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Sleep disorders and cognition in older adults with cardiovascular disease

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SLEEP DISORDERS AND COGNITION IN OLDER ADULTS WITH CARDIOVASCULAR DISEASE

by

Clare Thomson Humphreys

An Abstract

Of a thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Psychological and Quantitative Foundations in the Graduate College of
The University of Iowa

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Thesis Supervisors: Professor John Westefeld
Associate Professor David J. Moser

ABSTRACT

The elderly population in the United States is growing rapidly, presenting increasing challenges in health care provision. One of the most salient and complex issues facing the elderly is cognitive impairment. This condition often leads to dementia and has a significant quality of life and financial impact. One of the most common and preventable causes of cognitive decline is heart disease, specifically atherosclerotic vascular disease (AVD). This condition is related to myriad health risk factors and conditions, including sleep disorders. The current study examined 51 adults between the ages of 55 and 88 with a diagnosis of AVD. Participants were divided into sleep disordered (N = 20) and non sleep disordered (N =31) groups and compared in terms of fatigue, performance on neuropsychological testing, and a marker of inflammatory pathology. Participants with sleep disorders and AVD reported significantly greater levels of daytime fatigue and performed significantly more poorly on objective cognitive testing than those with AVD alone. Implications for the relationship of disordered sleep, AVD, and cognition as well as future research directions are discussed.

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PH.D. THESIS

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CHAPTER I

RATIONALE

The elderly population in the United States is growing at a rapid rate, producing an increased need for research into the unique issues facing older individuals. According to the US Census Bureau, the elderly population has increased eleven-fold over the past century while the non-elderly population increased only three-fold. Projections indicate that one in five Americans will be 65 or older by the year 2030, and those 65 and older comprised 12.8 percent of the population as of 2008. Furthermore, the oldest old (85 and above) are a rapidly growing group, showing an increase of 274 percent from 1960 to 1994, (U.S. Census Bureau). Overall, this segment of the population is expected to be the fastest growing in this century.

The rapidly growing elderly population faces significant unique health issues and also places a greater burden on the current health care system. The leading killer of the elderly is heart disease, a condition that brings multiple medical complications and requires careful medical management. At last estimate (2006) heart disease was responsible for the deaths of over 630,000 Americans per year (U.S. Census Bureau). In addition, the aging population is showing an increasing need for personal assistance with daily activities. In 1991, there were 4.5 million elderly individuals that required personal assistance to carry out activities of daily living. By the age of 85, 50 percent of the elderly require assistance with one or more activities of daily living (U.S. Census Bureau). These statistics give a general picture of both the rapidly growing elderly population and the growing need for health care and assisted living in the United States.

As stated previously, the growing elderly population presents a challenge to the

health care system, and provides a strong impetus for research into the needs of the aging population. The census data also make a clear case for the need to research cardiovascular disease in terms of its causes, effects, and possible routes to prevention. An aspect of aging not mentioned in the discussion of census data is cognitive impairment. This issue is intrinsically related to cardiovascular disease, as vascular dementia is the second most common form of dementia after Alzheimer's disease. Additionally, coexisting vascular pathology is estimated to be a factor in almost 30 percent of Alzheimer's disease cases (Langa, Foster, & Larson, 2004).

This paper will present a brief review of the literature surrounding aging, vascular disease, and related health conditions that affect cognitive functioning, followed by the presentation of original research on cardiovascular disease, disordered sleep, and cognition. First, the phenomenon of cognitive impairment will be examined, including its impact on the population and health care system. Additionally, the phenomenon of mild cognitive impairment will be explained and reviewed in terms of its significance and pathological course. Second, the relationship between two common health conditions (cardiovascular disease and obstructive sleep apnea) and cognition will be reviewed. These two health factors are related to one another as well as being related to increased risk of cognitive impairment. Finally, the less studied issue of disordered sleep in general will be examined. Disordered sleep is common in the elderly, but its relationship to cardiovascular disease and impact on cognition are not yet clear. After reviewing the phenomenon of disordered sleep, discussion will turn to original research and future directions related to disordered sleep, cardiovascular disease, and cognition in the aging population.

Cognitive Impairment

Cognitive impairment is a highly salient issue for the aging population. Estimates of the prevalence of cognitive impairment that does not yet meet criteria for dementia are variable, but generally range from 2 to 4 percent of the elderly population. This represents a large number of individuals in the population as a whole, due to the previously discussed growth of the elderly population in general (Ganguli, Dodge, Shen, & DeKosky, 2004). When cognitive impairment progresses to dementia, as it does in a high percentage of cases (discussed further below) the impact on health care costs is profound. Nationwide systemic costs are difficult to estimate, but the impact can clearly be seen on the individual level. One large-scale study found that out of pocket health care expenses averaged 1,350 dollars per year for elderly individuals without dementia. Those costs increased to 2,150 dollars per year for those with moderate dementia, and increased further to 3,010 dollars per year for those with severe dementia. The increased cost of dementia was significant at the $p < 0.01$ level (Langa et al. 2004). This study was able to demonstrate that dementia is independently associated with significantly higher medical expenses, and suggests that the phenomenon of cognitive impairment and dementia has a profound financial as well as emotional impact on patients and families.

Mild Cognitive Impairment: A Diagnostic Category

As mentioned above, the terms “cognitive impairment” and “dementia” are not synonymous. Most individuals demonstrate cognitive impairment before they meet DSM-IV diagnostic criteria for dementia. Thus, an additional diagnostic category has been developed and relative well accepted through research. Mild cognitive impairment (MCI) is a term developed to describe the clinical condition between normal aging and

dementia (Petersen et. al. 2001). Persons with MCI experience greater memory loss that would be expected for their age, but do not meet criteria for dementia. The criteria for a diagnosis of MCI are as follows: Memory complaints, preferably corroborated by a collateral source, impaired memory function for age and education, preserved general cognitive function, intact activities of daily living, and no presence of diagnosed dementia. These criteria describe the amnestic type of MCI, which most commonly progresses to Alzheimer's disease. Other presentations of MCI also exist, and also progress to dementia in a certain percentage of cases. The conversion rate of amnestic MCI to Alzheimer's disease has been found to be as high as 80 percent over a period ten years (Petersen et al. 2001). Additionally, while healthy controls convert to Alzheimer's disease at a rate of about 1 percent per year, those with amnestic MCI convert at a rate of 10 to 15 percent per year.

MCI can also present as slight cognitive impairment in multiple domains, or as impairment of a single non-memory domain. Both of these presentations have been linked to subsequent vascular dementia as well as Alzheimer's disease. In addition, it is important to recall the possible contribution of vascular risk factors to a high percentage of Alzheimer's cases. Thus, the formulation of MCI as a diagnostic entity has been important with regard to vascular disease as well as Alzheimer's disease. Furthermore, the identification of MCI presents an opportunity for intervention. In the case of pure amnestic MCI (with a high likelihood of conversion to Alzheimer's disease), the goal may be to slow disease progression though the use of cholinesterase inhibitors or anti-inflammatory drugs. In the case of mixed etiology MCI, there is the possibility to intervene though health factors, such as improving cardiovascular function, reducing the

risk of brain ischemia and stroke, and assessing for other conditions such as sleep disorders that may be contributing factors. These possibilities will be discussed further in the literature review.

Goals of the Current Study

The rationale and goal of the current study was to address the increased need for research into factors affecting the growing elderly population in the United States. As outlined above, cognitive impairment, including MCI and dementia, is one of the most salient of these issues. The purpose of this study was to examine a potential area of early detection of cognitive impairment, with an eye toward future research in prevention and intervention. If cognitive decline (e.g. cognitive performance that is below the expected mean for age and educational level but has not yet reached the level of impairment) can be detected earlier in aging individuals, there may be clinical implications and applications for neuropsychologists and other health care professionals involved in caring for aging individuals. This study focused on cardiovascular disease, disordered sleep, and cognition. In the following chapter, the relationships among these factors in aging individuals will be discussed, original research on this topic will be presented, and the clinical implications of the findings will be considered.

Cardiovascular disease and disordered sleep were selected as variables of interest due to their prevalence in the aging population, their relationship to one another, and the potential impact both can have on cognitive decline in aging individuals. The extensive research on a particular sleep disorder, obstructive sleep apnea, and its connection to cardiovascular disease and cognition in the aging was reviewed. This line of research helped to clarify the relationship between sleep breathing disorders and cognitive decline,

and a successful intervention (continuous positive airway pressure) with protective effects for cognition has been identified. However, similar research on disordered sleep without a breathing component has been lacking. Thus, the rationale for the current study was to investigate disordered sleep without an oxygenation component. In addition, expanding research into other sleep disorders may lead to interventions that can partially prevent or slow cognitive decline, much like interventions for sleep apnea. Thus, the current study, using research into sleep apnea as a guide, examined other forms of disordered sleep and their relationship with cardiovascular disease and cognition in the aging population.

CHAPTER II

REVIEW OF THE LITERATURE

Cognitive impairment is a major public health concern facing the aging population in the United States. The purpose of this paper to this point has been to introduce the issue of aging in general, and to define and describe the nature and prevalence of cognitive impairment. A more specific term, developed as a result of the increasing interest in early detection of cognitive decline (Mild Cognitive Impairment), was also defined and described. The purpose of the following sections is to discuss some specific health variables related to cognitive impairment and to review the relevant literature.

First, cardiovascular health and its relationship to cognition will be reviewed. A more specific term, atherosclerotic vascular disease, will be defined and reviewed as well. Next, the literature on obstructive sleep apnea (OSA) will be reviewed and the relationships among OSA, cardiovascular disease, and cognition will be discussed. The subsequent section will describe the physiology of normal sleep as well as the impact of sleep disorders and aging on the sleep process. Finally, the literature on disrupted sleep and cognition will be reviewed.

Although these topics are considered separately, the review of the literature elucidates the connections between cardiovascular disease, sleep, aging, and cognition that are central to the research question being posed here. Shared physiological mechanisms as well as medical comorbidity connect these issues and, as this study investigated, may combine to create an increased risk of cognitive impairment.

Cardiovascular Health and Cognition

The relationship between cardiovascular disease and dementia has been previously mentioned, and has also been made clear through autopsy studies. One such study found that vascular disease was the primary pathology in 16 percent of dementia cases (with dementia defined as significant impairment that interferes with functioning in memory and one or more other cognitive domains), and was a major contributing factor (e.g. significant vascular pathology was present in addition to Alzheimer's type neuropathology) in 54 percent of cases (Langa, Foster, & Larson 2004). Clearly, there is a significant relationship between vascular pathology in the brain and dementia that can be detected by pathological studies at autopsy. However, it is also important to understand the physiological processes involved in earlier stages of vascular disease and the relationship to other conditions (e.g. sleep disorders) and to earlier detectable declines from baseline levels of cognitive functioning.

Atherosclerotic Vascular Disease (AVD)

The terms "heart disease", "cardiovascular disease", and "vascular disease" are incredibly broad and cover a wide range of conditions. Therefore, it is important to clearly define the area of interest when discussing this large body of research. The specific type of cardiovascular disease that was examined here is referred to as atherosclerotic vascular disease, or AVD. Atherosclerotic vascular disease is a progressive disease process that involves accumulation of lipid-rich plaques on the walls of the arteries. AVD is the single leading cause of mortality in both males and females in the United States. The American Heart Association (2007 update) estimates that

coronary heart disease caused one in every five deaths in the United States in the year 2004.

AVD's primary role in mortality in the United States occurs through its link to myocardial infarction, stroke, peripheral artery disease, and other occlusive conditions. Consequently, AVD has a tremendous impact on medical resources, with an estimated 1,285,000 inpatient angioplasty procedures, 1,471,000 inpatient cardiac catheterizations, and 427,000 bypass procedures performed in the United States in 2004 (American Heart Association, 2007). These procedures are directly related to the diagnosis (in the case of catheterization) and treatment (angioplasty and bypass) of blocked arteries caused by AVD. This disease also has a significant financial impact. The AHA estimated the direct and indirect costs of heart disease in the United States for 2007 to be 151.6 billion dollars.

AVD was selected as a variable of interest in the current study for several reasons. First, as discussed above, it affects a large portion of the U.S. population, and often leads to serious complications such as stroke and heart attack. Second, AVD is particularly common in and devastating to the elderly, due to its relationship to cognitive impairment. Finally, AVD is at least partially preventable through the management of blood lipid levels, weight loss, smoking cessation, and the reduction of other health risk factors such as sleep disordered breathing (discussed further below).

AVD and Cognitive Impairment

The human heart is a carefully sequenced pumping system. The right ventricle pumps blood through the lungs, where red blood cells expel carbon dioxide and bind molecules of oxygen. The blood then returns to the heart, and is pumped through the left

ventricle, which sends the newly oxygenated blood out to the body's tissues and organs (American Heart Association, 2007). The brain, although it comprises only a small percentage of the body's total weight, requires a high percentage of this oxygenated blood, up to 20% (AHA 2007). Any interruption in the flow of oxygenated blood to the brain results in cerebral ischemia, a phenomenon in which the supply of oxygenated blood is not sufficient to support normal cell metabolism in the brain, resulting in cell death.

A severe interruption in oxygenated blood supply to the brain that occurs acutely is commonly known as ischemic stroke, or a cerebrovascular accident, and can cause large areas of cell death as well as severe cognitive impairment or even death. Smaller interruptions in blood flow to the brain that occur over long periods of time, or chronically, can also result in cognitive changes. Atherosclerosis, by nature of the plaques that form along artery walls, narrows the passage that oxygenated blood must use to reach the brain, and can block small vessels completely, resulting in chronic, milder ischemia (as opposed to an acute ischemic event).

Even mild ischemia can result in changes in neuronal metabolism that lead to cognitive impairments ranging from slight and temporary (for example, a transient ischemic attack) to more severe and lasting consequences, such as vascular dementia and stroke. The most common cause of ischemia affecting the brain is AVD. Despite the high prevalence of AVD and its potential affect on cognition, relatively little research has been conducted in this area, with much of the literature focusing on the cognitive consequences of late effects of AVD, particularly stroke. The following is a brief review

of the literature on atherosclerosis and its relationship to cognitive functioning in the aging population.

In a study of older adults with late-onset dementia (at or after age 85), researchers found that there was a dose-response relationship between the number of cardiovascular pathologies and cognitive impairment (defined here as performance greater than 1 standard deviation below the mean for age) in both men and women. Cardiovascular pathologies studied included myocardial infarction, myocardial ischemia, stroke, and claudication, (the blockage of peripheral arteries), all of which are related to AVD. These pathologies were collectively referred to as atherosclerotic burden. When subjects with stroke were excluded, the dose-response relationship remained significant (van Exel et al., 2002), suggesting that AVD is related to cognitive impairment even when an acute cerebrovascular event has not occurred.

A cross-sectional study of over 500 older males found that a higher degree of atherosclerosis (in this case, in the carotid arteries) was significantly associated with poorer performance on the Mini Mental State Exam as well as on tasks of verbal and visual memory, verbal fluency, and complex attention and cognitive flexibility (Kaplan, Everson, Koivisto, Salonen, & Salonen, 1996). Similarly, a cross-sectional study conducted in France also found a connection between atherosclerotic disease and cognitive performance. In this study, subjects with atherosclerosis (again, in the carotid arteries) showed significantly worse performance on the Mini Mental State Exam as well as on a test of psychomotor speed when compared to age-matched peers without carotid artery atherosclerosis (Auperin et al., 1996).

An additional large community-based research project, the Atherosclerosis Risk in Communities study, found similar results to the Auperin et al. study in terms of reduced psychomotor speed (compared to age matched controls) in individuals with higher levels of atherosclerosis in the carotid arteries, and also found that subjects with AVD performed significantly more poorly than those without on a test of delayed word recall (Cerhan et al. 1998). This study, unlike the previous two, included a specific measure of verbal memory and demonstrated a relationship between this cognitive domain and AVD. This is particularly significant given that subjects in this study had not experienced stroke, and provides further evidence that AVD is related to cognitive performance in the absence of an acute event.

