, *Sleep 35*(4), 491-499.

Qiu, C., De Ronchi, D., & Fratiglioni, L. (2007). The epidemiology of the dementias: an update. *Current opinion in psychiatry*, *20*(4), 380-385.

Radboud University Medical Center. (2018). "Segmentation and Quantification of White Matter Lesions". Retrieved from www.diagnijmegen.nl/index.php/White_Matter_Lesions

Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied psychological measurement, 1*(3), 385-401.

Rajkowska, G., Miguel-Hidalgo, J. J., Wei, J., Dilley, G., Pittman, S. D., Meltzer, H. Y., et al. (1999). Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biological Psychiatry, 45*, 1085-1098.

Rapp, M. A., Schnaider-Beeri, M., Grossman, H. T., Sano, M., Perl, D. P., Purohit, D. P., … & Haroutunian, V. (2006). Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. *Archives of general psychiatry, 63*(2), 161-167.

Rapp, M. A., Schnaider-Beeri, M., Wysocki, M., Guerrero-Berroa, E., Grossman, H. T., Heinz, A., & Haroutunian, V. (2011). Cognitive decline in patients with dementia as a function of depression. *The American Journal of Geriatric Psychiatry, 19*(4), 357-363.

Richard, E., Reitz, C., Honig, L. H., Schupf, N., Tang, M. X., Manly, J. J., … & Luchsinger, J. A. (2013). Late-life depression, mild cognitive impairment, and dementia. *JAMA neurology, 70*(3), 383-389.

Riemann, D., Berger, M., & Voderholzer, U. (2001). Sleep and depression - results from psychobiological studies: an overview. *Biological Psychology, 57*(1), 67-103.

Robert, P. H., Berr, C., Volteau, M., Bertogliati, C., Benoit, M., Sarazin, M., … & Dubois, B. (2006). Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease: a one-year follow-up study. *Clinical neurology and neurosurgery, 108*(8), 733-736.

Robert, P. H., Berr, C., Volteau, M., Bertogliati-Fileau, C., Benoit, M., Guerin, O., … & PreAL Study Group. (2008). Importance of lack of interest in patients with mild cognitive impairment. *The American Journal of Geriatric Psychiatry, 16*(9), 770-776.

Roberts, R. E., Shema, S. J., Kaplan, G. A., & Strawbridge, W. J. (2000). Sleep complaints and depression in an aging cohort: a prospective perspective. *American Journal of Psychiatry, 157*(1), 81-88.

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological medicine, 44*(10), 2029-2040.

Rogers, J., Cooper, N. R., Webster, S., Schulz, J., McGeer, P. L., Styren, S. D., … & Ward, P. (1992). Complement activation by beta-amyloid in Alzheimer disease. *Proceedings of the National Academy of Sciences, 89*(21), 10016-10020.

Saarelainen, T., Hendolin, P., Lucas, G., Koponen, E., Sairanen, M., MacDonald, E., et al. (2003). Activation of the trkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *Journal of Neuroscience, 23*, 349-357.

Saczynski, J. S., Beiser, A., Seshadri, S., Auerbach, S., Wolf, P. A., & Au, R. (2010). Depressive symptoms and risk of dementia: The Framingham Heart Study. *Neurology, 75*(1), 35-41.

Salthouse, T. A. (2011). Neuroanatomical substrates of age-related cognitive decline. *Psychological bulletin, 137*(5), 753.

Sapolsky, R. (2002). Chickens, eggs, and hippocampal atrophy. *Nature Neuroscience, 5*(11), 1111-1113.

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology, 7*(3), 273.

Sbarra, D. A. & Allen, J. J. (2009). Decomposing depression: On the prospective and reciprocal dynamics of mood and sleep disturbances. *Journal of Abnormal Psychology, 118*(1), 171.

Segers, L. S., Nuding, S. C., Dick, T. E., Shannon, R., Baekey, D. M., Solomon, I. C., … & Lindsey, B. G. (2008). Functional connectivity in the pontomedullary respiratory network. *Journal of neurophysiology, 100*(4), 1749-1769.

Shah, P., Ebmeier, K. P., Glabus, M. F., Goodwin, G. M. (1998). Cortical grey matter reduction associated with treatment-resistant chronic unipolar depression. *British Journal of Psychiatry, 172*, 527-532.

Sharpiro, A. M., Benedict, R. H., Schretlen, D., & Brandt, J., (1999). Construct and concurrent validity of the Hopkins Verbal Learning Test-revised. *The Clinical Neuropsychologist, 13*(3), 348-358.

Sheline, Y., Wany, P., Gado, M. H., Csernansky, J. G., & Vannier, M. W. (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Sciences, 93*, 3908-3913.

Sheline, Y., Sanghavi, M., Mintun, M. A., & Gado, M. H. (1999) Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *Journal of Neuroscience, 19*, 5034-5043.

Sheline, Y., Sanghavi, M., Mintun, M. A., & Gado, M. H. (2000). 3D MRI studies of neuroanatomic changes in unipolar major depression: The role of stress and medical comorbidity. *Biological Psychiatry, 48*, 791-800.

Sheline Y., Gado, M. H., & Kraemer, H. C. (2003). Untreated depression and hippocampal volume loss. *American Journal of Psychiatry, 160*, 1-3.

Sheline, Y. I., Barch, D. M., Garcia, K., Gersing, K., Pieper, C., Welsh-Bohmer, K., … & Doraiswamy, P. M. (2006). Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors, and processing speed. *Biological psychiatry, 60*(1), 58-65.

Smagula, S. F., Reynolds, C. F., Ancoli-Israel, S., Barrett-Connor, E., Dam., T. T., Hughes-Austin, J. M., … & Cauley, J. A. (2013). Sleep architecture and mental health among community-dwelling older men, *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, gbt125.

