AN INVESTIGATION OF THE RELATION BETWEEN

SLEEP DISORDERED BREATHING AND

COGNITIVE FUNCTION

by

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Abstract

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Obstructive sleep apnea (OSA) is the most prevalent sleep related breathing disorders, with an estimated 17% of adults in the U.S affected. Research has linked OSA to mood and cognitive disorders, including Alzheimer's disease. Structural changes in the brain have also been found to be associated with OSA. Several studies have shown deterioration of cognition in OSA patients because of structural and physiological changes due to apnea.

The purpose of this research is to study the correlational relationships between cognitive measures and 1) quantitative measures of sleep quality; 2) measures of sleep disordered breathing; and 3) hypoxia resulting from apnea.

Fifteen subjects (AHI 60.1±28.3, BMI of 34.3±7.0, ages 53±6.9 years) with OSA participated in an overnight study (4.90±1.68 hours) in an accredited sleep lab. Nocturnal polysomnography was used to identify multiple quantitative measures of sleep quality, disordered breathing, and hypoxia. A computerized neurocognitive testing battery was used to obtain measures of cognitive function. It was found that the composite memory aspect of cognition was inversely correlated with AHI (ρ value= -0.7216, p-value= 0.0024), total arousals (ρ value= -0.5998, p-value=0.0181), respiratory disturbance index (RDI) (ρ=-0.6224, p=0.0132), total number of events (ρ value= -0.6052, p-value=0.0168), time in obstructive sleep apnea (in mins) (ρ value= -0.5735, p-value=0.0254), and the percentage of total sleep time subjects spent in any type of sleep disordered breathing event (ρ value= -0.6589, p-value=0.0076). In addition to the composite memory, verbal memory- correct hits immediate scores were significantly correlated with AHI (ρ value= -0.5314, p-value= 0.0415) and BMI (ρ value= 0.5368, p-value= 0.0391); verbal memory was sensitive to AHI (ρ value= -0.6386, p-value=0.0104); visual memory- correct hits immediate was marginally significantly correlated with the total number of events the subjects experienced throughout the night (ρ value= -0.5139, p-value= 0.0501), and Stroop test- commission errors were correlated with the percentage of sleep time spent in REM sleep (ρ value= 0.6830, p-value=

0.005). No significant correlations were found with hypoxia—the amount of oxygen desaturation. This study showed that the current globally accepted method of quantifying the severity of apnea, AHI, is a good indicator with several measures of cognition. No metrics of hypoxia were sensitive to cognitive measures. Percentage of sleep time spent in only OSA throughout the night, stage shifts, and percentages of sleep time spent in any particular stage of sleep were not sensitive to cognitive measures; however, some absolute metrics of time, percentage of sleep time spent in all apnea hypopnea events, and sleep fragmentation parameters did show relationships with composite memory and other subset domains of cognition. These findings suggest that not only does increased sleep fragmentation affect cognition, but components of event durations also impact cognitive function.

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Chapter 1

The Basics of Sleep Apnea

Obstructive sleep apnea (OSA) is a type of sleep disorder that is the result of partial or complete cessations of airflow during sleep [1]. The partial cessations are called hypopneas, while the complete cessation of a breath is known as an apnea. During overnight polysomnography, which is the current gold standard for detecting apnea, subjects will sleep overnight at a sleep lab and be monitored using several different measures including electromyography, electrooculography, electroencephalogram, peripheral blood oxygen saturation, arousals, leg movements, and more. This type of study will be explained in further detail in later sections. One important indicator calculated using the apneas and hypopneas throughout the night is the apnea-hypopnea index (AHI). The AHI score the respiratory events per hour of sleep and is used to quantify the severity of the patient's sleep disorder.

In 2013, Peppard et. al [2] conducted research on the prevalence of sleep apnea and found 10% prevalence among 30-49-year-old men, 17% among 50-70-year-old men, 3% among 30-49-year-old women, and 9% among 50-70 year-old women.

1.1 Types of Sleep Apnea

There are two types of sleep apnea syndrome: obstructive and central. The focus will be upon the obstructive sleep apnea type rather than the central disorder because of the prevalence of this type of sleep apnea; Peppard and colleagues [2] estimated that among adults 30–70 years of age, approximately 13% of men and 6% of women have moderate to severe sleep disordered breathing, 14% of men and 5% of women have an AHI ≥5 plus symptoms of daytime sleepiness. With this criterion, diagnosis of OSA is possible. There are, however, similarities between the two distinct types. During sleep, the lack of airflow causes interruptions in the sleep cycle leading to arousals or awakenings. An arousal is an event that moves the subject from a deeper sleep stage to a lighter sleep stage and can last anywhere from 3 to 15 seconds. Any arousal lasting longer than 15 seconds becomes an awakening [3]. The American Sleep Apnea Association reports as few as 5 per hour disrupting sleep quality, while other cases can have an index of 100 or more awakenings per hour [4]. They also state on their website, accessed May 9, 2014, that although many may not be aware of arousals, they can be aware of an awakening event.