Other studies have used atherosclerosis in the body's periphery as a marker for AVD (for example, the arteries in the lower leg). Because atherosclerosis is a systemic process, plaque build-up in the periphery will mirror that occurring in the carotid arteries and in the brain itself. Despite the knowledge that AVD is a generalized process, patients with peripheral vascular disease are often not assessed for or thought to be at risk of cognitive changes. (Everson, Helkala, Kaplan, & Salonen, 2001). A well-known large investigation, the Rotterdam study, did find an association (albeit relatively weak) between peripheral vascular disease and poorer performance compared to controls on a mental status test (Breteler, Claus, Grobee, & Hofman, 1994).

Another study compared 16 subjects with peripheral vascular disease to healthy controls. The participants with peripheral vascular disease performed significantly worse than controls on measures of visual memory, attention, psychomotor speed, and problem-solving/executive function. The subjects with peripheral vascular disease were also

compared to 29 patients who had suffered strokes. Interestingly, those with vascular disease but no history of stroke did not perform significantly better than stroke victims on the majority of the cognitive tests (Phillips & Mate-Kole, 1997). These two studies are representative of a larger group that found similar results (see also Phillips, Mate-Kole, & Kirby, 1993) and help to dispel the notion that peripheral vascular disease is unrelated to cognitive impairment.

Longitudinal studies investigating the relationship between atherosclerosis and cognition have also been conducted. For example, more than 800 of the Rotterdam study subjects completed a two to three year follow-up study. The authors of this follow-up found that participants who had clinical evidence of atherosclerosis and were carriers of a certain allele involved in metabolism of cholesterol (APOE e4 allele) had significantly worse cognitive test scores at follow up than did healthy control subjects (Slooter et al., 1998). Another large-scale study that provided longitudinal data on this issue is the Cardiovascular Health Study. In this investigation, baseline measures of atherosclerosis and vascular disease were significantly related to later cognitive decline (defined as a statistically significant decrease in total score) on a global measure of mental status and a measure of psychomotor speed. In addition, those subjects with vascular disease and the APOE allele described above showed a more rapid rate of cognitive decline (Haan, Shemanski, Jagust, Manolio, & Kuller, 1999).

This brief review of the literature on atherosclerotic vascular disease and cognition demonstrates a consistent relationship between the atherosclerotic disease process and cognitive decline, defined as significantly lower scores than comparison groups or significant decline in scores over time on standardized cognitive assessments.

Although it is important to acknowledge that some studies have failed to show this relationship, it has generally been a strong and consistent finding. Therefore, the detection and treatment of even very early-stage atherosclerosis or peripheral vascular disease may play a role in the detection and prevention of early cognitive decline and impairment and subsequent conditions such as vascular dementia. Certainly, these findings argue for the aggressive treatment of vascular disease and its related health factors, such as hypertension, even in the very elderly. The benefits of treating systolic hypertension in the very elderly have previously been questioned, but given the higher rates of cognitive impairment in the oldest old, there is evidence that physicians should consider treatment regardless of age, in order to protect and maximize functioning throughout the life span (van Exel et al. 2002).

Atherosclerotic vascular disease is not an isolated process. This pathology occurs in combination with a variety of health risk factors and other conditions, such as obesity, diabetes, and lung disease. In addition, there is a demonstrated connection between cardiovascular disease and disordered breathing during sleep, as the following section will discuss.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) has been studied frequently (in comparison to other sleep disorders) due to its relationship to cognitive impairment as well as its relationship to cardiovascular disease. The research on this disorder also led to a successful intervention, CPAP, which has been shown to have a beneficial impact on cognitive functioning. Thus, the literature on OSA can serve as a successful example of research characterizing the relationship between a sleep disorder and cognitive

functioning that progressed to the development of an intervention. As the goal of the current study was to examine this relationship in other sleep disorders with an eye toward future directions, the OSA literature is a useful model. An understanding of this literature will help to underline the importance of continuing research on other sleep disorders, including the current study. Thus, the purpose of the following section is to define OSA and briefly review its connection to cardiovascular disease and cognition.

Obstructive sleep apnea is a sleep disorder characterized by intermittent obstruction of the upper airway during sleep. This obstruction disrupts the normal delivery of oxygen to the body (including the brain) as well as disrupting normal sleep architecture. Common symptoms of this disorder include loud snoring, gasping or cessation of breathing during sleep, and excessive daytime sleepiness or fatigue (Quan & Gersh, 2004). This daytime sleepiness is often quite severe in patients with OSA, and can be related to cognitive impairment including deficits in attention, concentration, memory, and judgment as well as psychomotor speed.

These fatigue-related deficits can have serious consequences for patients in the workplace (in terms of decreased productivity and increased rate of errors), and are related to an increased incidence of automobile accidents in this population (Kim, Young, Matthews, Weber, Woodward, & Palta, 1997). The incidence of this disorder in the general population is estimated to be 4% for men and 2% for women (Quan and Gersh, 2004). However, in the elderly population, estimates are dramatically higher. The rates for older men have been estimated from 28% to as high as 62%, while the rates for older women range from 19.5% to 60% (Ancoli-Israel, Kripke, Plauber, Mason, Fell, & Kaplan, 1991).

Sleep Apnea and Cardiovascular Disease

In addition to being more common in the elderly, sleep apnea is increasingly being connected to cardiovascular disease both in terms of shared risk factors and physiological mechanisms. For some time, the medical field has recognized that factors such as obesity, high blood pressure, male gender, and increasing age are risk factors for both obstructive sleep apnea and atherosclerotic heart disease, and that sleep apnea is more common in those with coronary artery disease (Quan & Gersh, 2004). More recently, research has begun to elucidate the pathophysiological mechanisms underlying this relationship. The National Center on Sleep Disorders and the National Heart, Lung, and Blood Institute held a special workshop on this issue, and the resulting report clarifies the relationship between hypertension, coronary artery disease, and the potential genetic links between OSA and AVD (Quan & Gersh, 2004).

Sleep Apnea and Hypertension

Epidemiological data has consistently shown that patients with obstructive sleep apnea have a higher prevalence of hypertension. For example, the Wisconsin Sleep Cohort study demonstrated a three-fold increase in the incidence of hypertension in OSA patients over 4 years, independent of other risk factors (Peppard et al., 2000). As this relationship was investigated further, it was shown that overactivity of the sympathetic nervous system (a known mechanism in the pathology of high blood pressure) was also present in sleep-disordered breathing (Quan & Gersh, 2004). The precise physiological mechanisms that underlie the relationship between OSA and hypertension have been investigated, and are now better understood, in terms of the effects of hypoxia as well as changes at the cellular level that contribute to this pathological relationship.

The repeated hypoxia that occurs with obstructive sleep apnea is related to changes in autonomic function, hormone levels, and hemodynamic function. These changes may continue to affect heart function and factors such as blood pressure even during waking hours when breathing is normal (Quan & Gersh, 2004). In addition, there is a link between sleep apnea and the endothelial dysfunction associated with hypertension. Endothelial cells produce substances that result in the constriction or relaxation of the blood vessels in the body. The substance endothelin (ET-1) is responsible for inducing constriction of the blood vessels (which raised blood pressure) while the substance nitric oxide (NO), also produced by endothelial cells, relaxes blood vessels. In patients with OSA, the phenomenon of hypoxia raises levels of ET-1 and reduces production of NO. Thus, dilation of the blood vessels does not occur normally and the vessels retain a high tone, leading to increased peripheral resistance and higher resting blood pressure.

Another shared physiological feature between vascular disease or dysfunction and OSA is the inflammatory cytokine known as C-reactive protein (CRP). The relationship between CRP and cardiovascular disease had received increased attention in the research literature over the past decade. CRP has been identified as marker for risk in terms of recurrent cardiac events as well as new cardiac events, particularly heart attack. CRP is produced by the liver, and is one of several endogenous substances that increase in response to inflammation. Because it can be measured through a simple blood draw and has been associated with vascular pathology as well as morbidity and mortality, it has become a standard laboratory test in many cases of vascular disease (AHA, 2007). The relationship between CRP and disordered sleep is somewhat less clear, but it has been

demonstrated that CRP is produced in response to both sleep deprivation and hypoxia (both of which occur in OSA), and that these increased levels can affect endothelial function and result in higher blood pressure (Quan & Gersh, 2004) through the mechanism described above. The role of CRP in other sleep disorders has not been extensively investigated, and examining this relationship was one goal of the current study. First, however, the literature on OSA and AVD will be briefly reviewed.

AVD and Sleep Apnea

As mentioned previously, AVD and sleep apnea share several risk factors, and the discussion above shows that they also share comorbid conditions such as hypertension and elevations in inflammatory markers such as CRP, among many others. Thus, it has been difficult to clarify a causal or unique relationship between the two conditions. However, recent research has suggested that there is an increase in cardiovascular risk factors with increased severity of sleep disordered breathing. Many potential physiological pathways and mechanisms have been suggested as ways in which sleep apnea may increase the risk of heart disease, including the so-called "metabolic syndrome", in which insulin resistance creates a worsening cycle of obesity, hypertension, and sympathetic nervous system dysfunction (Yun, Lee, & Bazar, 2003; Bixler, et. al. 2005). Sleep deprivation and hypoxia contribute to the development of insulin resistance and may play a role in triggering the metabolic syndrome (Bazar, Yun, Lee, Daniel, & Doux 2005).

Although the exact physiological cascade of events remains unclear, and is highly complex, it is clear that there is a physiological interaction between vascular disease and obstructive sleep apnea. For elderly persons, who are at greater risk for both conditions,

the burden placed on the body and brain can be highly detrimental. The impact of repeated hypoxia on the brain is clearly harmful, and is especially concerning in patients already experiencing disruption of oxygenated blood to the brain due to ischemia, as discussed in the section on AVD.

Like AVD, obstructive sleep apnea is at least partially preventable and is treatable. This reiterates the importance of the diagnostic category of mild cognitive impairment and the early detection of cognitive difficulties. As older adults are increasingly being screened for these early cognitive changes, risk factors such as AVD and sleep apnea can be identified. Treatment with continuous positive airway pressure (CPAP), a device worn during sleep, as well as weight loss and increased activity, can create dramatic improvement in the symptoms and cognitive abilities of those suffering from OSA and vascular disease. In addition, effective treatment of sleep apnea may help to reduce the risk of cardiovascular disease (Quan & Gersh, 2004).

Identifying MCI (and possibly even earlier stage cognitive changes, in which performance has dropped below expectations for age but is not yet in the impaired range) and intervening with respect to treatable health conditions is an important area of future research as we face an increasingly older population, and the example of sleep apnea is an excellent one due to the relatively severe cognitive effects of the disorder and its highly treatable nature. One of the purposes of this study was to present evidence that argues for the expansion of research to include other sleep disorders, with the hope that disrupted sleep in other forms will eventually be as rigorously researched as sleep apnea has been.

Sleep, Sleep Disorders, and Aging

As mentioned above, it is less clear from the research literature is how disordered sleep in general (rather than sleep apnea specifically) affects older adults, particularly those with cardiovascular disease. Also, it is unclear whether treatment of other, non-breathing-related sleep disorders would have a comparable impact on maintaining healthy cognition when viewed alongside CPAP treatment for sleep apnea. The remainder of this chapter will discuss this issue, beginning with a review of normal sleep. Next, the prevalence of sleep disorders in the elderly will be discussed, along with an explanation of the most common types of sleep disorders affecting the population. Finally, the existing literature on sleep disorders and cognition will be reviewed, with an eye to future research directions.

Normal Sleep

Normal sleep is a complex physiological phenomenon governed by multiple systems of the brain and body. Sleep was long assumed to be a single stage process in which one was simply passive and "absent" from the waking world of cognition. The fact that sleep is, in fact, and active state and has definable stages was not discovered until 1953 (Mahowald, 2004).

Sleep is now known to consist of two distinct stages, namely non-rapid-eye movement (NREM) and rapid-eye movement (REM) sleep. Along with wakefulness, these make up the three stages in which human being spend their existence. NREM sleep is further subdivided into four arbitrary stages that indicate increasing depth of sleep. REM sleep is defined as the stage during which continuous brain activity is evident on electroencephalogram (EEG), along with muscle atonia and rapid eye movements. REM

sleep is not divided into stages like NREM, but can be categorized as phasic or tonic type. NREM and REM sleep alternate through the night in approximately 90-minute cycles, with the first cycle of REM sleep normally occurring 80 or more minutes after initial sleep onset (Olejniczak & Fisch, 2003).

Each stage of sleep has its own particular physiological and neuroanatomical controls. The "control center" that determines which stage will occur (waking, NREM, or REM) is located primarily in the brainstem (specifically the pons) and the basal forebrain. The sites that generate and maintain wakefulness are also located primarily in the brainstem, with the reticular activating system playing a crucial role. NREM sleep is generated, generally speaking, by the medulla and the basal forebrain while generation of REM sleep is the job of the pons (Mahowald, 2004).

This general localization of brain centers involved in sleep barely begins to scratch the surface of the phenomenon. The components of the different states are controlled by multiple sites in the brain as well as by a variety of neurotransmitters and blood-borne cellular signaling mechanisms. New chemical factors and anatomical areas involved in sleep are being discovered at a rapid rate, making a current listing almost impossible. However, some common and well-accepted contributors include the neurotransmitters serotonin, GABA, and norepinephrine.

These neurotransmitters, along with numerous other chemical signals, selectively inhibit and activate pathways and brain regions in order to produce or maintain a certain stage of sleep or wakefulness. As an example, GABA (released by the thalamic reticular nucleus) globally inhibits thalamocortical neurons during NREM sleep. This results in a firing rate that is much lower than during the waking state, and acts as a "gate" against

the transmission of information that occurs in sensory relay areas during wakefulness (Hobson & Pace-Schott, 2002). An exploration of the multiple other mechanisms that regulate sleep is beyond the scope of this paper, but it is sufficient to understand that sleep exists in distinct stages and is regulated by complex neuroanatomical and neurochemical networks.

The precise function of normal sleep remains a mystery, but sleep deprivation has clear and severe physiological consequences. In animal studies, total sleep deprivation (NREM and REM sleep) has proven fatal within about 3 weeks, similar to total deprivation of food (Mahowald, 2004). Thus, it is clear that we need sleep, although less clear precisely why it is so critical. One theory involves the preservation of neuronal integrity and brain function. It is known that the structure and function of neural pathways is determined and maintained by the frequency and type of neural activity occurring in the brain. Thus, some researchers have suggested that sleep plays a role in maintaining neural networks by providing periodic and systemic activation of various pathways. In this way, sleep would help to preserve infrequently used pathways and help to produce optimal functioning during waking hours (Krueger & Obal, 1993; Kavanau, 1997).

As with the purpose of sleep in general, the specific effects of sleep on waking cognitive performance are still largely unknown. Again, it is clear that sleep deprivation is highly detrimental to cognitive tasks including attention, concentration, and memory, but exactly how sleep maintains these functions is a matter of theory. One such theory is known as the "dual-process hypothesis" which proposes that the two stages of sleep (NREM and REM) facilitate different areas of cognitive functioning. NREM is

hypothesized to facilitate explicit memory or declarative learning, while REM sleep facilitates procedural or non-declarative learning and memory (Ekstrand, Barrett, West, & Maier, 1977).

This theory has been supported by research showing that depriving subjects of early night sleep (usually NREM sleep) selectively impairs performance on paired word associate tasks (a type of task involving declarative memory) while depriving subjects of late night or REM sleep impairs performance on procedural tasks such as mirror-drawing (Hobson & Pace-Schott, 2002; Fenn, Nusbaum, & Margollash, 2003; Plihal & Born, 1997).

Sleep in the Aging/Elderly

A common misconception is that the elderly simply "need less sleep". However, some studies (e.g. Ohayon & Vecchierini, 2002) have indicated that older adults ex perience a greater degree of daytime sleepiness than younger adults. This suggests that older adults experience a decline in the quality and/or duration of sleep. If the need for sleep actually declined, there would be no corresponding increase in daytime sleepiness or decrease in alertness (Mahowald, 2004).

Other studies have examined the specific changes in the sleep-wake cycle that accompany the aging process. Studies using polysomnography to study healthy, elderly adults have found that total sleep time decreases with age. Additionally, the amount of slow-wave sleep decreases, and the time needed for sleep onset increases (Ohayon & Vecchierini, 2005). A survey by these authors of 1,026 subjects age 60 or older provided an epidemiological study of sleep in the elderly. This study reported that elderly subjects (76% of participants were 65 or older) had a mean nighttime sleep

duration of seven hours and eight minutes. Five percent of the sample reported sleeping four and a half hours or less per night, and an additional five percent reported sleeping nine and half hours or more.