Smagula, S. F., Stone, K. L., Fabio, A, & Cauley, J. A. (2016). Risk factors for sleep disturbances in older adults: evidence from prospective studies. *Sleep medicine review, 25*, 21-30.

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychological Bulletin, 139*(1), 81-132.

Steffens, D., Bryum, C. E., McQuoid, D. R., Greenberg, D. L., Payne, M. E., Blitchington, T. F., et al. (2000). Hippocampal volume in geriatric depression. *Biological Psychiatry, 48*, 301-309.

Stepanski, E. J. (2002). The effect of sleep fragmentation on daytime function. *Sleep, 25*(3), 268-276.

Stern, Y., Albert, S., Tang, M. X., & Tsai, W. Y. (1999). Rate of memory decline in AD is related to education and occupation Cognitive reserve?. *Neurology, 53*(9), 1942.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of International Neuropsychological Society, 8*(3), 448-460.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015-2028.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology, 11*(11), 1006-1012.

Stern, Y., Arenaza-Urquijo, E. M., Batres-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., … &
Okonkwo, O. (2018). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's & Dementia.*

Stickgold, R., & Walker, M. P. (2005). Sleep and memory: the ongoing debate. *Sleep, 28*(10), 1225-1227.

Stott, D. H. (1983). Brain size and "intelligence". *The British Journal of Developmental Psychology, 1*, 279-287.

Tam, J. W., & Schmitter-Edgecombe, M. (2013). Event-based prospective memory and everyday forgetting in healthy older adults and individuals with mild cognitive impairment. *Journal of clinical and experimental neuropsychology*, *35*(3), 279-290.

Tampi, R. R., Tampi, D. J., Canio, W. C., Alag, P., Dasarathy, D., & Dey, J. P. (2018). Neurocognitive Disorders. In Tampi, R., Tampi, D., & Boyle, L. (Eds.), *Psychiatric disorders in late life: a comprehensive review* (pp. 139-165), Springer.

Tanapat, P., Hastings, N.B., Rydel T.A., Galea, L.A.M., & Gould, E. (2001). Exposure to fox odor inhibits cell proliferation in the hippocampus of adult rats via an adrenal hormone-dependent mechanism. *Journal of Comparative Neurology, 437*, 496-504.

Taylor, W.D., MacFall, J. R., Payne, M. E., McQuoid, D. R., Steffens, D. C., Provenzale, J. M., & Krishnan, R. R. (2005). Greater MRI lesion volumes in elderly depressed subjects than in control subjects. *Psychiatry Research: Neuroimaging, 139*(1), 1-7.

Taylor, W. D., Aizenstein, H. J., & Alexopoulos, G. S. (2013). The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Molecular psychiatry, 18*(9), 963-974.

Tombaugh, T. N. (2004). Trail Making Test A and B: normative data stratified by age and education. *Archives of clinical neuropsychology, 19*(2), 203-214.

Trachtenberg, R. E., Singer, C. M., Cummings, J. L., & Thal, L. J. (2003). The Sleep Disorders Inventory: an instrument for studies of sleep disturbance in persons with Alzheimer's disease. *Journal of sleep research, 12*(4), 331-337.

Trebuchon-Da Fonseca, A., Benar, C. G., Bartolomei, F., Regis, J., Demonet, J. F., Chauvel, P., & Liegeois-Chauvel, C. (2009). Electrophysiological study of the basal temporal language area: a convergence zone between language perception and production networks. *Clinical Neurophysiology, 120*(3), 539-550.

Troese, M., Fukumizu, M., Sallinen, B. J., Gilles, A. A., Wellman, J. D., Paul, J. A., … & Hayes, M. J. (2008). Sleep fragmentation and evidence of sleep debt in alcohol-exposed infants. *Early human development, 84*(9), 577-585.

Tsigos, C. & Chrousos, G. P. (2002). Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *Journal of psychosomatic research, 53*(4), 865-871.

Tulsky, D. S., Saklofske, D. H., Wilkins, C., & Weiss, L. G. (2001). Development of a General Ability Index for the Wechsler Adult Intelligence Scale—Third Edition. *Psychological Assessment, 13*(4), 566.

UCI Institute for Memory Impairments and Neurological Disorders. (2017). "Mild Cognitive Impairment". Retrieved from http://www.mind.uci.edu/dementia/mild-cognitive-impairment/

Uttl, B. (2002). North American Adult Reading Test: age norms, reliability, and validity. *Journal of clinical and experimental neuropsychology, 24*(8), 1123-1137.

Vakali, K., Pillay, S. S., Lafer, B., Fava, M., Renshaw, P. F., Bonello-Clinton, C. M., Yurgelun-Todd, D. A. (2000). Hippocampal volume in primary unipolar major depression: A magnetic resonance imaging study. *Biological Psychiatry, 47*, 1087-1090.

van der Hart, M., Czeh, B., de Biurrun, G., Michaelis, T., Watanabe, T., Natt, O., et al (2002). Substance P receptor antagonist and clomipramine prevent stress-induced alterations in cerebral metabolites, cytogenesis in the dentate gyrus and hippocampal volume. *Molecular Psychiatry, 7*, 933-941.

Van Cauter, E., Leproult, R., & Plat, L. (2000) Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *Jama, 284*(7), 861-868.

Veiel, H. O. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of clinical and experimental neuropsychology, 19*(4), 587-603.

Vermetten, E., Vythilingam, M., Southwick, S. M., Charney, D. S., & Bremner, J. D. (2003). Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. *Biological Psychiatry, 54*, 693-702.

Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A., & Stickgold, R. (2002). Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron, 35*(1), 205-211.

Walker, M. P. & Stickgold, R. (2004). Sleep-dependent learning and memory consolidation. *Neuron, 44*(1), 121-133.