Across age groups, men slept significantly longer than women, and sleep duration was not significantly related to age group (broken into 5-year increments) for either men or women (Ohayon & Vecchierini, 2005). This portion of the study provides a relatively normal distribution of sleep for the healthy elderly, helping to dispel the notion that the need for sleep simply decreases with age. However, the authors also mention that sleep disturbance does increase in the elderly population, with rates as high as 50% reported in the literature (Ohayon & Vecchierini, 2005). Thus, it is important to discuss both the high frequency of disrupted sleep in the elderly and its correlates.

Two large-scale surveys have investigated the correlates of disrupted sleep in the elderly population. The first followed a presentation of the normal sleep distribution in the elderly (Ohayon & Vecchierini, 2005) with an investigation of the correlates of disrupted sleep in the participants who fell in the lower fifth percentile in terms of hours of sleep as well as those who were at the upper end of the distribution in terms of daytime sleepiness. The authors found that short nighttime sleep duration (four and a half hours or less) was significantly associated with several health variables. Obese individuals were significantly more likely to report short sleep duration, as were subjects with poor physical health. Unfortunately, "poor health" was not specifically operationalized in this study. Daytime sleepiness, defined as sleeping one hour or more during the day, was also associated with several health factors in addition to being significantly associated with

male gender. Sleeping one or more hours during normal waking time each day was also associated with high blood pressure and obesity (Ohayon & Vecchierini, 2005).

The second large-scale survey was conducted by the National Sleep Foundation (Foley, Ancoli-Israel, Britz, & Walsh 2004). The survey was completed by 1,506 community-dwelling older adults (ages 55-84) with a 20-minute telephone interview regarding their sleep and physical health. The participants reported a variety of health conditions, with the most common being hypertension (47%), arthritis (46%) and heart disease (18%). Four out of five participants had at least one health condition (others included diabetes, cancer, lung disease, stroke, and memory problems) and nearly one in four participants over age 65 had four or more of these conditions comorbidly.

These participants also reported on the quality of their sleep, and this variable was found to be significantly correlated with the number of medical conditions present. Forty percent of participants with major comorbidity (four or more conditions) reported that their sleep quality was fair to poor. In participants without medical conditions, only 10% reported fair to poor sleep quality.

Specific sleep problems (defined here as difficulty falling or staying asleep, snoring, breathing pauses, restless legs, or daytime sleepiness) were also associated with physical health. Of participants with no reported medical conditions, 36% reported one or more sleep problems. This is higher than would be expected in a younger sample, but consistent with epidemiological data that has shown rates of sleep problems as high as 50% in the older and elderly. In participants with one to three health conditions, 52% reported one or more sleep problems, and that percentage climbed to 69% in participants with major comorbidity. Heart disease, a condition of interest in the current study, was

significantly associated with shorter nighttime sleep duration (6 hours or less) and with unpleasant feelings in the legs (a symptom of Restless Leg Syndrome).

In terms of the high rate of disrupted sleep in the elderly, health status (and cardiovascular disease specifically) emerge as important variables. These studies reiterate the necessity of investigating sleep quality in populations of elderly with chronic conditions such as AVD, as well as the need to add cognitive functioning to the research picture. One of the surveys above included "cognitive dysfunction" as a variable, but relied on a self-report measure of cognitive difficulty. These instruments are controversial, and have been shown to be uncorrelated with actual cognitive functioning in older adults with AVD (Humphreys, Moser, Hynes, Reese, & Haynes, 2007).
In addition, before moving forward it is important to understand what constitutes "sleep problems" or "sleep disturbance". To further understand the phenomena of disrupted sleep, health, and cognition, it is necessary to more clearly define these general terms. The following section gives an overview of common sleep disorders (other than sleep apnea) that are often factors underlying the blanket term "disrupted sleep".

Sleep Disorders

In sleep medicine, the definitive guide to sleep disorders is the International Classification of Sleep Disorders (ICSD), which was published by the American Academy of Sleep Medicine in 1990 (updated in 1997), and developed in conjunction with the European Sleep Research Society, the Japanese Society of Sleep Research, and the Latin American Sleep Society (ASDA, 1997). The ICSD divides sleep disorders into four major categories: (1) dyssomnias; (2) parasomnias; (3) sleep disorders associated with mental, neurologic, or other medical disorders; and (4) proposed sleep disorders

(Olejinczak & Fisch, 2003). The first two categories represent primary disorders of sleep and are briefly described below.

The dyssomnias are defined as disorders that result in excessive daytime sleepiness or cause difficulty in falling asleep or staying asleep. There are three groups of dyssomnias: (1) intrinsic sleep disorders, (2) extrinsic sleep disorders, and (3) circadian rhythm sleep disorders. Examples include insomnia, hypersomnia, restless legs syndrome, periodic limb movement disorder, and sleep phase disorders (Olejinczak & Fisch, 2003).

Parasomnias are a group of disorders that are characterized by physical phenomena that disrupt normal sleep, rather than abnormalities of the sleep-wake cycle itself. There are four groups of parasomnias: (1) arousal disorders, (2) sleep-wake transition disorders, (3) REM-related parasomnias, and (4) other parasomnias. Examples of parasomnias include disorders and phenomena such as sleep terrors, somnambulism (sleepwalking), REM behavior disorder (including violent behavior during sleep), and abnormal motor activity during sleep, such as nocturnal paroxysmal dystonia (Olejinczak & Fisch, 2003).

The Diagnostic and Statistic Manual of Mental Disorders (DSM-IV) also divides sleep disorders into dyssomnias and parasomnias, but from that point, it groups conditions rather than subdividing them. To illustrate, the DSM-IV provides only six diagnoses in the dyssomnia category and four in the parasomnia category. In contrast, the ICSD identifies 34 disorders under the dyssomnia classification alone. Those in the sleep medicine field feel that the numerous available diagnostic distinctions are

important, and hence the ICSD has enjoyed wider use than the DSM-IV in this specific area (Roehr & Roth, 2004).

For the purposes of this paper, it is primarily important to understand the most common disorders of the sleep-wake cycle that result in daytime sleepiness. Thus, the remainder of this section will focus on defining and describing common dyssomnias, including insomnia, restless leg syndrome, and circadian rhythm disorders. It is important to note that obstructive sleep apnea is the most common reason for referral to a sleep laboratory (Olejinczak & Fisch, 2003), but since OSA has been previously discussed in terms of hypoxia and its connection to heart disease, it will not be reviewed in the present section.

Insomnia, defined as difficulty initiating or maintaining sleep associated with functional impairment the following day, is one of the more common dyssomnias. Chronic insomnia (defined by the ICSD as lasting more than 6 months) is estimated to affect 10 to 14 % of the population. Less severe insomnia, which occurs occasionally or has a shorter duration, is estimated to affect 20-40% of the population (Roehrs & Roth, 2004). The difficulty in defining insomnia, according to the literature, lies in determining whether it is a primary or an associated insomnia. As the terms suggest, primary insomnia is a solitary disorder, while the associated insomnias are "associated" with primary mental or physical disorders. Few studies have attempted to disentangle the two, but from those available, associated insomnia seems to be the more common of the two types. Population-based surveys have found that primary insomnia accounts for only 16% of cases, while a clinic-based study found a rate of 25%. Survey data have also

been consistent in the finding that insomnia is more common in women and that its prevalence increases with age (Roehrs & Roth, 2004).

The American Association of Sleep Medicine has established practice parameters for the diagnosis and evaluation of chronic insomnia:

1) The health care practitioner should screen patients for symptoms of insomnia during health examinations.

2) An in-depth sleep history is essential in identifying the cause of insomnia. Additionally, a physical examination is an important element in the evaluation of insomnia patients with medical symptoms.

3) Polysomnography is not indicated for the routine evaluation of chronic insomnia. Symptoms of insomnia, however, do not exclude PSG evaluation in assessing the complaint. There should be a valid indication and a clear rationale, based on specific elements of the history, to support PSG evaluation (Olejiniczak & Fisch, 2003, pp. 819).

These criteria are meant as guidelines for experts in sleep medicine as well as general practitioners, and are geared toward an effective diagnosis of insomnia while avoiding an expensive sleep laboratory study when possible. Polysomnography (PSG) is a diagnostic procedure for sleep disorders that involves the recording of brain wave activity (EEG), eye movement (electro-oculography or EOG) and muscle activity

(electromyography or EMG). In addition, the patients' heart rate, breathing, airflow, and oxygen saturation are constantly monitored. This extensive testing is more commonly indicated for obstructive sleep apnea, narcolepsy, violent sleep behavior, or atypical parasomnias, whereas an extensive history and physical exam is usually sufficient to diagnose insomnia (Olejiniczak & Fisch, 2003).

Once diagnosis has occurred, treatment of insomnia is aimed at reducing the "hyperarousal" that is hypothesized to underlie the disorder (Roehr & Roth, 2004). The first line pharmacological treatment of this disorder is a drug from the benzodiazepine or benzodiazepine receptor agonist class. In addition, there are multiple behavioral treatments such as relaxation, sleep restriction to increase sleep drive, cognitive restructuring, and lifestyle changes (Roehr & Roth, 2004). Insomnia is a treatable disorder, although not all patients choose to seek treatment and untreated insomnia is a significant health issue, particularly in the elderly. One study estimated that the direct and indirect medical costs (including direct medical and pharmacy costs as well as absenteeism and use of short-term disability) to be about $1400 greater over a 6 month period for elderly people with untreated insomnia when compared to those without insomnia (Ozminkowski, Wang, & Walsh, 2007).

Restless legs syndrome was first identified as a disorder in 1945, and is characterized by unpleasant sensations in the legs that occur before sleep and create an irresistible urge to move (Olejiniczak & Fisch, 2003). Prevalence estimates have ranged from five to 15 percent of the population. In 2005, a large-scale survey by the National Sleep Foundation contacted over 1500 adults and obtained a prevalence rate of 9.7% (Phillips, Hening, Britz, & Manino, 2006). The mean age of onset is between the ages of

27 and 41, but about 40% of patients experience their first symptoms of restless legs syndrome before age 20.

The diagnostic criteria for this disorder include unpleasant sensation in the legs at night along with difficulty initiating sleep. The leg sensations are often described as "creeping" or "tightening" inside the calves and are relieved by movement (Olejiniczak & Fisch, 2003). Supporting evidence for the diagnosis also includes a family history of the disorder, as restless legs syndrome is thought to have a genetic component (Phillips, Hening, Britz, & Mannino 2006). Because the symptoms occur while awake and are quite distinctive, diagnosis is usually based on self-report and family history rather than sleep laboratory studies.

The physiology of this disorder is still not well understood, but is believed to be related to problems in the dopaminergic system and to iron deficiency (Phillips, Hening, Britz, & Mannino 2006). Restless legs syndrome has also been related to pregnancy, and is more common in women than men. Like insomnia, the prevalence increases with age (Phillips, Hening, Britz, & Mannino 2006; Olejiniczak & Fisch, 2003).

The AASM published treatment guidelines for restless legs syndrome as well as periodic limb movement disorder (a related syndrome) in 1999.

1) Pharmacologic treatment of RLS or PLMD should be limited to patients who meet specific diagnostic criteria.

2) The physician who evaluates and treats patients with RLS or PLMD should be aware of the existence of idiopathic and secondary forms, and should be knowledgeable about risk factors and comorbid conditions for these disorders.

3) Individuals with RLS or PLMD who are being treated with medication should be followed by a physician at appropriate intervals and monitored for adverse side effects, augmentation, and tolerance (Olejiniczak & Fisch, 2003, pp. 822).

As these guidelines suggest, the primary treatment for restless legs syndrome is pharmacological. Dopaminergic agonists and medications such as Levodopa (also used in other movement disorders, including Parkinson's disease) as well as opioids and clonidine have been shown to be effective. Correcting any iron deficiency is also a key component of treatment.

There are two common forms of primary circadian rhythm abnormalities, or sleep phase disorders. The first is delayed sleep phase syndrome, which is characterized by late sleep onset and late awakening (i.e. the patient is unable to fall asleep until 3 am and remains asleep until 10 am). This disorder frequently interferes with obligations such as work and school, as well as producing fatigue as the patient tries to conform to desired sleep and wake schedules. Prevalence of this disorder is less well researched, but is thought to represent perhaps 5 to 10 percent of cases that present to sleep disorder clinics complaining of insomnia (Mahowald, 2004). Onset of delayed sleep phase syndrome often occurs in adolescence, and some research has suggested that it may have a genetic component (Mahowald, 2004).

The second disorder in this category is advanced sleep phase syndrome. As the name suggests, the normal sleep and wake phases are advanced so that patients fall asleep early and awaken early (i.e. falling asleep at 7 pm and awakening at 3 am) and are unable to remain awake until their desired bedtime. This disorder has been subject to even less research than its delayed sibling, and statistics on incidence and prevalence are not available. It is thought to be less common than delayed sleep phase, but this may also represent underreporting. Although advanced sleep phase also produces fatigue, it is somewhat less likely to interfere in the classroom or with traditional work hours. However, patients may avoid evening events and experience distress and daytime sleepiness due to early awakening (Mahowald, 2004).

The physiology of both disorders is related to the body's circadian rhythms, which are regulated by light and the timed release of various hormones. When the release of certain hormones is not synchronized with the desired sleep-wake cycle of the individual, delayed or advanced sleep phase can result. Many people have experienced this temporarily in the form of "jet lag", and it is also common in shift work. However, when the phase-response curve is chronically advanced or delayed, a sleep disorder is diagnosed.

There are three types of treatment commonly used to treat advanced or delayed sleep phase. One is chronotherapy, simply meaning "time therapy", in which (for example) the bedtime is advanced, for example, by three hours every two days until the desired bedtime is reached. After this time, the schedule must be carefully maintained or relapse can occur (Mahowald, 2004). Another common therapy is the use of bright light exposure. Using 2000 to 2500 lux light from six to 9 am has been shown to be effective

in delayed sleep phase, in combination with wearing dark goggles from 4 pm to dusk. For advanced sleep phase, the use of 2500 lux light from 8 pm to midnight or 4000 lux light from 9 pm to 11 has successfully restored normal sleep-wake cycles (Olejiniczak & Fisch, 2003).

The most popular over-the-counter remedy for sleep phase disorder is the chemical melatonin. Melatonin acts in the opposite direction of bright light exposure, delaying sleep phase when administered in the early morning and advancing it when given in early afternoon. Melatonin has been studied for its effects on jet lag, and while results have generally been encouraging, the dosing, mechanism of action, and consistency of its effects remain unclear, and some researchers feel that its use for sleep disorders cannot be justified (Olejiniczak & Fisch, 2003).

The dyssomnias described above have diverse clinical presentations, physiologic mechanisms, and treatments. However, they all have a common effect, in that they disrupt normal sleep, producing fatigue and daytime sleepiness that can have functional and cognitive consequences. After a basic review of the different sleep disorders and their cognitive correlates, the focus of this chapter will turn to the common factor of fatigue or daytime sleepiness in order to examine the cognitive effects of sleep disorders more generally.

Sleep Disorders and Cognition

Fulda and Schulz (2001) performed a meta-analysis of studies examining cognitive dysfunction in patients with sleep disorders. The analysis included studies on sleep-disordered breathing (sleep apnea), insomnia, and narcolepsy. For the purposes of

this paper, the reviews of sleep apnea and insomnia will be covered. Narcolepsy, although a debilitating disorder, falls outside the scope of this paper.

In patients with sleep-disordered breathing, effects on cognition were studied across several neuropsychological dimensions. Cognitive dysfunction in these patients followed a complex pattern. One of the most compelling results across studies included in the meta-analysis was the evidence for impairment in driving simulation performance. Patients with sleep disordered breathing of varying severity consistently performed worse than controls on simulated driving tasks in 11 separate studies reviewed by the authors. In other areas, links were less conclusive. Cognitive tasks measuring basic (e.g. digit span forward), complex/divided (e.g. trails B, digit span backward) and sustained (e.g. digit cancellation) attention showed some evidence of impairment in apnea patients. Other areas such as visual memory, verbal immediate memory, construction, and reasoning showed inconsistent results or had an insufficient number of studies.

The meta-analysis of studies on insomnia did not show unequivocal evidence of cognitive dysfunction in any specific neuropsychological domain. However, attention span and vigilance were impaired in some studies reviewed by the authors. However, the authors pointed out that only a small number of studies have been conducted in this area, and that insomnia is a more heterogeneous construct than sleep apnea (Fulda & Schulz, 2001). As discussed in the section on sleep phase disorders, a certain percentage of insomnia cases may in fact be delayed sleep phase. Also, as previously discussed, insomnia can be primary in nature or associated with other conditions that affect cognition in various ways. The authors also did not mention their inclusion criteria for studies (i.e. duration of insomnia).

This meta-analysis provided an introduction to the research on sleep disorders and cognition and also introduced some of the inherent problems with this type of research. While there is a large literature on sleep apnea, the research on other specific sleep disorders and their relationship to cognition is more limited, and presents more equivocal results. Researchers in this area have taken two primary routes in efforts to understand the relationship between non-apnea sleep disorders and cognition. First are studies of subjects with specific individual sleep disorders and their performance on cognitive tasks. Second are studies focused on the concept of daytime sleepiness, which is often examined independent of the specific underlying etiology or disorder. Studies of both types will be considered, in order to review the literature on non-apnea sleep disorders and cognition.

Phillips et al. (2006) examined Restless Leg Syndrome (RLS) and its relationship to daily cognitive difficulties. Patients endorsing RLS symptoms reported significantly more difficulties than controls (without RLS or another sleep disorder) in multiple areas. They were more likely than those without RLS to report being late to work, making errors at work, missing events, and driving while drowsy. This study differs from the meta-analysis presented above in that assessment was focused on ability to manage daily activities rather than performance on standardized neuropsychological tests. In addition, this study relied on self-report of daily cognitive difficulties rather than objective measurement.

Another recent study (Gamaldo, Benbrook, Allen, Oruntimein, & Early, 2008) examined cognitive functioning in subjects with RLS compared to sleep-restricted controls. The control group experienced restricted sleep to six hours nightly for 12 days,

and then they spent two nights in an inpatient sleep lab where sleep was restricted to 5 hours each night. They were then compared to age and gender matched RLS patients on several cognitive tasks. These researchers found that the RLS subjects performed better than sleep restricted controls on several cognitive tasks that measured processing speed, verbal fluency, and executive functioning . The authors hypothesized that these results are due to "sleep loss adaptation" in the RLS subjects. However, there is also a question of how comparable the two groups were, in terms of total sleep and degree of sleep disruption. No measure of daytime sleepiness was used to determine if either group reported more fatigue, and the paper did not specify how many hours of sleep per night the RLS group was getting on average. This, and the lack of a non-sleep restricted control group, leaves several questions regarding these results.

Another research group (Bastien et. al. 2003) examined chronic insomnia and its relationship with cognitive performance in elderly individuals. This study evaluated sleep quality and cognitive performance in 20 insomnia sufferers and 20 self-reported "good sleepers" ages 55 and older. The researchers found that difficulties with sleep onset and maintenance (measured by polysomnography) were correlated with poorer performance on measures of verbal memory, motor speed, attention, and concentration. However, these correlations were present in both the chronic insomnia group and the "good sleeper" group (both of whom showed sleep difficulties on PSG), illustrating the problems inherent in using self-report of sleep quality for classification of subjects.

Studies examining specific sleep disorders and their correlates are relatively few, and vary both in terms of methodology and results as indicated by the meta-analytic review and the studies summarized above. The failure of these studies to provide

consistent results (especially in the case of insomnia) suggests that there may be another line of research to investigate. Some researchers have attempted to remedy this problem by examining a common factor (daytime sleepiness) rather than specifically diagnosed sleep disorders.

One such study (Ohayon & Vecchierini, 2002) examined daytime sleepiness and cognitive impairment in 1,026 individuals age 60 or over. Within this sample, just over 14% had moderate to severe daytime sleepiness. The authors distinguished this group from the 14.5% that reported taking an intentional nap daily. Daily napping and reported excessive daytime sleepiness were not significantly associated. Using a logistic regression analysis, the researchers found that excessive daytime sleepiness was an independent predictor of self-reported cognitive difficulty as well as a predictor of performance on a mini-mental state exam. The researchers controlled for possible confounding variables such as age, sex, and medications.

These results do appear to support the notion that daytime sleepiness may be a more effective route of research into cognitive impairment than investigation of individual sleep disorders. However, it is important to note that the study relied on self-report data regarding sleep, as well as a self-report instrument of cognitive difficulties (CDS). As mentioned previously, the CDS has been shown to be unrelated to actual neuropsychological test performance in some elderly adults (Humphreys et al. 2007), although the authors do point out that another study has shown the CDS to be a predictor of incident Alzheimer's disease (Ohayon &Vecchierini, 2002).

A second large-scale study (Whitney, Enright, Newman, Bonekat, Foley, & Quan, 1998). also examined the correlates of daytime sleepiness in elderly persons. The

researchers assessed 4,578 participants age 65 and above using the Epworth Sleepiness Scale (ESS), cognitive tests, and standardized health questionnaires They found that about 20 percent of participants reported they were “usually sleepy in the daytime”, a figure which is comparable to the 2002 study by Ohayon and Vecchierini. Cognitive functioning in this study was assessed via an interview that included portions of the Mini Mental State Exam (e.g. counting backward from 100 by 7’s and spelling “world” backward).

In contrast to the previous study, these researchers found a positive but not statistically significant association between excessive daytime sleepiness and cognitive impairment. Interestingly, the researchers specifically state that there was no relationship between daytime sleepiness and cognition in elderly Iowans. This study did find a significant correlation between markers of sleep apnea and daytime fatigue, which is not surprising. However, they failed to find any correlation between daytime sleepiness and cardiovascular disease, a finding that the authors acknowledge is inconsistent with some other papers. Also surprisingly, the authors found that brain abnormalities on MRI (i.e. stroke, atrophy) were unassociated with daytime sleepiness. Other factors that were correlates of daytime sleepiness were depression, frequent awakening, sedentary lifestyle, and certain medications. These finding are somewhat intuitive, and unfortunately do not add a great deal to the question surrounding the functional or cognitive effects of daytime sleepiness.

There have been other, more recent studies that have examined the phenomenon of disrupted sleep and cognitive performance in the aging population specifically, which are of particular interest given the current study. One such study (Nebes, Buysse,

Halligan, Houck, & Monk, 2009) examined correlates of sleep quality in community-dwelling subjects between the ages of 65 and 80. Sleep quality was measured using a questionnaire, the Pittsburgh Sleep Quality Index (PSQI). Cognitive performance was measured using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) as well as measures of executive functioning, verbal memory, and processing speed. Poor sleepers (N = 49) were compared to good sleepers (N = 108) as defined by scores on the PSQI.

Poor sleepers performed significantly worse on the RBANS Total Scale Score as well as one test of executive function (Trails B) and one of two working memory tasks. No significant difference was found between the two groups on measures of processing speed or verbal memory. This study did not analyze performance on the five cognitive domains of the RBANS, but used Total Scale score only. An additional notable finding in this study was that the poor sleepers reported significantly more depressive symptoms than good sleepers on the Geriatric Depression Scale, representing a potential confound in terms of cognitive functioning (Nebes, Buysse, Halligan, Houck, & Monk, 2009). This study illustrated the importance of considering mood and psychological symptoms as a contributing factor when examining the relationship between disordered sleep and cognition.

One research group has examined the issue of sleep, aging and cognition using an alternative approach. Rather than examining disordered sleep, this study (Driscoll et. al. 2008) was a descriptive examination of sleep in so-called "successful agers" 75 and older. Successful agers, for the purpose of this study, were defined as individuals without significant medical comorbidities and without sleep-wake complaints. In order to study

the relationship between sleep and other factors in these participants, the researchers used sleep diaries and laboratory based measures of sleep quality and then examined correlations between these measures and quality of life variables. The researchers found that healthy individuals age 75 and older can experience satisfactory sleep quality and daytime alertness, helping to dispel the notion that reduced sleep and daytime fatigue are an inevitable consequence of aging. Furthermore, the researchers found that these successful agers with good sleep quality also scored high on measures of quality of life and showed a general absence of depression or cognitive impairment. Although objective neuropsychological tests were used, the performance of the participants was not specifically quantified in terms of scores. The researchers simply reported that better sleep quality was associated with "high" scores on cognitive measures including the Mini Mental Status Exam. This study provided an interesting alternate perspective and took the important step of establishing that satisfactory sleep and daytime alertness do occur in the elderly. However, it leaves many questions regarding the relationship between sleep and cognitive test performance in the elderly population.

A recent study (Malhotra & Desai, 2010) reviewed published research that investigated sleep, cognition, and aging. The number of published studies reviewed by the authors varied considerably between those focused on sleep apnea (27 references cited) and those on "other sleep disorders" in the elderly (3 references cited). The article went on to state that much of the current research on sleep and memory has focused on sleep apnea, with very few studies on other sleep disorders and even fewer specifically examining the elderly population. The authors discussed the need for additional research linking sleep disorders to cognitive impairment in older adults, and subsequent research

showing that treatment of sleep disorders leads to improved cognitive functioning or slows cognitive decline in the elderly

Clearly, the research on sleep, cognition and aging is far from complete, especially with regard to sleep disorders other than sleep apnea. The studies reviewed above are an effective illustration of the need for further replication and expansion of methodology in this area, due to their sometimes conflicting results and necessary reliance on self-reports and very brief cognitive measures. It is not often financially or logistically feasible to conduct extensive cognitive testing or sleep studies on a large scale, so it may be that smaller, more in-depth projects can begin to fill in the outline provided by these population-based projects.

Summary and Research Hypotheses

This chapter has reviewed numerous areas relevant to the aging population. Although they may seem disparate at times (especially in a paper of this length), the issues of cognitive impairment, atherosclerotic vascular disease, and sleep disruption form an interactive conglomerate of health concerns for a growing part of the population. As discussed earlier in this paper, the concept of mild cognitive impairment has emerged as a useful diagnostic tool in identifying older adults at risk for further cognitive decline or dementia. The potential to identify cognitive impairment at an earlier stage raises the possibility of intervention to slow or prevent progression to dementia, which is a major burden for elderly people, caregivers, and the health care system.

Next, health-related causes of cognitive impairment were reviewed. Cardiovascular disease was introduced as a major contributor to cognitive impairment, and the increasingly prevalent phenomenon of vascular dementia was discussed. Strongly

related to vascular disease is the sleep disorder known as obstructive sleep apnea. This sleep disorder is also known to be related to cognitive impairment in the elderly. What is less clear is the mechanism underlying this relationship. Certainly, repeated hypoxia is detrimental to the brain, much like the ischemia of vascular disease. However, patients who receive treatment for sleep apnea often improve dramatically in terms of cognition, raising questions about the relative contributions of hypoxic brain damage and the disruption of sleep in OSA. If sleep disruption in general is a culprit in early cognitive changes, it will be important to examine other sleep disorders in depth, in addition to the large body of research available on OSA. The physiological mechanisms reviewed at the beginning of this paper suggest that sleep deprivation and vascular disease may have common factors that negatively affect the brain, such as the inflammatory cytokine C-reactive protein. This would place older adults suffering from disrupted sleep and vascular disease at a heightened risk of cognitive impairment, underscoring the importance of expanding the research literature to include other sleep disorders.

The research on specific sleep disorders other than OSA, however, tends to ignore the common effects of sleep disruption caused by different mechanisms, and also encounters difficulty in defining heterogeneous disorders like insomnia. On the other hand, studies that do examine a common factor such as daytime sleepiness often rely solely on self-report measures, which have been found to be unreliable, especially with regard to sleep and cognition. A combined approach would seem to be the logical next step in this area. Studies that combine self-report with medical chart review and confirmed diagnosis of sleep disorders will help to close the gap.

In addition, studies of sleep and cognition should attempt to incorporate objective assessment in other areas. Neuropsychological testing (as opposed to brief measures or self-report and blood levels of common factors such as C-reactive protein will add a great deal to this field of research. Sleep studies, obviously, would be a desirable component as well, but due to their prohibitive expense and inconvenience to research subjects, previous diagnosis by a physician may be the most feasible method of assessing for sleep disorder in most studies. Smaller scale but rigorous studies utilizing these types of measures will enable researchers to present a more complete picture of older adults who suffer from atherosclerotic vascular disease and sleep disorders. This type of research will also go beyond the area of sleep apnea, and identify more potential targets for intervention. Sleep apnea serves as an excellent example and success story in which a highly effective intervention was found for a condition with serious health and cognitive consequences. If sleep disorders in general and the physiology of their connection to vascular disease and aging are studied in the same in-depth way that sleep apnea has been, other interventions as effective as CPAP may present themselves. Sleep hygiene and vascular health are both excellent targets for behavioral and/or pharmacologic intervention, and further research in these areas, in addition to elucidating the connection between these health conditions, may eventually help to prevent or delay many cases of cognitive impairment as well as improving quality of life in the aging population. These are critical issues given the rapidly aging demographics of the United States, and the amount of care that is required by those with conditions such as chronic heart disease, and dementia.

The present study, discussed in the following chapters, attempted to address many of the issues discussed above through an examination of sleep and cognition in adults with atherosclerotic vascular disease. The study used a sample of older adults (age 55-90) with known AVD in order to examine the relationships among vascular disease, disordered sleep and cognition in a population frequently seen in numerous care settings. Specifically, the following research hypotheses were tested:

1) Participants with diagnosed sleep disorders and AVD will be more likely to report significant daily fatigue than subjects with AVD alone, but the two groups will not differ on a measure of psychological distress.

2) Participants with diagnosed sleep disorders and AVD will perform significantly worse on objective neuropsychological testing than subjects with AVD alone.

3) Participants with diagnosed sleep disorders and AVD will have increased physiological markers of inflammatory processes, as measured by blood levels of C-reactive protein.

CHAPTER III

RESEARCH DESIGN AND METHODOLOGY

Participants in the current study were individuals enrolled in a study of aging, cardiovascular disease, and cognition at the University of Iowa Carver College of Medicine, Department of Psychiatry (Dr. David Moser, Ph.D. principal investigator). This study was fully reviewed and approved by the University of Iowa IRB. Participants were recruited for this study through the Cardiology Clinic at the University of Iowa Hospitals and Clinics. Recruitment occurred via review of medical charts by this investigator or a trained research assistant. With the permission of the potential participant's physician, patients were contacted and invited to learn more about participation in the study of cardiovascular disease and cognition. Potential participants who expressed interest were interviewed by telephone regarding inclusion and exclusion criteria and informed about the study, including time commitment, risks, benefits, and the optional nature of participation. If a potential participant appeared eligible and expressed interest, their medical records were reviewed by a physician at the University of Iowa Hospitals and Clinics in order to confirm eligibility and safety of participation. Enrolled participants who completed study visits were monetarily compensated for their participation in the study in the amount of two hundred fifty dollars for completion of all visits. Payment was prorated according to visits completed for participants who partially completed the study.

In order to be eligible for the study, potential participants were required to be between the ages of 55 and 90 with a diagnosis of atherosclerotic vascular disease made by a physician. Diagnosis was considered to have been made if the potential participant

had had one or more of the following: angina pectoris, myocardial infarction, coronary artery stent placement, percutaneous transluminal coronary angioplasty (PCTA), or peripheral vascular disease, also known as claudication. These diagnostic markers are considered to be evidence of early stage atherosclerotic vascular disease. Exclusion criteria for the study sought to minimize potentially confounding factors that might cloud the relationships among early stage AVD and cognition, such as medical events or procedures known to have significant cognitive sequelae. Exclusion criteria included the following: History of coronary artery bypass grafting surgery (CABG), history of heart valve replacement surgery or history of carotid artery endarterectomy. Also excluded were patients who had suffered a cerebrovascular accident (stroke), those who had a history of traumatic head injury with a loss of consciousness greater than 30 minutes, and patients with a history of any neurological disorder or other illness that would affect cognition, including seizure disorders, demyelinating disorders, and degenerative disorders such as Parkinson's Disease. Potential participants with a diagnosis of dementia or with a history of major psychiatric illness were also excluded (examples of these diagnoses include Alzheimer's disease, bipolar disorder, and schizophrenia). Potential participants who had suffered a transient ischemic attack (TIA) were included provided there was neuroimaging available to confirm that the event was a TIA and not a stroke.