World Health Organization. (2016, April). "Mental health and older adults". Retrieved from www.who.int/mediacentre/factsheets/fs381/en/

Wright, S. L. & Persad, C. (2007). Distinguishing between depression and dementia in older persons: neuropsychological and neuropathological correlates. *Journal of geriatric psychiatry and neurology*, *20*(4), 189-198.

Wu, K. Y., Lin, K. J., Chen, C. H., Chen, C. S., Liu, C. Y., Huang, S. Y., … & Hsaio, I. T. (2018). Diversity of neurodegenerative pathophysiology in nondemented patients with major depressive disorder: Evidence of cerebral amyloidosis and hippocampal atrophy. *Brain and behavior,* e01016.

Xu, X., Xiao, S., Rahardjo, T. B., & Hogervorst, E. (2015). Risk factors for possible dementia using the Hopkins Verbal Learning Test and the mini-mental state examination in Shanghai. *Diagnostics, 5*(4), 487-496.

Zunszain, P.A., Anacker, C., Cattaneo, A., Carvalho, L. A., & Pariante, C. M. (2011). Glucocorticoids, cytokines, and brain abnormalities in depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *25*(3), 722-729.

APPENDIX A: CENTER FOR EPIDEMIOLOGICAL STUDIES DEPRESSION SCALE

Center for Epidemiologic Studies Depression Scale (CES-D), NIMH

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2. I did not feel like eating; my appetite was poor.	☐	☐	☐	☐
3. I felt that I could not shake off the blues even with help from my family or friends.	☐	☐	☐	☐
4. I felt I was just as good as other people.	☐	☐	☐	☐
5. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
6. I felt depressed.	☐	☐	☐	☐
7. I felt that everything I did was an effort.	☐	☐	☐	☐
8. I felt hopeful about the future.	☐	☐	☐	☐
9. I thought my life had been a failure.	☐	☐	☐	☐
10. I felt fearful.	☐	☐	☐	☐
11. My sleep was restless.	☐	☐	☐	☐
12. I was happy.	☐	☐	☐	☐
13. I talked less than usual.	☐	☐	☐	☐
14. I felt lonely.	☐	☐	☐	☐
15. People were unfriendly.	☐	☐	☐	☐
16. I enjoyed life.	☐	☐	☐	☐
17. I had crying spells.	☐	☐	☐	☐
18. I felt sad.	☐	☐	☐	☐
19. I felt that people dislike me.	☐	☐	☐	☐
20. I could not get "going."	☐	☐	☐	☐

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.

APPENDIX B: SUPPLEMENTAL QUESTIONS ON DEPRESSIVE HISTORY

1. Have you ever thought you may be depressed at any point in your life?

2. Have you ever been formally diagnosed with depression at any point in your life?

3. When did you first experience depressive symptoms?

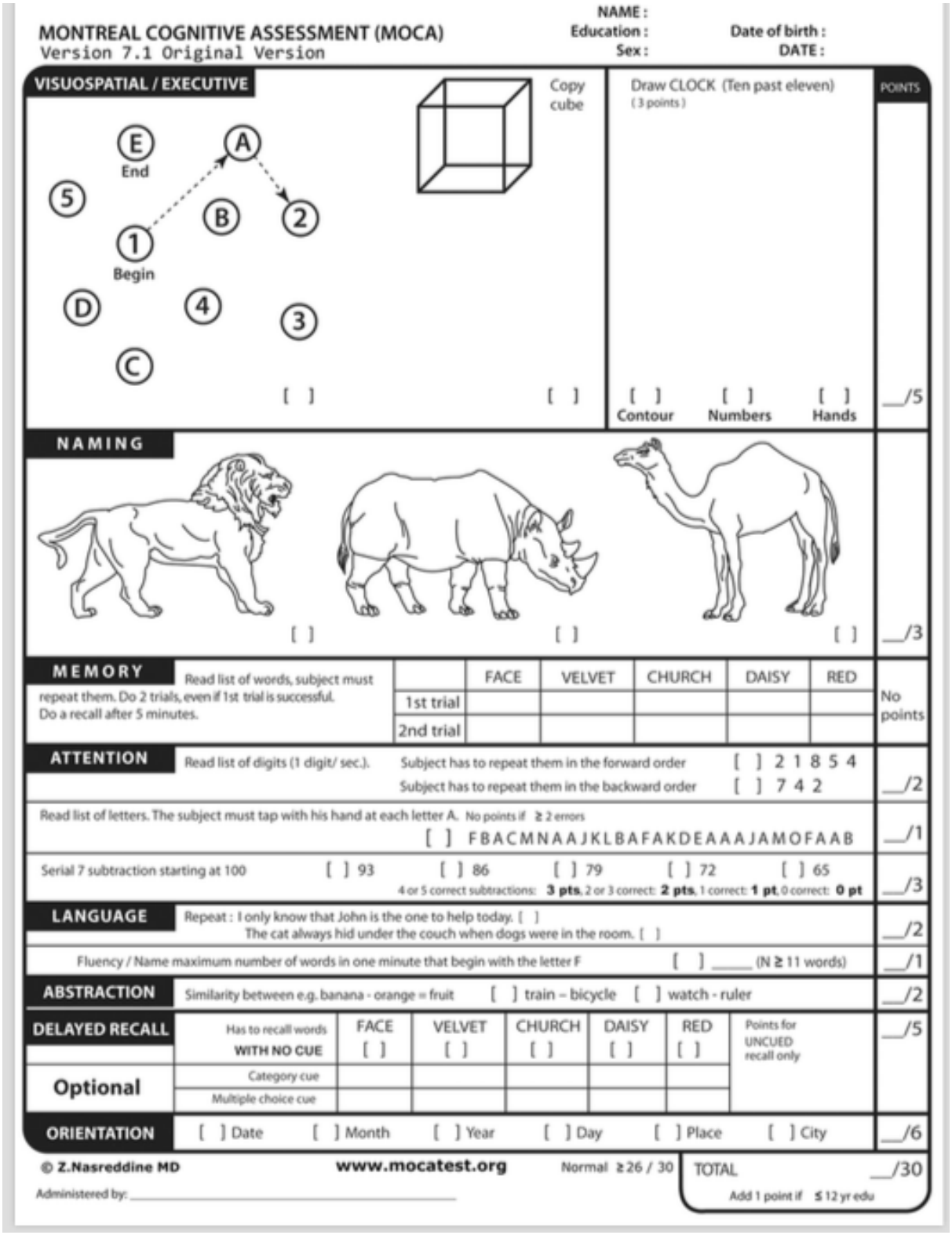
4. For how long did you experience these depressive symptoms?

5. Have you ever taken medication for depression? If so, what medication did you take? When did you start and for how long did you take this medication?

6. Are you still experiencing any symptoms of depression? Do you take medication for these symptoms currently?

7. Have you ever experienced any other types of mental health issues (e.g. bipolar disorder, schizophrenia, or related disorders, etc.)? If so, what are they? Do you feel you struggle with these issues currently?

APPENDIX C: MONTREAL COGNITIVE ASSESSMENT



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube [ ] [ ]

Draw CLOCK (Ten past eleven) (3 points) [ ] Contour [ ] Numbers [ ] Hands /5

NAMING [ ] [ ] [ ] /3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 /2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B /1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** /3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] /2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) /1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler /2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City /6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL /30
Add 1 point if ≤ 12 yr edu

Administered by: _____

APPENDIX D: TRAIL MAKING TESTS PARTS A & B

Trail Making Test (TMT) Parts A & B

Instructions:

Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed both parts after five minutes have elapsed.

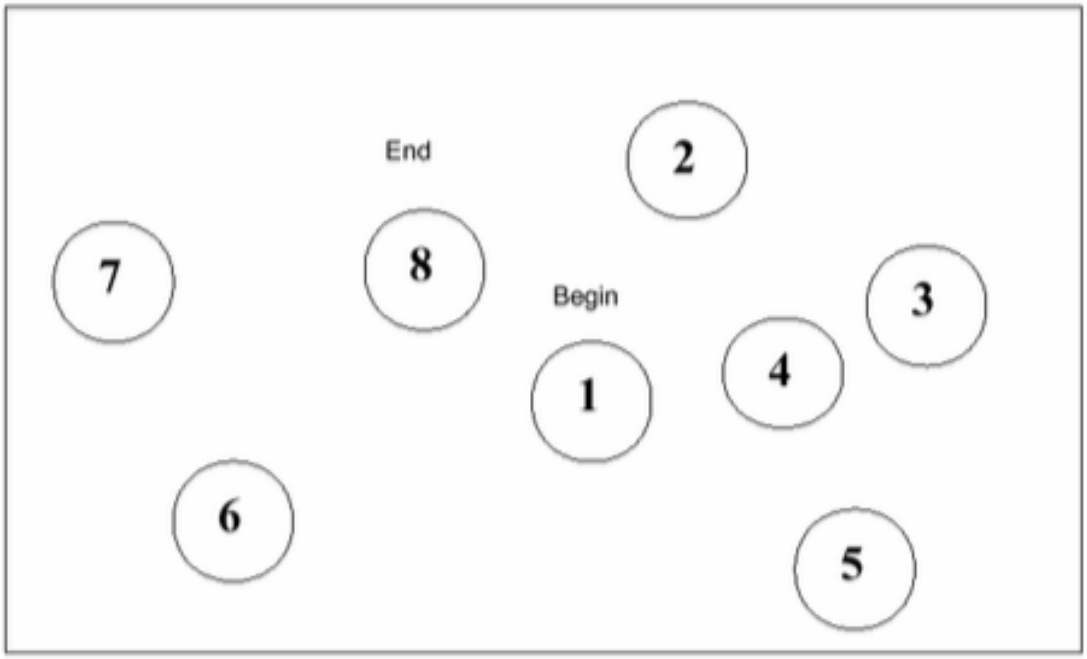
Step 1:	Give the patient a copy of the Trail Making Test Part A worksheet and a pen or pencil.
Step 2:	Demonstrate the test to the patient using the sample sheet (Trail Making Part A – *SAMPLE*).
Step 3:	Time the patient as he or she follows the “trail” made by the numbers on the test.
Step 4:	Record the time.
Step 5:	Repeat the procedure for Trail Making Test Part B.

Scoring:

Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment.