In order to be eligible for the sleep disorder substudy, participants were required to meet all criteria above and be actively enrolled in the larger study of aging, vascular disease, and cognition described above. Participants who had withdrawn from the larger study due to relocation, illness, or had declined to complete follow-up visits were not

recruited for participation in the sleep disorder substudy. Actively enrolled participants were contacted by phone and asked if they were interested in participating in the substudy. The sub-study procedures were explained briefly, and participants who expressed interest received further information about study procedures. Those who agreed to participate, when possible, completed the sub-study materials at the time of their regular study visit. For those participants who had already completed their study visit, a cover letter and sub-study materials were mailed to them within 6 months of their most recent study visit (at the time of a regularly scheduled follow-up call) and returned by mail, using a provided addressed and stamped envelope. No additional compensation was provided for participation in the sleep disorder substudy.

Instrumentation

Participants in the larger aging, vascular disease and cognition study completed a variety of physical and neuropsychological assessments at their regular study visits, which will be described in this section. In addition, participants in the sleep disorders sub-study completed an additional measure specifically focused on disordered sleep and fatigue, which will be described following the details of the overall study instrumentation.

History and Physical Examination

All participants completed a medical history interview and a brief physical examination in the Human Cardiovascular Physiology Laboratory in the University of Iowa Hospitals and Clinics. All interviews and examinations were conducted by a physician or nurse, in order to obtain basic demographic and health related information from each participant. Information obtained included age, highest level of education obtained, current

medications, smoking status, substance use history, and previous medical diagnoses. During the physical examination, vital signs and laboratory values were obtained by a physician, nurse, or other trained medical technicians. These values included height, weight, blood pressure, heart rate, and body mass index. Participants also underwent an electrocardiogram (ECG) and a blood draw. The blood samples were analyzed to obtain serum C-reactive protein levels, as well as other variables of interest to the overall line of research. Prior to undergoing the blood draw for analysis, participants were required to fast for 12 hours, as well as withhold medications. Safety information and protocol for medication withholding was provided by a physician.

Cognitive Assessment

All participants completed a battery of tests designed to measure cognitive and psychological functioning. The instruments used were selected to provide a relatively brief (approximately 2 hours) but thorough assessment of cognitive and emotional functioning across multiple domains, including verbal and non-verbal intellectual abilities, immediate and delayed memory, attention, psychomotor speed, visuospatial abilities, executive functioning, and psychological/emotional status. In addition, the test battery allowed the investigators to exclude any participant who met DSM-IV criteria for dementia and was not excluded through medical history. The neuropsychological assessment was administered by a licensed neuropsychologist, a trained graduate student (this investigator) or a trained research assistant. All instruments used for the purposes of this study were standardized assessments with norms appropriate for the age group under investigation (55 to 90 years of age).

For the purposes of the current study, overall neuropsychological functioning as well as performance in specific cognitive domains was measured using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The RBANS yields a Total Scale Score as well as age-corrected scaled scores in the following domains: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory, each of which will be discussed further below (Randolph, 1998). Each domain score is expressed as an age-corrected scaled score with a mean of 100 and a standard deviation of 15. The total scaled score is based on the sum of the index scores, and also has a mean of 100 and a standard deviation of 15. The instrument consists of 12 subtests that measure abilities in the five domains, with each domain score derived from scores on two to four subtests. The specific subtests contributing to each domain are described in more detail below.

The Immediate Memory domain assesses a participant's ability to recall information immediately following its presentation. Two subtests comprise this domain. The first is a list learning task, in which the participant is presented with a list of ten semantically unrelated words, and asked to immediately recall as many as possible after each of four learning trials. Total recall across the four learning trials comprises the raw score for this subtest. The second subtest in the Immediate Memory domain consists of an orally presented short story. The story memory test has two learning trials, and the participant is asked to repeat as many story details as possible after each learning trial. Again, total recall across learning trials comprises the total raw score. These raw scores are combined and converted to an age-corrected scaled score (Mean = 100; SD = 15) using the appropriate conversion table provided in the RBANS manual.

The Visuospatial/Constructional domain was used to asses a participant's ability to accurately perceive spatial relations and to perform a visual construction task. Again, the domain is comprised of two subtests. In the first, the participant is shown a geometric figure with multiple distinct parts and details. The participant is then asked to produce a copy of the design that is as accurate as possible. In the second subtest, the participant is presented with a semi-circular array of 13 numbered lines. In each trial, the participant is required to match two novel stimulus lines to the lines in the numbered array with the same angle and orientation. Again, the raw scores on these subtests are combined and converted to an age-corrected scaled score.

The Language domain consists of a naming task and a verbal fluency task. The first task assesses confrontation naming ability and expressive vocabulary. The participant is shown a series of black and white line drawings of objects and asked to name each one. The second task assesses verbal fluency and lexical access, as the participant is presented with a category and asked to name as many objects in that category as possible in sixty seconds.

The Attention domain assesses both auditory and visual attention. One task requires the participant to repeat gradually longer strings of presented digits, assessing basic auditory attention. Credit is given for each string correctly repeated. In the visually-based task, the participant is required to use a key to rapidly fill in the appropriate numbers corresponding to certain geometric shapes. The raw score on this subtest consists of the number of correct responses produced in ninety seconds.

The tasks in the Visuospatial, Language, and Attention domains create a filled delay between the tasks in the Immediate Memory domain and the figure copy task, and

the final domain, Delayed Memory. Following completion of all other tasks, the participant is asked to recall or reproduce as much as possible of the 10 word list, the orally presented story, and the complex geometric figure. In addition, the participant is read a word list consisting of the ten target word and ten distracters and asked to indicate which words were on the earlier presented list, in order to assess recognition discrimination. Together, the raw scores on these tasks make up the total score in the Delayed Memory domain. The Total Scale Score can then be calculated from the five individual index scores. The sum of the five index scores is converted to the Total Scale Score, again using the appropriate conversion table provided in the RBANS manual.

Reliability of the RBANS

The reliability of a test consists of several properties, including accuracy, consistency, and stability of test characteristics and score across situations (Anastasi & Urbina, 1997). During the development and norming of the RBANS, reliability coefficients were calculated for each index, as well as the total scale score, with separate reliability coefficients calculated for each of six age groups. The overall reliability of each index was also calculated by averaging the coefficients across the six age groups using Fisher's z transformation. For the age groups under investigation in the current study, reliability coefficients (Cronbach's alpha) for the five index scores and the total scale score ranged from .78 to .94, with the average reliability coefficients for the five index scores all falling in the .80 to .88 range. The average reliability across age groups for the total scale score was .94 (Randolph, 1998).

Standard error of measurement (SEM), an indicator of the amount of error in an observed test score, is inversely related to reliability. The greater the reliability of a test

or index score, the lower the standard error of measurement, and the greater the level of confidence that can be placed in an observed score. Based upon this concept, the SEM is used to calculate the confidence interval, a range of scores within which an individual score is likely to fall. For the RBANS, SEM for each index (in index units) and the Total Scale Score was calculated across the six age groups, and the average SEM was calculated using the sum of the squared SEM for each age group and taking the square root of the result. The resulting SEMs ranged from 3.84 to 6.65, and were used to calculate the 90 and 95% confidence intervals for RBANS index and Total Scale scores, provided in Appendix 2 of the RBANS stimulus booklet (Randolph, 1998).

Test-retest reliability of the RBANS was also assessed, using a group of 40 individuals who were tested twice with identical forms of the RBANS. The average age of this group was 70.7 years, and the average time from first test to retest was 38.7 weeks. The five index scores were shown to have adequate test-retest stability, with alpha coefficients ranging from .55 to .78, and a test-retest reliability coefficient of .88 for the total scale score (Randolph, 1998). In addition, the RBANS has been shown to have an adequate degree of internal reliability consistency in a normal geriatric sample in a recent study, with a Cronbach's alpha of .86 and index score intercorrelations in the range of .25 to .79 (Gontkovsky, Beatty, & Mold, 2004).

Validity of the RBANS

The construct validity of a test is the degree to which it measures the trait or theoretical concept of interest (Anastasi & Urbina, 1997). First, it is important to establish that different subscales of a test are, in fact, measuring different constructs. In the case of the RBANS, this was determined by examining the intercorrelations between

the Index scores. As expected, the highest correlation was seen between the Immediate Memory and Delayed Memory indices, (.63) as they measure similar constructs. Correlations between these memory indexes and the other index scores ranged from .28 to .44 (Randolph, 1998). Intercorrelations between the Visuospatial, Attention, and Language index scores were similarly modest, and fell within the .30 to .40 range. This overall pattern indicates that the index scores (with the exception of the two memory indexes) are measuring substantially separate and distinct constructs (Peterson, 1998).

Comparison studies were also carried out, in order to evaluate the relationship between the RBANS and other measures. This type of study is important in examining the convergent and divergent validity of the indexes. The RBANS was compared to other measures in the categories of general intellectual ability, memory, spatial processing, attention, and language. In the area of general intellectual achievement, performance on the RBANS Total Scale score was compared with performance on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Full Scale IQ (FSIQ) score in a mixed clinical sample of adults. The correlation between the RBANS Total Scale Score and FSIQ was reasonably strong at .78 (Randolph, 1998).

The individual RBANS indexes were also compared to external measures. The Immediate and Delayed Memory indices were compared to the Verbal Memory Index of the Wechsler Memory Scale-Revised (WMS-R), and scores were correlated at .61 and .69, respectively. The Visuospatial/Constructional Index of the RBANS was compared to well-established measures of spatial processing and visual construction, the Judgment of Line Orientation test (total score) and the Rey Complex Figure test (copy total score).

The correlations between scores on these two instruments and scores on the RBANS Visuospatial/Constructional Index were .62 and .79, respectively.

The RBANS Attention Index was compared to three scores/measures: The WMS-R Attention/Concentration Index, the WAIS-R Digit Symbol subtest, and the WAIS-R Arithmetic subtest. The RBANS Attention Index was most highly correlated with the WMS-R Attention/Concentration Index at .82. Correlations with the Digit Symbol and Arithmetic subtest of the WAIS-R were more modest, at .57 and .52, respectively.

The Digit Symbol subtest was also correlated with the Visuospatial/Constructional Index of the RBANS (.62), an association that probably reflects the constructional demands of copying the required symbols. The Arithmetic subtest was also correlated with an additional domain, the Immediate Memory Index (.58), which may reflect the requirement of holding verbal arithmetic problems in working memory for processing. Finally, the RBANS Language Index was strongly correlated with two well-known measures of confrontation naming and verbal fluency. The correlation with the Boston Naming Test was .75, and the correlation with the Controlled Oral Word Association Test was .59 (Randolph, 1998). These comparisons with external measures, across domains, were used to demonstrate the RBANS measures the intended constructs, both with regard to overall intellectual/cognitive functioning and with regard to more specific cognitive skills and domains.

Psychological Functioning

Assessment of mood and psychological functioning was conducted using the Symptom Checklist-90-Revised (SCL-90-R). SCL-90-R is a self-report measure that

allows participants to rate the extent to which they were distressed by particular symptoms along a continuum from zero (not at all) to four (extremely). It provides an overall T-score (Mean of 50, standard deviation of 10) measuring level of psychological distress as well as T-scores in nine individual domains (Derogatis, 1994). The domain scores that can be obtained using this instrument are listed below, along with example symptoms (which respondents rate from zero to four) from each domain. On the questionnaire itself, each symptom is preceded by the statement "How much were you distressed by:" and the respondent is asked to rate how much that symptom or problem has distressed or bothered them in the past seven days.

1) Somatization: 12 items make up the somatization score, including "headaches," "nausea or upset stomach," and "soreness of muscles."
2) Obsessive-Compulsive: The score on this domain is obtained from 10 items, including "repeated unpleasant thoughts that won't leave your mind", "having to check and double-check what you do", and "having to repeat the same actions".
3) Interpersonal Sensitivity: This score is derived from 9 items, including "your feelings being easily hurt" and "feeling very self-conscious with others".
4) Depression: This domain is comprised of 13 items, including "loss of sexual interest or pleasure", "thoughts of ending your life", "feeling blue", and "feelings of worthlessness".
5) Anxiety: This score is determined by responses to 10 items, including "trembling", "feeling fearful" and "feeling so restless you couldn't sit still".
6) Hostility: Composed of 6 items, including "feeling easily annoyed or irritated" and "getting into frequent arguments".

7) Phobic Anxiety: Seven items, including “feeling afraid in open spaces or on the streets” and “having to avoid certain things, places, or activities because they frighten you”.
8) Paranoid Ideation: Six items, including “feeling that most people can’t be trusted” and “having ideas or beliefs that others do not share”.
9) Psychoticism: This final dimension consists of 10 items, including “hearing voices that other people do not hear”, “other people being aware of your thoughts” and “never feeling close to another person”.

In addition, the SCL-90-R contains seven items or symptoms that are not categorized under any of the nine symptom dimensions, but rather load concurrently on several of the dimensions. These items contribute to the global scores provided by the SCL-90 and include items such as “poor appetite”, “feelings of guilt” and “sleep that is restless or disturbed”.

The SCL-90-R generates three global scores, which are general indices of distress. These are the Positive Symptom Distress Index (PSDI), the Positive Symptom Total (PST), and the Global Severity Index (GSI). The PSDI reflects the average level of distress reported for symptoms that were endorsed, and functions as a measure of response style and symptom intensity. The PST is an indicator of the number of symptoms endorsed, regardless of intensity, and can be interpreted as a measure of breadth of overall symptoms. The GSI combines these factors, and this global score provides an indicator of both number of symptoms endorsed and the intensity of associated distress. According to the test manual, the GSI is recommended for use in most instances when a single summary score is needed (Derogatis, 1994).

For the purposes of the current study, only the GSI was used. There are several reasons for this. First, it is not feasible from a statistical power standpoint to compare groups on all nine domains. While a single domain (e.g. depression) could be used, this process could result in participants with other sources of psychological distress being missed. For the purposes of this study, an overall summary score of psychological distress was desired, and the GSI is the best option for providing this information, according to both the test manual and additional separate studies.

For example, one study found that the GSI accounted for 30.5% of the variance in SCL-90-R responses (Steer, Clark, & Ranieri, 1994), suggesting that using overall responses on this instrument to generate a global measure of psychological distress is a valid scoring approach. Some researchers have also called into question the dimensionality of the SCL-90-R, due to difficulty replicating the nine factor groups (Clark & Freidman, 1983). The finding that the SCL-90-R measures a single global distress factor rather than nine distinct domains has been replicated with several populations, including psychiatric outpatients (Evenson, 1980), patients with substance abuse disorders (Zack et al. 1998), psychiatric inpatients (Rauter et. al. 1996), and community samples in Germany and Norway (Schmitz et. al 1999; Vassend & Skrondal, 1998). While some factor analytic studies have suggested between two and six separate dimensions (Derogatis 2000), the research outlined above raises questions about using the SCL-90-R as a dimensional instrument. This, combined with statistical power issues and the desire for an overall measure of psychological distress, led to the use of GSI rather than any of the nine domain scores in the present study.

In terms of psychometric properties of the SCL-90-R and the GSI specifically, internal reliability coefficients for the individual domains ranged from .77 to .90 in two separate studies (one conducted with non-patient volunteers and one with psychiatric outpatients), with coefficients for the GSI of .82 and .85 (Derogatis, 1994). Test-retest reliability coefficients were similar across the two studies, ranging from .68 to .90 with 10 weeks elapsed between testing (Derogatis, 1994). A series of validity studies published by Peveler and Fairburn (1990) compared the SCL-90-R to numerous other instruments, including the Present State Examination and the Beck Depression inventory. These studies found correlations of between .60 to .82 between the SCL-90-R and the like domains of the PSE. A comparison of the SCL-90-R depression domain and the BDI showed a correlation of .80.

Sleep Disorder Sub-Study Instrumentation

Participants who agreed to participate in the current sleep disorder study and were actively enrolled in the overall aging, vascular disease and cognition parent study completed all the measures above and an additional measure of fatigue and sleep disruption. As part of the sleep disorder study, the University of Iowa Hospitals and Clinics medical records of all participants enrolled were thoroughly reviewed to confirm the absence or presence of a sleep disorder diagnosis. A participant was classified as sleep-disordered if the medical chart contained a diagnosis of sleep disorder made by a physician. For the purposes of the current study, diagnosis may have been made either through a careful history and review of symptoms or a formal sleep study. If the diagnosis of sleep disorder was made outside the University of Iowa Hospitals and Clinics, it was confirmed by the subject's current physician or through the presence of

scanned documentation from an outside institution in the University of Iowa electronic medical record. While there is variability in the process of diagnosing a sleep disorder, it was assumed for the purposes of this study that physicians utilized substantially similar criteria in reaching a diagnosis, such as the criteria provided by the ICSD or the AASM (previously reviewed in this paper).

Self-reports of sleep disruption and its associated symptoms were assessed using the Berlin Questionnaire. This measure used questions selected from the sleep disorder literature that consistently predicted the presence of sleep disordered breathing across studies (Redline & Strohl, 1998). Although the Berlin Questionnaire was originally designed to identify patients with sleep apnea, its content and psychometric characteristics make it very suitable for the current study of sleep disruption.

The Berlin Questionnaire, unlike many self-report measures of sleep, addresses multiple domains of sleep disruption. The respondent is asked to report on snoring, fatigue upon awakening, daytime fatigue, and certain cardiovascular risk factors. Additional unique features of Berlin Questionnaire include a question on collateral awareness of sleep disruption (i.e. a sleeping partner or roommate) and a question concerning sleepiness while driving. Respondents are also asked whether they suffer from high blood pressure, and are asked to report height and weight for the purpose of a body mass index calculation. These assessments of multiple components of sleep disruption and the consideration of cardiovascular risk factors make the Berlin Questionnaire well suited for the population and questions under investigation in the current study.

The Berlin Questionnaire was designed as a way to identify patients at risk for obstructive sleep apnea without a costly sleep study. Because of the serious nature of OSA, it was essential that any diagnostic instrument used to identify this disorder be valid and reliable. Consequently, the Berlin Questionnaire was subjected to validation studies in the primary care setting. The primary validation study of the Berlin Questionnaire was carried out with 744 adults who completed the questionnaire, with 100 of the subjects also undergoing a comprehensive clinical sleep study, or polysomnography. (Netzer, Stoohs, Netzer, Clark & Strohl, 1999).

The researchers found that the measure had adequate internal validity, as measured by reliability among individual questions within symptom categories. For sleep disordered breathing symptoms, the Cronbach's alpha value was 0.92, and for fatigue symptom questions, Cronbach's alpha was 0.86. In addition, results from the 100 subjects who underwent a sleep study showed that the Berlin Questionnaire has good predictive sensitivity. The questionnaire was examined in relationship to the respiratory distress index (RDI) which is used in the diagnosis of sleep apnea after a clinical sleep study. The researchers found that those who scored above clinical cut-off ("high risk") on the Berlin questionnaire were more likely to have a RDI of greater than 5 during sleep study, which is indicative of obstructive sleep apnea. The Berlin Questionnaire predicted an RDI of greater than 5 with a sensitivity of 0.86, specificity of 0.77, and a positive predictive value of 0.89 (Netzer et. al. 1999). The researchers conclude that the Berlin Questionnaire is an acceptable instrument for identifying patients at high risk for obstructive sleep apnea, pointing out that the sensitivity of 86% is higher than any strategy currently in clinical practice.

Although originally intended for the identification of patients at high risk for sleep apnea, the Berlin Questionnaire was selected for the current study of disordered sleep, vascular disease, and cognition for several reasons. First, it is the only available self-report measure that assesses multiple symptom domains including cardiovascular risk factors, and it allows for the generation of a separate daytime fatigue score based on multiple items, rather than a single question. Secondly, the questionnaire was subjected to study of its psychometric properties and was found to be a sound instrument. The daytime fatigue items were shown to have adequate internal reliability, and the questionnaire was shown to be valid in terms of predictive sensitivity. In the current study, many of the difficulties of using a self-report instrument will be eliminated due to the availability of complete medical records including any sleep studies for all participants. However, it is still important to use a self-report measure that is well-accepted and studied. The Berlin questionnaire is used frequently throughout the sleep disorder literature, and importantly, has been used and validated in the primary care setting, rather than exclusively relying on sleep disorder referrals (Netzer et al. 1999; Netzer et al 2003; Harding 2001). Because the population under investigation is not a sleep clinic population, it is desirable that the instrument used has been validated in the primary care setting. Finally, the Berlin Questionnaire was designed to take into account cardiovascular risk factors. Again, the current study has the advantage of medical records and specifically collected research data on these factors, and need not rely on self-report of variables such as blood pressure and body mass index. However, the suitability of the instrument to the population remains important, and again the Berlin

Questionnaire provides a good match through its consideration of certain cardiac variables.

In order to make the questionnaire suitable for the current study, one additional item was added. This final item asks respondents to report if they have ever been diagnosed with a sleep disorder, including insomnia, restless leg syndrome, REM sleep disorder, or any other sleep disorder (See Appendix 1 for a complete copy of the revised version of the Berlin Questionnaire used in the current study). Again, this self-report was confirmed by medical record review, but the opportunity to self-report assists in facilitating the review and gives the opportunity for respondents to report a diagnosis that may have occurred outside the University of Iowa health care system. In case of a discrepancy, medical record review and/or physician report were the deciding factor in determining whether a diagnosis exists, and served as the deciding factor for the purposes of dividing the participants into two groups (sleep disordered versus non sleep disordered).

When dividing participants into these groups, a diagnosed sleep disorder was the grouping variable. However, a number of participants in the current study had a diagnosis of obstructive sleep apnea. While this is clearly a sleep disorder that produces disruption of normal sleep patterns and fatigue/daytime sleepiness, OSA has the additional complicating factor of hypoxia. Since it was not possible, in the current study, to separate the cognitive consequences of hypoxia from the cognitive consequences of disrupted sleep in OSA patients, all participants with diagnosed OSA were excluded from the analysis. In addition to the complicating factor of hypoxia, OSA patients had varying ongoing treatments with varying degrees of compliance and success, introducing the

additional complication of cognitive amelioration by CPAP versus long-term, irreversible hypoxic changes. While the OSA subset of the sample may provide data for future analyses, these complicating factors resulted in their exclusion from the current analyses. The table below summarizes the inclusion and exclusion criteria and decision process for the sleep disorder sub-study.

Table 1. Criteria for inclusion in sleep disordered, non sleep disordered, and excluded groups.

Grouping Variable	Included: Sleep Disordered	Included: Non-sleep disordered	Excluded
Diagnostic Status	Diagnosis of a known sleep disorder is self-reported AND documented in medical chart, with diagnosis by a physician.	Presence of a sleep disorder is self-reported, but not documented in medical chart. No diagnosis by a physician.	Current diagnosis of obstructive sleep apnea
	No self-report of sleep disorder. Diagnosis of known sleep disorder is documented in medical chart with diagnosis by physician	No self report, AND no sleep disorder diagnosis documented in medical chart. No diagnosis by physician.	Previous diagnosis of obstructive sleep apnea with surgical correction documented in medical chart.

Statistical Analysis

All statistical analyses were conducted using SPSS 15.0 for Windows. Analysis of variance or independent sample T tests were used to compare groups for each of the following research hypotheses:

1) Subjects with diagnosed sleep disorders and AVD will report higher levels of daily fatigue than subjects with AVD alone. However, the two groups will not differ significantly in terms of psychological distress, a potentially confounding variable. An independent samples T test will be used to compare the daily fatigue score (measured using the Berlin Questionnaire) and the GSI score on the SCL-90-R of the two groups.

2) Subjects with diagnosed sleep disorders and AVD will perform significantly worse on objective neuropsychological testing than subjects with AVD alone. Performance on the RBANS Total Scale score will be compared using an independent samples T test. Multivariate analysis of variance will be used to further analyze performance on the RBANS, as subscales of the overall instrument are correlated with one another. If the overall MANOVA is significant, the separate cognitive domains assessed by the subscales will be examined individually.

3) Subjects with diagnosed sleep disorders and AVD will have increased physiological markers of inflammatory processes, as measured by serum levels of C-reactive protein. The two groups will again be compared using an independent samples T test with regard to blood levels of the inflammatory marker.

Summary

Participants in a longitudinal study of aging, vascular disease and cognition at the University of Iowa Hospitals and Clinics completed a history and physical examination, laboratory tests of cardiovascular function and risk factors, and a neuropsychological assessment during their regularly scheduled study visit. Eligible (currently enrolled)

participants in this longitudinal study were recruited for participation in a sub-study examining disordered sleep and its relationship to cognitive performance and cardiovascular disease. Participants who agreed to participate in the substudy completed the Berlin Questionnaire as a measure of sleep disruption during their regular study visit or by mail within six months of their study visit. The mean time that elapsed between a participant's study visit and the completion of the Berlin Questionnaire was 4.2 weeks (SD = 2.7), with a range of zero days (for participants who completed the questionnaire during the study visit) to 38.4 weeks, for one participant who completed the questionnaire following their scheduled 6-month follow up call. The Berlin Questionnaire in combination with medical record review was used to assess fatigue, symptoms of sleep disruption, and the presence of a sleep disorder diagnosis. Participants were grouped according to the presence or absence of a sleep disorder diagnosis, including but not limited to insomnia, restless leg syndrome, and REM sleep disorder. Although these are heterogenous disorders, the purpose of the current study was to examine the common factor of disrupted sleep in general and its impact on cognition and inflammatory cardiovascular disease processes. Therefore, participants with a diagnosis of sleep apnea (who have disrupted sleep, but whose clinical picture is complicated by hypoxia and treatment factors) were excluded.

Subsequent to grouping of participants into "sleep disordered" and "non sleep disordered" categories, data from the two groups was compared using T tests or MANOVA. The two groups were compared in terms of daily fatigue, psychological distress, performance on standardized neuropsychological tests, and a serum marker of cardiovascular and inflammatory disease processes. These analyses allowed for a closer

examination of the relationship between disordered sleep, cardiovascular disease, and cognitive impairment in the aging population.

CHAPTER IV

RESULTS

A total of 71 participants met eligibility requirements, were recruited for participation, and completed participation in the sleep disorders substudy. Of those 71 participants, one was diagnosed with dementia in the course of the study and was subsequently excluded from analysis. Nineteen subjects had a previous diagnosis of sleep apnea and were excluded from the current analysis, as discussed previously in the methods section. Thus, 51 total individuals completed participation and are included in the analysis. The overall sample was comprised of 23 women (45 percent) and 28 men (55 percent). With regard to ethnicity, the composition of the sample was Caucasian (50 participants) and African American (1 participant).

Table 2. Gender composition of overall sample (N = 51)

Gender	N	Percent
Male	28	55
Female	23	45

Table 3. Ethnic composition of overall sample (N = 51)

Ethnicity	N	Percent
Caucasian	50	98
African American	1	2

Participants had an average age of 68.25 years, and had completed an average of 14.5 years of education. In terms of health status, participants had cardiovascular disease for an average of 8.5 years at the time of their enrollment, and the sample had an average body mass index of 29.6, which falls in the "overweight" range according to the Center for Disease Control criteria. See Table 4 for a summary of the overall sample characteristics.

Table 4. Overall Sample Demographics and Health Status (N = 51)

Variable	Minimum	Maximum	Mean	SD
Age	55	88	68.25	8.1
Education	9	20	14.5	2.8
CVD Duration (Years)	<1	35	8.5	8.9
BMI	17.8	53.8	29.6	6.7

Non Sleep Disordered Group Characteristics

The demographic and health related characteristics of the two study groups were also examined separately. In the non sleep disordered group, there were 31 total participants. The gender composition of this group consisted of 18 males and 13 females, and 31 participants (or 100 percent) were Caucasian. With regard to demographics and health status, characteristics were similar to the overall group and are summarized in Table 5.

Table 5. Non Sleep Disordered Group Demographics and Health Status (N = 31)

Variable	Minimum	Maximum	Mean	SD
Age	55	88	68.7	8.9
Education	11	20	15	2.7
CVD Duration	<1	35	6.1	7.4
BMI	17.8	42.8	28.9	5.2

Sleep Disordered Group Characteristics

The sleep disordered group consisted of 20 total participants, with an evenly split gender distribution (10 males and 10 females) and an ethnic composition similar to the overall sample (19 Caucasian, 1 African American). Additional demographics and health status information for the sleep disordered group of participants are summarized in Table 6 below.

Table 6. Sleep Disordered Group Demographics and Health Status (N = 20)

Variable	Minimum	Maximum	Mean	SD
Age	55	80	67.7	6.8
Education	9	20	13.7	2.8
CVD Duration	.25	30	12.6	10
BMI	22.3	53.8	30.7	8.5

Group Comparisons: Demographics

When the sleep disordered and non-sleep disordered groups were compared in terms of demographic variables, there were no significant differences between groups in age, education, cardiovascular disease duration, or BMI. A trend was seen in which the

sleep disordered group had a longer duration of cardiovascular disease (M = 12.6, SE =2.41) than the non sleep disordered group (M = 6.1, SD = 1.37) prior to enrollment, but this result did not reach significance using a Bonferroni-corrected significance level of .007.

Table 7. Demographic Group Comparison (N = 51)*

Variable	Sleep Disorder	Mean/SD	Standard Error	t	DF	Sig.
Age	N	68.7/8.9	1.6	.427	49	.671
	Y	67.7/6.8	1.5			
Education	N	15/2.7	.48	1.72	49	.092
	Y	13.7/2.8	.63			
CVD Duration	N	6.1/7.4	1.4	-2.54	49	.015
	Y	12.6/10	2.4			
BMI	N	28.9/5.2	.94	-.937	49	.354
	Y	30.7/8.5	1.9			

*Bonferroni-corrected significance level = .007

Research Hypotheses

The sleep disordered and non sleep disordered groups were next compared with respect to the main research hypotheses, concerning fatigue/emotional distress, blood levels of an inflammatory pathology marker, and performance on cognitive testing. The first three variables were analyzed using independent sample T tests, and are discussed individually below.

Fatigue

The two groups were compared on their self-reported level of daily fatigue, as measured by subjects' responses on the Berlin Questionnaire. On average, the sleep disordered group reported a higher degree of daily fatigue (M = 5.6, SE = .47) than the non sleep disordered group (M = 3.2 SE = .52): ($t(49) = -3.8$; $p<.001$).

Psychological Distress

The sleep disordered and non sleep disordered groups were compared on psychological distress, using scores on the Global Severity Index of the SCL-90-R. Average scores were within the normal or (non-clinical) range for both the sleep disordered group (M = 55.2, SE = 1.4) and the non sleep disordered group (M = 51.9, SE = 1.8) and the difference between the two group was not significant ($t(49) = -1.3$); $p > .05$)

Inflammatory Marker Levels

In order to provide a measurement of inflammatory pathology, participants underwent a blood draw that was subsequently analyzed for the presence of an inflammatory marker known as C-reactive protein. When the two groups were compared, both had CRP levels that fell in the elevated range (>3mg/L) with the sleep disordered group having a slightly higher average CRP level (M = 6.2, SE = 1.55) than the non-sleep disordered group (M = 5.0, SE = 1.34). However, this difference was not significant ($t(46) = -.55$; $p >.05$).