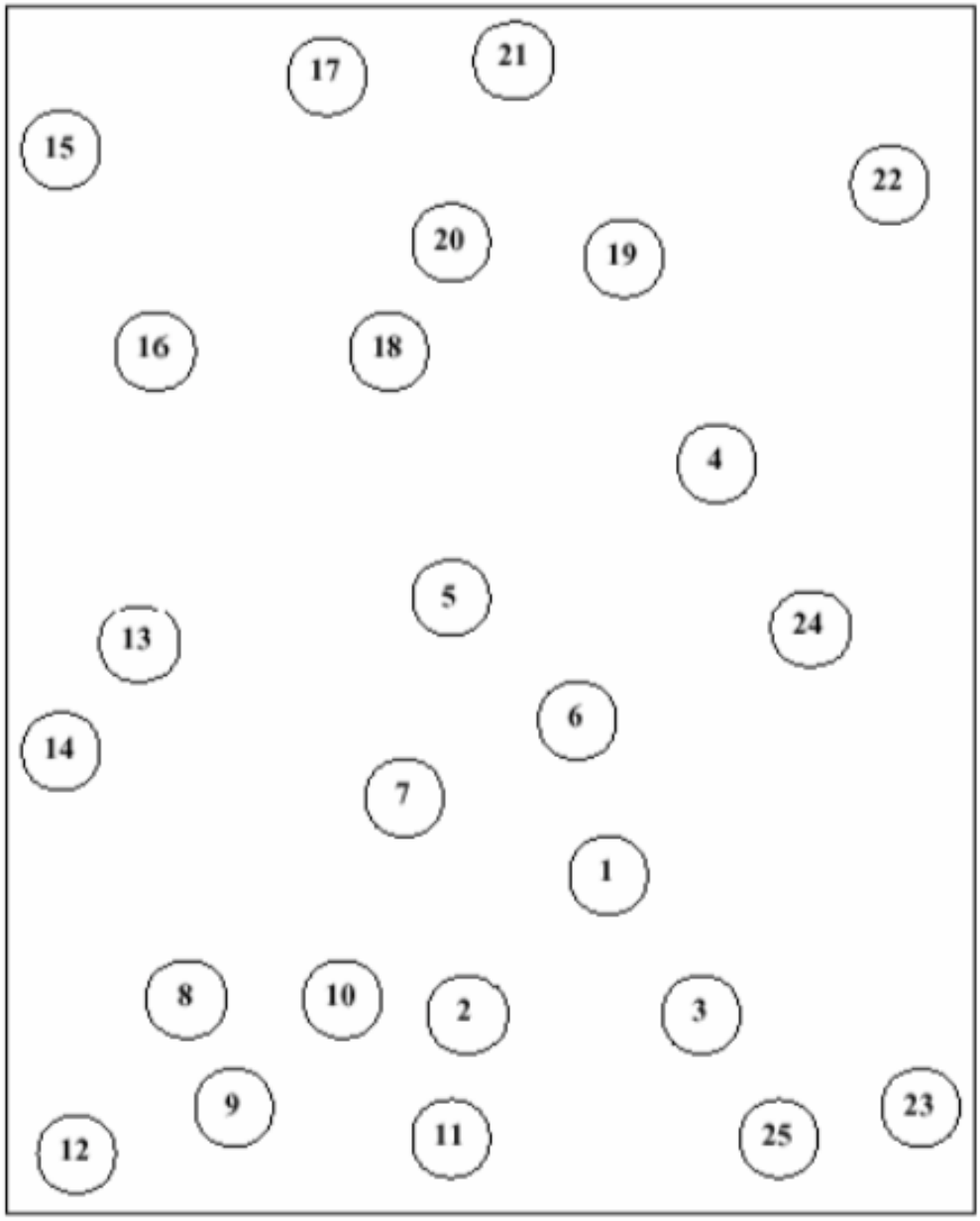
	Average	Deficient	Rule of Thumb
Trail A	29 seconds	> 78 seconds	Most in 90 seconds
Trail B	75 seconds	> 273 seconds	Most in 3 minutes

Trail Making Test Part A – *SAMPLE*

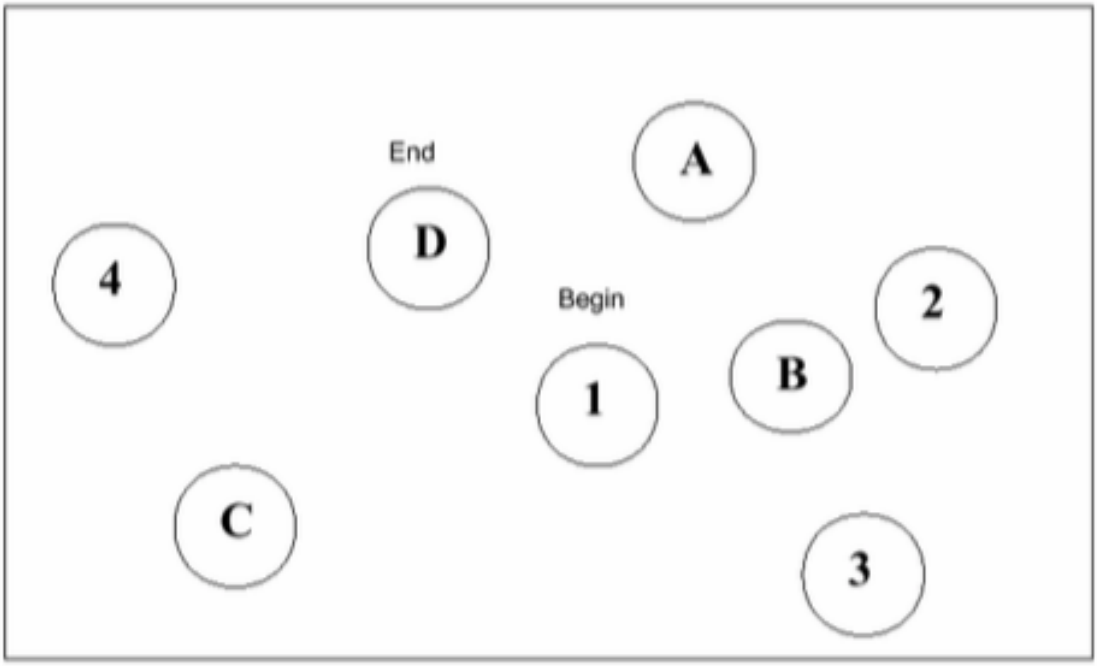


Trail Making Test Part A

Patient's Name: _____ Date: _____

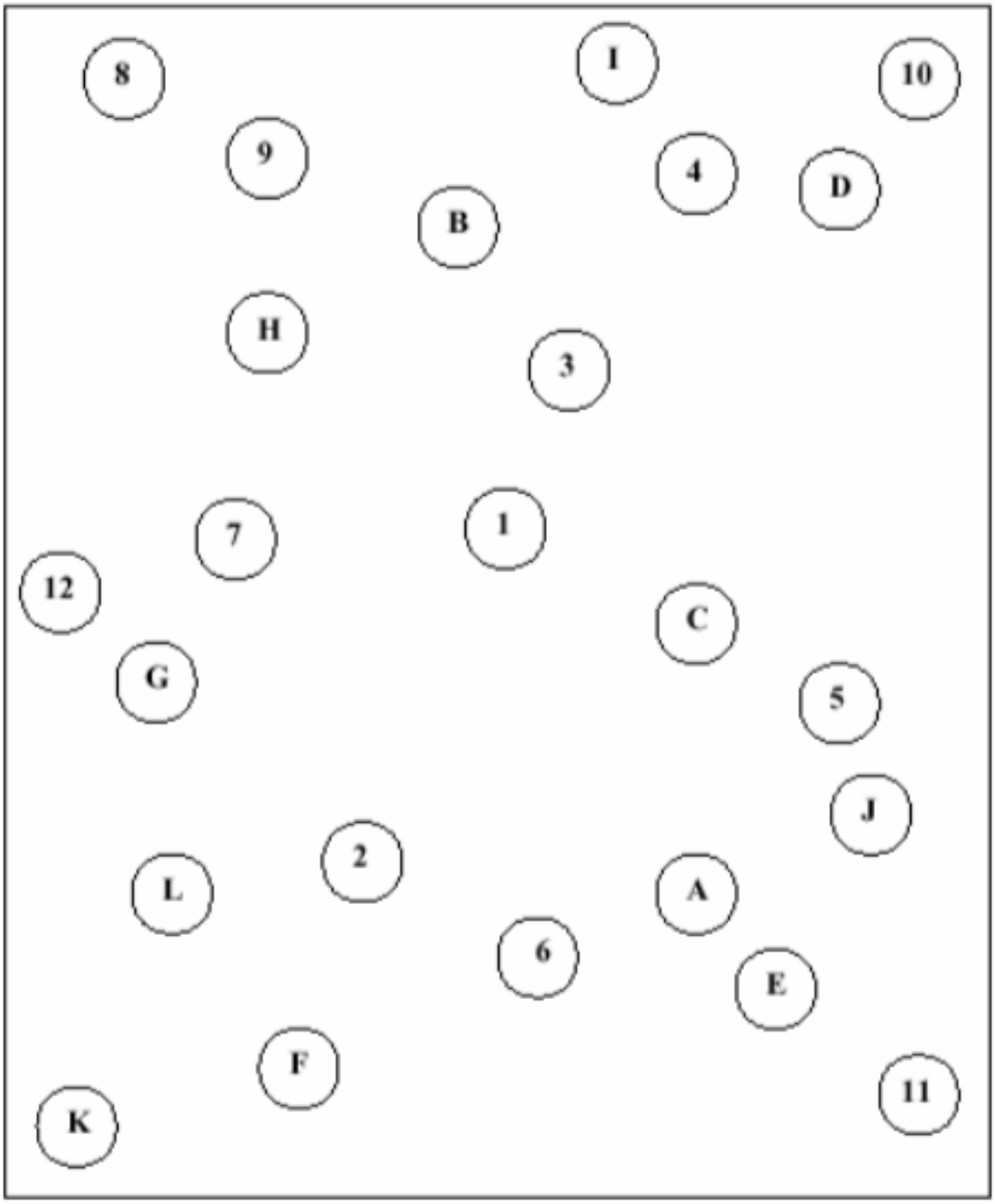


Trail Making Test Part B – *SAMPLE*



Trail Making Test Part B

Patient's Name: _____ Date: _____



APPENDIX E: AMERICAN NATIONAL ADULT READING TEST

Use the following script when introducing the AMNART:

I want you to read slowly down the list of words starting here (indicate first word) and continuing down this column and onto the next. After each word please wait until I say 'Next' before reading the next word. I must warn you that there are many words that you probably won't recognize; in fact, most people don't know them, so just guess at these, ok? Go ahead.

The examinee should be encouraged to guess and all responses should be reinforced ("good", "that's fine", etc.). The examinee may change response if he or she wishes to do so but if more than one version is given, the examinee must decide on the final choice. No time limit is imposed.

ACHE
AISLE
CAPON
DEBT
CHORD
HEIR
DENY
BOUQUET
CAPRICE
GAUGE
WORSTED
DEPOT
NAUSEA
NAIVE
SUBTLE
PUGILIST
FETAL
BLATANT
PLACEBO
HIATUS
SIMILE
MERINGUE
SIEVE

CHASSIS
CELLIST
ALGAE
SUPERFLUOUS
CHAMOIS
THYME
APROPOS
VIRULENT
ZEALOT
FACADE
CABAL
ABSTEMIOUS
DETENTE
SCION
PAPYRUS
QUADRUPED
PRELATE
EPITOME
BEATIFY
HYPERBOLE
IMBROGLIO
SYNCOPE

APPENDIX F: PITTSBURGH SLEEP QUALITY INDEX

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 G: STANFORD SLEEPINESS SCALE

Stanford Sleepiness Scale

"Alertness Test"

The Stanford Sleepiness Scale is a quick and easy way to assess how alert you are feeling.
Discover your own pattern of alertness by recording your "degree of sleepiness" at different times throughout the day.

Using the 7-point scale below pick what best represents how you are feeling and note the corresponding number on the chart below.

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

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
7am							
8am							
9am							
10am							
11am							
12pm							
1pm							
2pm							
3pm							
4pm							
5pm							
6pm							
7pm							
8pm							
9pm							
10pm							
11pm							
12am							

What does this all mean?

Ideally, you would like a score of "1" for each of the hours you are awake. A result of 4 or below may indicate that you could be suffering from a lack of sleep. Getting a better nights rest could improve your level of alertness and day to day performance.

Use this tool to help schedule your classes during times you are most alert!