Table 8. Fatigue, Emotional Distress, and Inflammatory Pathology Group Comparisons (N = 51)

Variable	Sleep Disorder	Mean/SD	Standard Error	t	DF	Sig.
Fatigue	N	3.2/2.6	.47	-3.8	49	.001*
	Y	5.6/2.3	.52			
Psychological Distress	N	51.9/9.8	1.7	-1.3	49	.186
	Y	55.2/6.4	1.4			
C-Reactive Protein Level	N	5.0/8.4	1.6	-.55	46	.583
	Y	6.2/5.8	1.3			

* Significant at Bonferroni-corrected significance level of .007

Cognitive Test Performance

Cognitive performance was measured using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the two groups were compared on the total score as well as on the individual cognitive domain scores produced by the instrument. First, the two groups were compared with regard to their overall performance on cognitive testing, as measured by the RBANS Total Scale score. Recall that the Total Scale score is obtained from the five index scores, and is an age-corrected scaled score with a mean of 100 and a standard deviation of 15. When the two groups were compared, the non sleep disordered group had a higher mean RBANS Total Scale Score (M = 102.8, SE = 1.7) than the sleep disordered group (M = 92.9, SE = 2.4). This difference was significant (p = .001), indicating that the non sleep disordered group had significantly better overall performance on the RBANS than the sleep disordered group. The performance of the sleep disordered group, while still within the average range for age, was (on average) below the mean of 100 and somewhat below expectations,

particularly given that this group of participants had a relatively high level of education (an average of approximately 14 years).

Table 9. RBANS Total Scale Score group comparison (N = 51)

Variable	Sleep Disorder	Mean/SD	Standard Error	t	DF	Sig.
RBANS Total Scale Score	N	102.8/9.5	1.7	3.475	49	.001
	Y	92.9/10.7	2.4			

To further analyze the performance of the two groups, additional analysis was carried out to examine the RBANS index scores, representing performance on the five subscales of the instrument. Because scores on the individual subscales of the RBANS are correlated with one another, analysis of the cognitive test scores was conducted using a one-way Multivariate Analysis of Variance (MANOVA). The dependent variables used were the five subscales of the RBANS: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. The independent variable was presence of a diagnosed sleep disorder. A significant difference was seen between groups on the combined dependent variable, representing overall RBANS performance ($p = .012$). When the results of the dependent variables (Specific cognitive domains) were examined separately, using an alpha level of .05, three individual domains reached statistical significance: Immediate Memory ($p = .044$) Visuospatial/Constructional ($p = .01$) and Attention ($p = .004$). An inspection of mean scores revealed that the sleep disordered participants scored consistently lower that the

non-sleep disordered participants on all measures of cognitive functioning. However, only the domains noted above reached the level of significance.

Table 10. Cognitive testing group comparison (N = 51)

Manova	Wilk's Lamda Value		F		Sig
Overall	**.**663		2.42		**.**012*
Variable	Sleep Disorder	Mean/SD	Standard Error	F (1, 49)	
Immediate Memory	N	106.2/12	2.1	3.3	.044*
	Y	95/13	3		
Visuospatial	N	101.6/13.7	2.5	4.99	.010*
	Y	89.3/17	3.8		
Language	N	100.6/11.2	2.0	.095	.909
	Y	100.4/9.7	2.2		
Attention	N	103.4/12.5	2.2	6.1	.004*
	Y	91.3/15.9	3.6		
Delayed Memory	N	100.1/14.3	2.6	.24	.790
	Y	99.3/8.2	1.8		

*Significant ($p < .05$)

Summary

When sleep disordered and non-sleep disordered participant groups were examined with regard to demographics and research hypotheses, the following results

were found: The two groups did not differ significantly in terms of age, education, duration of cardiovascular disease, or BMI. There was a significant difference in reported fatigue level, with the sleep disordered group reporting a significantly higher level of daily fatigue that the non sleep disordered group. No significant differences were seen between groups with regard to psychological distress as measured by the SCL-90-R or inflammatory pathology as measured by C-reactive protein. With regard to cognitive functioning, the two groups differed significantly in terms of their overall RBANS performance, as shown by a T test of RBANS Total Scale score as well as a significant overall MANOVA. In addition, the performance of the sleep disordered group, on average, fell below the mean and somewhat below expectations for the age and education of the participants. When dependent variables were examined specifically, mean scores on cognitive testing were consistently lower for the sleep disordered group. This difference reached the level of significance in the domains of Immediate Memory, Attention and Visuospatial/Constructional functioning.

CHAPTER V

DISCUSSION

The results of the current study indicate that sleep disordered and non sleep disordered individuals differ significantly in terms of daily fatigue and aspects of cognitive functioning, while significant differences were not seen in psychological distress or inflammatory pathology. Each research hypothesis and the relevant results will now be discussed with respect to relationship to the available literature, implications, and possible future directions of avenues of investigation. Finally, the strengths and limitations of the current study will be outlined and discussed and, following a summary of discussion points, clinical implications of the current study will be considered.

Research Hypothesis: Fatigue

The finding that, as hypothesized, the sleep disordered group reported a significantly higher level of daily fatigue is a somewhat intuitive result, but important to examine due to the population being studied. Fatigue is consistently related to disrupted sleep in the literature, particularity in the case of older adults (Cooke & Ancoli-Israel, 2006), but a strong relationship has also been shown between cardiovascular disease and increased fatigue levels (e.g. Denollet, 1993). In the present study, a significant difference in reported fatigue was seen between the two groups although both groups had a significant cardiovascular disease history, reinforcing the idea that there is a strong link between disrupted sleep and daytime fatigue in a cardiovascular population, and that fatigue levels did not reach a "ceiling" as a result of the participants' health status.

The construct under investigation in the current study was a general definition of disrupted sleep, defined through the assumption that those with diagnosed sleep disorders

experience some form of disruption of the sleep-wake cycle with consequent reduced restful sleep and increased daytime fatigue. However, some literature (e.g. Durmer and Dinges, 2005) has recently begun to distinguish between sleep deprivation and sleep fragmentation as distinct forms of disrupted sleep. Sleep deprivation is defined as an increase in wake time and decrease in total sleep time, while sleep fragmentation refers to brief, frequent arousals that occur during sleep, and may not result in full awakening. Sleep deprivation is thought to be more characteristic of insomnia, while sleep fragmentation is thought to be related to disorders such as restless leg syndrome and sleep apnea (Durmer & Dinges, 2005). The current study examined the larger construct of disrupted sleep, which itself remains somewhat understudied. However, a possible future research direction in the area of sleep and fatigue may include examining deprivation and fragmentation as separate constructs, either through sleep studies or through division by diagnosis (e.g. separating insomnia, RLS, and apnea into distinct groups) and analyzing their differential relationships with daytime fatigue levels.

Research Hypothesis: Psychological Distress

The two groups in the current study were both in the non-clinical or "normal" range with regard to their scores on a measure of psychological distress, and were not significantly different from one another, as hypothesized. This result is important for several reasons. First, older adults with a chronic illness may experience increased rates of depression. When older adults with cardiovascular disease are examined specifically, research suggests that 15-22% meet criteria for major depression (Carney, Freedland, Eisen, Rich, & Jaffee, 1995; Carney et. al. 1990). Compounding this issue is the question of chronic disrupted sleep, which has also been related to depressed mood and increased

psychological distress (Vanderputte & de Weerd, 2003). As a result, it was important to examine the distress levels of both groups and determine whether there was a differential effect on the sleep disordered group, or whether both groups had elevated levels of psychological distress as a result of their health status. As hypothesized, the two groups in this case did not differ in terms of their emotional distress level, and in addition, both were within the normal or non-clinical range with regard to their total distress level.

This is also important due to the potential effects of psychological distress on the other variables being examined. Psychological distress level can affect both fatigue (discussed above) and aspects of cognitive functioning (discussed below). Since the two groups did not differ in terms of their distress levels, we can have a reasonable level of certainty that differences seen in other domains are not related to psychological distress. One possible reason for the lack of difference in psychological distress between the two groups may be related to sample characteristics. The sample in the current study was comprised of individuals with a relatively high level of educational attainment and good access to health care. They were all generally medically well-managed and closely followed by their healthcare teams. Thus, participants in this study may be more apt to have sought treatment for depression or other sources of psychological distress.

In addition, participants with obstructive sleep apnea were excluded from the present analysis. Research suggests that patients with OSA have a higher degree of depression and psychological distress than the general population and than patients with other sleep disorders, as outlined in an extensive 2005 review by Schroder and O'Hara. Possible explanations for this include the association of OSA with obesity and metabolic syndrome, as well as the subcortical white matter brain changes that are seen in chronic

hypoxia and have been shown to be related to depression in OSA (Macey et. al, 2006). A potential future direction for investigation is to compare a group of patients with sleep apnea to those with other sleep disorders as well as non-sleep disordered controls in terms of their level of psychological distress. For the purposes of the present study, however, the two groups did not differ and neither group's average score on the Global Severity Index of the SCL-90-R was outside the normal range, indicating that the observed group differences in fatigue and cognitive functioning are not likely to have been impacted by psychological distress levels.

Research Hypothesis: Inflammatory Pathology

As discussed earlier in the literature review, there is some indication that cardiovascular disease and disordered sleep may share some common physiological and pathological factors, one of which is inflammatory pathology. C-reactive protein (CRP) has been found to be elevated in both atherosclerotic vascular disease and sleep apnea (Quan & Gersh, 2004), but its association with other forms of disordered sleep (e.g. those that do not involve a hypoxic process) is less clear. In the current study, contrary to the original hypothesis, no significant difference in C-reactive protein levels was seen between the sleep disordered and non sleep disordered groups. Both groups had moderately elevated levels of CRP, which is an expected finding given that both groups suffer from atherosclerotic vascular disease. The sleep disordered group had a higher mean CRP level, but not significantly so.

There are several potential reasons for this finding. First, as mentioned previously, this is a relatively tightly medically managed group who, as a whole, are pharmacologically well-controlled with regard to blood pressure, diabetes, and other

pathological processes related to CRP levels. This may have resulted in a ceiling effect on their serum CRP levels. An additional factor that may be at work, as with psychological distress, is the exclusion of the subjects with sleep apnea. Since there is a known relationship between sleep apnea and elevated CRP, those subjects with the highest values may have been excluded from analysis. This leads to the next point for consideration: Sleep disorders other than sleep apnea may not have as strong a relationship with inflammatory pathology. Given that the disrupted sleep under consideration here does not involve hypoxia, there may be less effect on the inflammatory cascade, leading to similar levels to those found in cardiovascular disease alone. However, this is an avenue for further investigation. Comparing larger groups of subjects with apnea, other sleep disorders, and non sleep disordered individuals will help to clarify this issue. Additionally, future studies working to clarify this relationship may wish to examine multiple physiological markers in addition to CRP. Although no significant difference was found in CRP levels in the current study, there is still ample evidence to suggest a physiological connection between disrupted sleep and cardiovascular (as discussed in the literature review) and this is clearly an area that merits further investigation.

Research Hypothesis: Cognitive Functioning

At the study outset, it was hypothesized that the sleep disordered group would perform more poorly on standardized cognitive testing than the non sleep disordered group, and this hypothesis was borne out both in terms of overall neuropsychological functioning and in terms of specific cognitive domains. First, the two groups differed significantly in the expected direction on RBANS Total Scale score and the combined

dependent variable representing overall cognitive test performance. This is an important finding for several reasons. First, it establishes that there is a relationship between disrupted sleep and cognitive functioning using a standardized, objective instrument. As discussed previously, many studies of disordered sleep and cognition rely on self-report of cognitive difficulties rather than objective cognitive testing (e.g. Ohayron & Vecchierini, 2002; Phillips et al., 2006). While this allows the collection of larger sample sizes, this method of cognitive assessment is problematic. Previous research by this investigator showed that self-reported cognitive difficulties were not correlated with objective cognitive test performance in older adults with cardiovascular disease (Humphreys et. al., 2007). Therefore, the current study took the important step of using an objective, standardized instrument to assess cognitive functioning.

In previous studies that did make use of objective tests, measures were often very brief (e.g. a single test such as the Mini Mental Status Exam) or tests were used in isolation to assess various cognitive constructs. The use of the RBANS in the present study allows for a measure of overall cognitive functioning as well as validated subscales that allow examination of individual cognitive domains. There have been relatively few studies that make use of a multi-domain overall cognitive score in examining the cognitive effects of disordered sleep. The significant result in this case is important in establishing that a total scale score on a multi-scale instrument can detect cognitive dysfunction in disordered sleep, which is often thought to be highly domain-specific (e.g. limited to basic attention). This result suggests that the cognitive impacts of sleep disorders may be more global and pervasive than some of the research literature suggests (e.g. Fulda and Schulz, 2001). However, it remains essential to examine the individual

cognitive domains involved in order to elucidate the specific relationships between sleep and cognitive functioning.

In the current study, there was a significant difference in the expected direction in the Attention domain score on the RBANS. This finding is highly consistent with previous research in two main areas. First, the relationship between obstructive sleep apnea and impaired attention has been well established in the literature. There have been numerous studies documenting that patients with OSA perform more poorly on auditory and visual tests of attention, including driving simulations, across the life span (e.g. Arens et. al. 2000; Kim et. al. 1997). Secondly, the relationship between impaired attention and total sleep deprivation has been established in multiple studies though controlled laboratory research (See e.g. Durmer & Dinges, 2005; Kavanau 1997; Pandi-Perumal & Monti, 2005).

Currently, some research suggests that brief but total sleep deprivation (often 1-2 days) does not accurately replicate chronically disrupted sleep and some studies have moved toward a method of chronic partial sleep restriction. In this research paradigm, subjects experience repeated days of restricted sleep but are not completely deprived. This method is considered to be a closer replication of disordered sleep and subjects in these conditions have also shown deficits in attention (Durmer & Dinges, 2005). While a closer approximation, it remains difficult to adequately replicate a sleep disorder in laboratory conditions. In addition, 14 days of partial sleep restriction may not create effects comparable to disordered sleep that lasts for months to years.

Thus, the current study adds an important piece to the literature on sleep and attention by using subjects with known sleep disorders other than sleep apnea. This is an

area that has been studied infrequently, and often, as discussed previously, with heavy reliance on self-report measures. In addition, there have been very few studies on the impact of non-apnea sleep disorders in a cardiovascular population. Therefore, the result obtained here, while consistent with previous literature, is novel in many ways. Attention score, as measured by both an auditory and visual task that combine to form a standardized domain score, is significantly lower in a sleep-disordered group of cardiovascular patients, even when those with apnea (and probably hypoxia) are excluded. In the future, it will be both beneficial and interesting to compare the two groups studied here to the third available group of subjects with sleep apnea, in order to further clarify the roles of sleep, hypoxia, and cardiovascular disease in attentional function.

In addition to the domain of attention, a significant difference was seen in the expected direction on the Visuospatial/Constructional domain of the RBANS. As mentioned previously, this domain assesses skills in spatial relations and ability to visually synthesize and construct (draw) an object. Visuospatial skills have traditionally received little attention in the sleep disorder literature. Again, the majority of the sleep disorders research has historically focused on sleep apnea. In apnea studies, tests of sustained and brief attention, working memory, vigilance, and immediate and delayed verbal memory have been used most frequently (Durmer & Dinges, 2005) with little to no assessment of visuospatial functions found in most studies (with the exception of a handful of pediatric sleep apnea studies, e.g. Gozal et. al. 2006; Arens et. al. 2000).

An explanation for this omission can be found in the proposed model for cognitive dysfunction in sleep apnea, which implicates the prefrontal cortex.

Dysfunction in the prefrontal cortex is thought to result from the combination of disrupted sleep and intermittent hypoxia that occurs in sleep apnea, and leads to cognitive sequelae in the realm of attention and executive dysfunction (e.g. regulation of attentional arousal, working memory, cognitive flexibility). This carefully developed model has lead to a focused approach in assessing the daytime effects of OSA (Beebe & Gozal, 2002), which often does not allow for the inclusion of visuospatial testing. Perhaps because sleep apnea has served as a model for subsequent sleep disorder research, visuospatial testing continues to be rare in the literature, with research on all types of sleep disruption focused heavily, and in many ways accurately, on attention and working memory (Durmer & Dinges, 2005).

In the present study, the structure of the RBANS presented the opportunity to examine the relatively unstudied area of visuospatial dysfunction in sleep disorders, and a significant difference was seen. The tasks involved require both accurate visual perception and construction, and are not timed in order to avoid the impact of processing speed. The fact that the sleep disordered group performed more poorly in this domain indicates that they had increased difficulty with the synthesis, organization, and accurate judgment of visual information. Although visuospatial functioning is not often formally assessed in sleep disorder studies, there are commonly used tasks that may be tapping these abilities. The most salient example is perhaps the prevalence of driving simulation studies in sleep research (Durmer & Dinges, 2005). While often categorized as a test of divided attention, reaction time, and vigilance, performance in a driving simulator also requires significant use of visuospatial skills (Juniper, Hack, George, Davies, & Stradling, 2000).