APPENDIX H: CONSENSUS SLEEP DIARY

Sleep Diary Instructions (CSD-M)

General Instructions

What is a Sleep Diary? A sleep diary is designed to gather information about your daily sleep pattern.

How often and when do I fill out the sleep diary? It is necessary for you to complete your sleep diary every day. If possible, the sleep diary should be completed within one hour of getting out of bed in the morning.

What should I do if I miss a day? If you forget to fill in the diary or are unable to finish it, leave the diary blank for that day.

What if something unusual affects my sleep or how I feel in the daytime? If your sleep or daytime functioning is affected by some unusual event (such as an illness, or an emergency) you may make brief notes on your diary.

What do the words "bed" and "day" mean on the diary? This diary can be used for people who are awake or asleep at unusual times. In the sleep diary, the word "day" is the time when you choose or are required to be awake. The term "bed" means the place where you usually sleep.

Will answering these questions about my sleep keep me awake? This is not usually a problem. You should not worry about giving exact times, and you should not watch the clock. Just give your best estimate.

Sleep Diary Item Instructions

Use the guide below to clarify what is being asked for each item of the Sleep Diary.

Date.: Write the date of the morning you are filling out the diary.

1. What time did you get into bed? Write the time that you got into bed. This may not be the time you began "trying" to fall asleep.

2. What time did you try to go to sleep? Record the time that you began "trying" to fall asleep.

3. How long did it take you to fall asleep? Beginning at the time you wrote in question 2, how long did it take you to fall asleep.

4. How many times did you wake up, not counting your final awakening? How many times did you wake up between the time you first fell asleep and your final awakening?

5. In total, how long did these awakenings last? What was the total time you were awake between the time you first fell asleep and your final awakening. For example, if you woke 3 times for 20 minutes, 35 minutes, and 15 minutes, add them all up (20+35+15= 70 min or 1 hr and 10 min).

6a. What time was your final awakening? Record the last time you woke up in the morning.

6b. After your final awakening, how long did you spend in bed trying to sleep? After the last time you woke-up (Item #6a), how many minutes did you spend in bed trying to sleep? For example, if you woke up at 8 am but continued to try and sleep until 9 am, record 1 hour.

6c. Did you wake up earlier than you planned? If you woke up or were awakened earlier than you planned, check yes. If you woke up at your planned time, check no.

6d. If yes, how much earlier? If you answered "yes" to question 6c, write the number of minutes you woke up earlier than you had planned on waking up. For example, if you woke up 15 minutes before

the alarm went off, record 15 minutes here.

7. What time did you get out of bed for the day? What time did you get out of bed with no further attempt at sleeping? This may be different from your final awakening time (e.g. you may have woken up at 6:35 a.m. but did not get out of bed to start your day until 7:20 a.m.)

8. In total, how long did you sleep? This should just be your best estimate, based on when you went to bed and woke up, how long it took you to fall asleep, and how long you were awake. You do not need to calculate this by adding and subtracting; just give your best estimate.

9. How would you rate the quality of your sleep? "Sleep Quality" is your sense of whether your sleep was good or poor.

10. How restful or refreshed did you feel when you woke up for the day? This refers to how you felt after you were done sleeping for the night, during the first few minutes that you were awake.

11a. How many times did you nap or doze? A nap is a time you decided to sleep during the day, whether in bed or not in bed. "Dozing" is a time you may have nodded off for a few minutes, without meaning to, such as while watching TV. Count all the times you napped or dozed at any time from when you first got out of bed in the morning until you got into bed again at night.

11b. In total, how long did you nap or doze? Estimate the total amount of time you spent napping or dozing, in hours and minutes. For instance, if you napped twice, once for 30 minutes and once for 60 minutes, and dozed for 10 minutes, you would answer "1 hour 40 minutes." If you did not nap or doze, write "N/A" (not applicable).

12a. How many drinks containing alcohol did you have? Enter the number of alcoholic drinks you had where 1 drink is defined as one 12 oz beer (can), 5 oz wine, or 1.5 oz liquor (one shot).

12b. What time was your last drink? If you had an alcoholic drink yesterday, enter the time of day in hours and minutes of your last drink. If you did not have a drink, write "N/A" (not applicable).

13a. How many caffeinated drinks (coffee, tea, soda, energy drinks) did you have? Enter the number of caffeinated drinks (coffee, tea, soda, energy drinks) you had where for coffee and tea, one drink = 6-8 oz; while for caffeinated soda one drink = 12 oz.

13b. What time was your last caffeinated drink? If you had a caffeinated drink, enter the time of day in hours and minutes of your last drink. If you did not have a caffeinated drink, write "N/A" (not applicable).

14. Did you take any over-the-counter or prescription medication(s) to help you sleep? If so, list medication(s), dose, and time taken: List the medication name, how much and when you took EACH different medication you took tonight to help you sleep. Include medication available over the counter, prescription medications, and herbals (example: "Sleepwell 50 mg 11 pm"). If every night is the same, write "same" after the first day

15. *Comments*: If you have anything that you would like to say that is relevant to your sleep feel free to write it here.