While driving, in life or in a simulation, we are required to make frequent spatial judgments and synthesize and mentally organize visual information. The fact that subjects with sleep disorders perform more poorly in driving simulations may be, in part, due to increased difficulty with visuospatial functioning. The current results suggest this interesting possibility, and also raise the question of an additional option for assessment. While the value of driving simulator studies is unquestionable (particularly in a clinical setting where there is a question of safety), it is possible that there are briefer and less prohibitively expensive ways of assessing many of those same skills. These results suggest that tests of visuospatial and visual organization/construction ability may be an underutilized tool in sleep research. While these results are preliminary and replication and further study may be needed, it may be possible that there are visuospatial tests, in addition to commonly used attention tasks, that are sensitive to the cognitive effects of disordered sleep. The results of the present study raise this as a possible future research direction, and as a possible useful addition to cognitive testing in sleep research.

Finally, a significant difference was seen between groups in the domain of Immediate Memory, with the sleep disordered group performing significantly worse than the non-sleep disordered group. This is not entirely surprising, given that immediate recall, or the ability to repeat just-heard information, draws heavily on attention. As we have already seen, attention is significantly different between the two groups. However, the immediate recall tasks are differentiated from pure tests of attention by the presence of learning trials. Rather than relying exclusively on basic attention and working memory, learning trials allow for encoding of information across trials into longer term storage (Lezak, 1995). If only the initial learning trial were examined, the effects of

attention might be seen even more strongly. However the fact that this result was significant when scores on repeated learning trials were examined suggests that there was an effect at work in the sleep disordered group that interfered with the learning/encoding process, which goes beyond basic auditory attention.

Despite repeated learning trials, the sleep disordered group did not "catch up" or overcome the presumed effects of worse attention. This suggests that disrupted sleep can have an impact on learning curve and the process of encoding. In order to examine this effect more closely, it would be helpful for future studies to use additional tasks with repeated learning trials and a greater number of to-be-learned items in order to specifically examine and compare the learning curves of sleep disordered and non-sleep disordered participants. This would help to clarify the role of attentional arousal in immediate memory performance, and allow examination of the ameliorative effects (if any) of encoding across trials. In this more in-depth examination of immediate memory and encoding, differences in the learning process might emerge, and a point at which learning trials allow sleep deprived subjects to "catch up" to controls might become evident.

In the domain of Language, no significant difference was seen between the two groups. As discussed previously, the Language domain of the RBANS involves both a naming task and a semantic fluency task. Most subjects who are not severely cognitively impaired perform well on the naming task, and basic confrontation naming can be preserved even in patients with vascular dementia (Roman, 2005). Thus, one would not necessarily expect naming ability to be affected by or related to sleep disruption, as it is a relatively robust cognitive skill in this population. However, the semantic fluency aspect

of this domain might be expected to be more sensitive to the effects of sleep disruption. Decreased semantic fluency has been shown to be associated with disrupted sleep (Pandi-Perumal & Monti, 2008) and with vascular function (Moser et al., 2007).

The lack of a significant relationship between the Language domain score and disordered sleep in the current study may be a function of the combined score derived from both naming and semantic fluency. In a future analysis, it would be beneficial to examine the two tasks separately to determine if this is the case. Alternatively, the two groups may not have performed significantly differently on the semantic fluency task. Since it has been shown that, in this specific population, semantic fluency is related to blood vessel function (Moser et al., 2007), it may be the case that these two groups have similar endothelial functioning levels. Again, the exclusion of the sleep apnea group may have impacted this result. Given the well-accepted evidence that sleep apnea and cardiovascular disease are strongly related, the exclusion of the sleep apnea subjects may have also excluded those participants with the poorest blood vessel functioning. Again, an interesting future direction will be to add a sleep apnea group for comparison with the two groups already under examination here.

The final cognitive domain under examination in the present study is Delayed Memory. This domain of the RBANS requires the subject to retrieve and reproduce previously learned information. When scores in this domain were examined, no significant differences were seen between the two groups, indicating no significant difference in the ability to recall and retrieve previously encoded information. Recall from the section on Immediate Memory that there was a significant difference between the two groups in encoding ability. However, the lack of difference in Delayed Memory

scores suggests that the sleep disordered group did not have significantly more difficulty recalling and retrieving the information that they were able to successfully encode. This indicates that disrupted sleep may have a greater impact on immediate recall, but a lesser impact on long-term storage and retrieval of successfully learned information. This is consistent with research that has suggested that one can be at a cognitive disadvantage due to sleep deprivation but still benefit significantly from the effects of learning (Durmer & Dinges, 2005).

Again, an interesting future direction would be a more specific and in-depth examination of patterns of learning, encoding, and retrieval in sleep disordered and non sleep disordered participants. Research using cognitive tasks that ensure successful encoding prior to delay (e.g. a drilled word span task in which a participant receives as many trials as necessary to successfully encode a word list) would also allow further examination of delayed memory and decay over time, with encoding differences controlled for by the task demands.

Strengths and Limitations of the Current Study

Discussion of the strengths and limitations of this study has, to a degree, been incorporated throughout this paper but will be revisited more specifically here. Several of the previously discussed strengths concern the well-characterized nature of the study sample and the instrumentation used. Rather than relying on self-report of sleep quality for group categorization, the current study used diagnosis of a sleep disorder by a physician as the classifying variable. This lends increased certainty that one group of participants had more significantly disrupted sleep than the other, whereas reliance on self-report (particularly self-report about an unconscious state) would raise concerns

about the composition of the groups and the actual construct being studied. This was possible due to the nature of the sample being used. The participants in this study were well managed medically, and were all seen for care at the University of Iowa Hospitals and Clinics, where the current research was conducted. In addition to the extensive physiological data gathered for research purposes, the participants' complete medical records were available for review. This eliminated the need for the use of self-report data about sleep as well as about any other medical information.

Although self-report data were not used for subject classification, subjects were given the opportunity to report on their level of daytime fatigue, and these data were included in the analysis. This eliminates some of the inherent difficulties related to self-report on sleep quality (as subjects are presumably more reliable when reporting on their waking experiences) but still allows for a variable that captures the experience of the research subjects and gives them an opportunity to voice the impact that disrupted sleep has on their daily life. While self-report may not be the most reliable method, it is an essential part of social and psychological research, and this researcher believes it is important that studies do not entirely lose sight of the individual experience related to the disorders and phenomena that we investigate. Additionally, this particular study afforded an opportunity to examine how self-report is related to medically diagnosed disordered sleep. In this case, the sleep-disordered group reported significantly greater daily fatigue levels, as hypothesized, indicating that there is a relationship between medical classification and self-report data in the current study.

Additional strengths of the current study include a more comprehensive cognitive assessment than in many other studies of disordered sleep. While there are laboratory

studies of disrupted sleep that include comprehensive cognitive testing (see e.g. Durmer & Dinges, 2005), studies of disrupted sleep in the community have, in many cases, relied on a brief mental status exam (often conducted over the phone) or on self-report of cognitive difficulties. While the latter methods allow for the collection of very large sample sizes, the methods of cognitive assessment may be problematic. The current study used objective cognitive testing that assessed overall functioning as well as individual cognitive domains, which provides considerably more information. In addition, subjects completed a measure of psychological distress with a well-validated overall index score. Relative to many other previous studies, the instrumentation used here was more comprehensive and provided more focused and relevant data.

While it was more comprehensive than some previous research and used an extremely well-characterized sample, there were also significant limitations to the current research. Due in part to the extensive testing and multiple visits required for participation in the longitudinal parent study, the overall sample size was small in comparison to some previous survey or phone based studies. In addition, the nature of the population (older and medically at risk) meant that there was significant attrition during the course of the parent study, and the sample available for this sub-study had decreased over time.

In addition, this sample was somewhat homogeneous, particularly with regard to ethnicity. While not drastically different from the ethnic makeup of the surrounding geographical area, the ethnic composition current sample was overwhelmingly Caucasian. In addition, participants were generally well educated and had good access to health care. Expanding this line of research to include more diverse populations will be an important future consideration.

Other future considerations were discussed in the preceding discussion sections, and some key points will be summarized here. First, due to the scope of this paper and the desire to focus on the relatively understudied issue of disrupted sleep in general, the subset of participants with sleep apnea were excluded. Although this decision was sound with regard to the construct under investigation and the complex separate issues raised by chronic hypoxia, the exclusion of this group leaves some questions unanswered. An important follow-up to the current research will be an analysis that compares the "normal", sleep apnea, and sleep disordered groups in terms of inflammatory pathology and cognitive functioning.

In addition, there is potential to examine certain cognitive constructs in more detail in future research. As mentioned previously, there are several potential avenues for investigation. First, the role of learning could be examined more specifically, to see if and how repeated trials impact encoding, overcome decreased attention, and create different learning curves in normal and sleep disordered participants. Another possibility presented was to examine the Language domain more specifically, to determine whether there are in fact differences in semantic fluency between the two groups.

In addition to expansion of the cognitive aspects of this research, there are numerous exciting future directions related to physiological variables. Combining the current research with available data on blood vessel functioning, for example, would help to further clarify the relationship between sleep and cardiovascular disease and further explore the possibility of an underlying shared physiological mechanism or cascade. In addition, neuroimaging of these research subjects presents another avenue of follow up. The issue of white matter damage in the brain was mentioned briefly, and the use of MRI

allows for the comparison of white matter pathology in the current research groups as well as the sleep apnea group in the future. This area of research and this particular set of research participants present multiple exciting areas of future inquiry, with the contributions of the current study acting as a stepping stone to further analysis and understanding of the wide-spread impact of aging, sleep, and cardiovascular disease.

Summary

Results of the current study supported the hypotheses that sleep disordered participants would report higher levels of fatigue and perform more poorly on cognitive testing, in the absence of elevated levels of psychological distress. Contrary to the original hypothesis, sleep disordered participants did not have significantly higher levels of C-reactive protein, a measure of inflammation. The current study had significant strengths with respect to the extensive medical data available, the appropriate use of self-report data, and the instrumentation used for neuropsychological assessment. Limitations of the current study included a relatively small and homogenous sample size, and several future directions of research and follow-up were suggested by the current results. These include analysis of the sleep apnea group, more specific examination of aspects of cognitive functioning, and the investigation of additional physiological variables. Addressing these limitations and investigating these additional questions will strengthen this important line of research and continue to clarify the roles of sleep, aging, and cardiovascular disease in neuropsychological functioning.

Clinical Implications of the Current Study

The results of this study have several implications for the clinical practice of neuropsychologists and other health professionals that are involved in the assessment and

care of older adults. While the implications are focused on psychologists conducting neuropsychological assessments with older individuals, the implications can easily be generalized to other care providers.

The first implication for clinical practice suggested by the current study and by the review of the research literature is awareness of sleep issues in the older population. As professionals who conduct comprehensive assessments, it is essential that neuropsychologists have a basic understanding of the prevalence of disordered sleep in the aging population. Included in this is the misperception that elderly individuals need less sleep, or that disordered sleep is an inevitable consequence of aging. Continued research will help to educate and increase awareness of these issues, and as health care professionals become more aware of these issues, they can educate their patients and use the research literature to inform their practice.

One clear message from the research literature, as well as the current study, is that the prevalence of disordered sleep and sleep complaints is high in the elderly population. This suggests that consistent assessment for sleep difficulties should be included in the clinical interview preceding a neuropsychological assessment, just like other chronic conditions common in the elderly (e.g. heart disease, diabetes, depression). It is hoped that studies such as this one, which demonstrate the relationship between disordered sleep and cognition, will make the assessment of sleep quality more salient and a more common aspect of the neuropsychological assessment.

An additional implication for clinical practice concerns the dissemination of results. Neuropsychologists write reports that are read by numerous referral sources, including primary care physicians, psychiatrists, and neurologists among others.

Conducting a comprehensive evaluation of a patient's sleep quality utilizing an interview or a questionnaire provides the opportunity to convey information about a patient's sleep difficulties to a multi-disciplinary team of care providers. In addition, the neuropsychologist is in a unique position to comment on the impact that disordered sleep may be having on a patient's cognitive functioning. Conveying this information, based on a thorough understanding of the relevant research, to other health care providers is essential in addressing the issue of disrupted sleep in order to maximize cognitive functioning.

Addressing and treating disrupted sleep is the eventual goal of increasing awareness, assessment, and dissemination of information. Again, neuropsychologists and psychologists are uniquely suited to address these issues, in terms of recommending behavioral treatments for disrupted sleep and providing referrals and coordination of care. In addition, it will be important for neuropsychologists to emphasize the important of reassessment following treatment of disordered sleep. By carrying out careful and thorough neuropsychological assessments pre and post-treatment in sleep disordered individuals, neuropsychology can make an essential contribution not only to patient and caregiver quality of life, but to the overall knowledge of the relationship between sleep, aging, and cognition in their patients. It is hoped that this study, and future studies in this line of research, will emphasize the importance of these issues and help to make thorough sleep assessment a standard part of the neuropsychological evaluation. Subsequently, neuropsychologists can play an important role in raising the awareness of other health care providers by conveying their results with an eye to the impact of sleep, and consistently suggesting more intensive evaluation of sleep (e.g. PSG) when indicated,

and recommending or providing brief behavioral interventions or resources for improved sleep quality. Subsequent reassessment of patients who have completed sleep studies and treatment of sleep disorders will help to close this "loop" in the health care system by providing evidence that sleep assessment and intervention can have an impact on cognition and quality of life. In this way, assessment and treatment of the "other" sleep disorders may become a success story comparable to the example of sleep apnea, and have a comparably favorable impact on the lives of many future patients.

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APPENDIX

Berlin Questionnaire

This questionnaire is three pages long and has 14 items. Please choose the correct answer for each item based on your current sleep habits. If there are any particular questions that you would prefer not to answer, feel free to leave those blank. When you are finished, please return your responses in the stamped, self-addressed envelope provided.

1. Have you ever been diagnosed with sleep apnea?

4) Yes

5) No *(If "No" proceed to item 4 below)*

2. Have you received treatment for sleep apnea?

a. Yes

b. No *(If "No" proceed to item 4 below)*

3. Please indicate type of treatment:

a. CPAP (Breathing machine worn during sleep)

b. Dental device

c. Surgical treatment

d. Other (Please describe):_____

4. Do you snore?

a. Yes

b. No *(If "No" proceed to item 8 on the next page)*

c. Don't know *(If "Don't know" proceed to item 8 on the next page)*

5. Is your snoring:

a. Slightly louder than breathing

b. As loud as talking

c. Louder than talking

d. Very loud – can be heard in adjacent rooms

6. How often do you snore?

a. Nearly every day

b. 3-4 times a week

c. 1-2 times a week

d. 1-2 times a month

e. Never or nearly never

7. Has your snoring ever bothered other people?

a. Yes
b. No
c. Don't know

8. Has anyone noticed that you quit breathing during your sleep?

a. Nearly every day
b. 3-4 times a week
c. 1-2 times a week
d. 1-2 times a month
e. Never or nearly never

9. How often do you feel tired or fatigued immediately after sleep?

a. Nearly every day
b. 3-4 times a week
c. 1-2 times a week
d. 1-2 times a month
e. Never or nearly never

10. During your waking time, do you feel tired or fatigued?

a. Nearly every day
b. 3-4 times a week
c. 1-2 times a week
d. 1-2 times a month
e. Never or nearly never

11. Have you ever nodded off or fallen asleep while driving a vehicle?

a. Yes
b. No

12. How often have you nodded off or fallen asleep while driving a vehicle?

a. Nearly every day
b. 3-4 times a week
c. 1-2 times a week
d. 1-2 times a month
e. Never or nearly never

13. Do you have high blood pressure (Systolic over 135 -OR- Diastolic over 85 –OR- currently taking blood pressure medication)?

a. Yes
b. No
c. Don't know

14. Have you ever been diagnosed with any of the following (circle all that apply)?

a. Restless Leg Syndrome
b. Insomnia
c. REM sleep disorder
d. Other sleep disorder (please describe): _____