Sample ID/Name: ____________________

Today's date	4/5/11						
1. What time did you get into bed?	10:15 PM						
2. What time did you try to go to sleep?	11:30 PM						
3. How long did it take you to fall asleep?	55 min						
4. How many times did you wake up, not counting your final awakening?	6 times						
5. In total, how long did these awakenings last?	2 hours 5 min						
6a. What time was your final awakening?	6:35 AM						
6b. After your final awakening, how long did you spend in bed trying to sleep?	45 min						
6c. Did you wake up earlier than you planned?	☒ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
6d. If yes, how much earlier?	1 hour						
7. What time did you get out of bed for the day?	7:20 AM						
8. In total, how long did you sleep?	4 hours 10 min						
9. How would you rate the quality of your sleep?	☐ Very poor ☒ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good
10. How rested or refreshed did you feel when you woke up for the day?	☐ Not at all rested ☒ Slightly rested ☐ Somewhat rested ☐ Well-rested ☐ Very well-rested	☐ Not at all rested ☐ Slightly rested ☐ Somewhat rested ☐ Well-rested ☐ Very well-rested	☐ Not at all rested ☐ Slightly rested ☐ Somewhat rested ☐ Well-rested ☐ Very well-rested	☐ Not at all rested ☐ Slightly rested ☐ Somewhat rested ☐ Well-rested ☐ Very well-rested	☐ Not at all rested ☐ Slightly rested ☐ Somewhat rested ☐ Well-rested ☐ Very well-rested	☐ Not at all rested ☐ Slightly rested ☐ Somewhat rested ☐ Well-rested ☐ Very well-rested	☐ Not at all rested ☐ Slightly rested ☐ Somewhat rested ☐ Well-rested ☐ Very well-rested	☐ Not at all rested ☐ Slightly rested ☐ Somewhat rested ☐ Well-rested ☐ Very well-rested
11a. How many times did you nap or doze?	2 times						
11b. In total, how long did you nap or doze?	1 hour 10 min						
12a. How many drinks containing alcohol did you have?	3 drinks						
12b. What time was your last drink?	9:20 PM						
13a. How many caffeinated drinks (coffee, tea, soda, energy drinks) did you have?	2 drinks						
13b. What time was your last drink?	9:20 PM						
14. Did you take any over-the-counter or prescription medication(s) to help you sleep? If so, list medication(s) dose, and time taken	☒ Yes ☐ No Medication(s): Relaxo-Herb Dose: 50 mg Time(s) taken: 11 PM	☐ Yes ☐ No Medication(s): Dose: Time(s) taken:	☐ Yes ☐ No Medication(s): Dose: Time(s) taken:	☐ Yes ☐ No Medication(s): Dose: Time(s) taken:	☐ Yes ☐ No Medication(s): Dose: Time(s) taken:	☐ Yes ☐ No Medication(s): Dose: Time(s) taken:	☐ Yes ☐ No Medication(s): Dose: Time(s) taken:	☐ Yes ☐ No Medication(s): Dose: Time(s) taken:
15. Comments (if applicable)	I have a cold						

APPENDIX I: EPWORTH SLEEPINESS SCALE

THE EPWORTH SLEEPINESS SCALE

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

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

APPENDIX J: DEMOGRAPHIC QUESTIONS

Demographic Questions

1. How old are you currently? What is your date of birth?
2. What is your current marital status?
    1. Never married
    2. Divorced
    3. Widowed
    4. Have a partner but not married
    5. Married
3. What is your current living situation?
    1. Live alone
    2. Live with partner or spouse
    3. Live with a relative, friend, or roommate
    4. Live with a group in a private residence
    5. Live in a group home
4. What is your dominant hand?
5. What is the highest level of education you have completed?
6. What was your longest-held career?
7. What is your current height and weight?
8. Have you ever been diagnosed with a sleep disorder (e.g. parasomnia, REM sleep disorder, etc.)?
9. Have you ever been diagnosed with obstructive sleep apnea (OSA)?
10. Have you ever been diagnosed with arthritis?
11. Have you ever been diagnosed with cardiovascular disease (e.g. a-fib, cardiac bypass, pacemaker, etc.)?
12. Have you ever been diagnosed with a neurodegenerative disease (e.g. mild cognitive impairment, Alzheimer's Disease, Parkinson's Disease, dementia, etc.)?
13. Have you ever been diagnosed with cerebrovascular disease (e.g. stroke, cerebral infarct, aneurysm, etc.)?
14. Have you ever been diagnosed with diabetes? If so, what type?

15. Have you ever had a heart attack or cardiac arrest?
16. Have you ever had a traumatic brain injury (TBI)?
17. Have you ever been diagnosed with high cholesterol?
18. Have you ever been diagnosed with high blood pressure?
19. Have you ever had seizures or been diagnosed with a seizure disorder?
20. Have you ever been diagnosed with thyroid disease?
21. Have you ever been diagnosed with a developmental disability?
22. How would you rate your average pain level from 0 (no pain) to 10 (the worst pain) over the last month?
23. Have you ever been prescribed any medications? If so, what are they and what is the dosage?
24. Do you currently smoke cigarettes? If so, how many:
    1. None
    2. 1 cigarette to less than ½ a pack a day
    3. ½ pack to less than 1 pack a day
    4. 1 pack to less than 1 ½ packs a day
    5. 1 ½ packs to 2 packs a day
    6. 2+ packs a day
25. Have you ever tried to quit smoking?
26. How often in the past three months have you had an alcoholic beverage?
    1. Never
    2. Less than once a month
    3. About once a month
    4. About once a week
    5. A few times a week
    6. Daily or almost daily
27. Have you ever been addicted to a substance of any kind? If so, what was it and when was the last time you took this substance?

BIOGRAPHY OF THE AUTHOR

Jessica B. Aronis was born on September 26th, 1993 in Framingham, MA. She was raised in Reading, MA and graduated from Bishop Fenwick High School in 2012. Following high school, Jessica moved to Maine to attend Colby College from which she received a Bachelor's degree in Psychology with a concentration in neuroscience in 2016. Immediately after college graduation, she moved to Orono, Maine to begin the Psychological Sciences graduate program at the University of Maine. Upon receiving her degree, Jessica will continue as the clinical lead on Dr. Marie Hayes' NIH Phase II study utilizing a novel, non-invasive sleep device in home sleep studies before applying to PhD programs in a variety of big cities. Jessica is a candidate for the Master of Arts degree in Psychological Sciences from the University of Maine in August 2019.