1.1.1 Obstructive Sleep Apnea

Obstructive sleep apnea is characterized by a mechanical problem, where there is a collapse in the upper airway of the patient, whether it is partial or complete. Muscle tone decreases and the airway becomes flaccid, thus collapsing—this can happen in any stage of sleep. A study in 2013 by Ahbab et. al [5] concluded that the neck circumference, as well as BMI, played a role. Subjects with higher OSA severity had a higher neck circumference and body mass index than subjects who had a mild-moderate AHI severity. The mild to moderate group had a neck circumference of 36.11±3.18 cm and BMI of 29.83±4.53, while the severe apnea group had a neck circumference of 40.84±4.34 cm and a BMI of 34.55±7.39 [5].

1.1.2 Central Sleep Apnea

Central sleep apnea (CSA) is characterized by the periodic occurrence of apnea caused by and the lack of accompaniment of respiratory effort [6], [7]. Whereas in OSA, the diaphragm is active and there is effort for breathing, the CSA patient has no diaphragm movement.

1.1.3 Mixed Sleep Apnea

Mixed sleep apnea, sometimes referred to as complex sleep apnea, is the occurrence of both central and obstructive types of sleep apnea within the same event. Typically, the person experiencing the

apnea has OSA and, upon CPAP therapy, will have their airway opened but will still experience difficulty breathing. This occurs because they are now experiencing central sleep apnea. In 2006, Mayo Clinic [7] did a study on 223 subjects diagnosed with sleep disordered breathing, plus 20 additional subjects with CSA, to study this phenomenon—findings suggested that 15% of those subjects had mixed sleep apnea.

1.2 Prevalence of Obstructive Sleep Apnea

1.2.1 Body Mass Index (BMI)

In many cases of diagnosing sleep apnea, the patient's body mass index (BMI) is measured. BMI is measured by looking at the combination of the height and weight. This number is calculated by the following:

$$\frac{Weight\ (kg)}{Height^2(m^2)}$$

In 1993, Hoffstein et. al [8] conducted a study to see what characteristics were good predictors of sleep apnea. Age, sex, BMI, and snoring were all selected as significant values to predict sleep apnea. Non-OSA patients had a BMI and age of 28±5 and 44±12 years, respectively. OSA patients had a range of 31±6 for BMI and 50±11 years. When comparing the gender, a ratio of 3:1 was found for non-OSA men to women and 6:1 for OSA subjects. The OSA subjects reported snoring and

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choking more frequently; their bedmates also witnessed very frequent snoring.

1.2.2   Excessive Daytime Sleepiness (EDS)

Obstructive sleep apnea is characterized by patients experiencing poor quality of sleep, causing excessive daytime sleepiness, cognitive dysfunctions, and negative effects on the cardiovascular system of those affected [9].

Karimi et. al [10] used the Epworth Sleepiness Scale (ESS) and the Karolinska Sleepiness Scale (KSS) to assess daytime sleepiness, while the Functional Impact of Sleepiness (FIS) scale was used to assess the impact of the exhaustion on different domains. One hundred and one volunteers, who were bus or tram drivers, participated in the study—baseline symptoms of EDS, restless leg syndrome (RLS), and insomnia severity were reported before treatment. If OSA or a sleep disorder was detected, the appropriate treatment was administered. Patients kept a diary of their quality of sleep, which included total sleep time, sleep quality, sufficiency of sleep, and more. They were also previously interviewed in regards to their previous instances of motor vehicle accidents from the past year and also the past 5 years, regardless of the accidents magnitude or type. Since OSA is known to cause EDS, the risk of auto accidents is higher; it is very probable that the increase in vigilance that

was noticed with treatment in this study will also decrease the risk of future accidents due to sleepiness.

<div align="center">1.3   Cardiovascular Effects of Sleep Apnea</div>

Multiple papers have reviewed the effects of sleep apnea on the cardiovascular system. Many patients who have OSA may suffer from comorbidities. Some of these cardiovascular comorbidities include hypertension, coronary artery disease, myocardial infarction, arrhythmias, and heart failure. As aforementioned, because of the reduction of muscle tone in sleep, the upper airway can collapse during sleep causing apneic episodes. Apneic events can result in periods of hypoxia and hypercapnia, leading to changes in the sympathetic nervous system of the patient and oscillations in hemodynamics [11].

1.3.1 Hypertension and Atrial Fibrillation

Obstructive sleep apnea has an existing relationship with various cardiovascular anomalies. OSA can be a possible cause of systemic arterial and pulmonary hypertension, as well as play a role in causing heart failure, coronary artery disease, and irregular heartbeats, known as arrhythmias [12].

Atrial fibrillation is the most common arrhythmia among adults [13]. The chances of the epidemic increase with age as well as with the

presence of comorbidities such as hypertension, diabetes, age and stroke [13], [14].

1.4 Cerebrovascular Changes Due to Obstructive Sleep Apnea

1.4.1 Brain Physiology

At rest, approximately 15% of the blood pumped by the heart goes to the brain [15]. This is to ensure oxygen and glucose, through various pathways, are always in adequate supply for the consumption of the brain, as well as removal of CO_2 and catabolites.

Currently, there are multiple ways to measure the oxygenation of the brain. Two commonly used methods are functional near infrared spectroscopy (fNIRS) and functional magnetic resonance imaging (fMRI). In fNIRS measurements for the quantification of oxygenated to deoxygenated blood, the absorbance of two wavelengths of infrared light are measured and changes in the relative oxygenated and deoxygenated hemoglobin are obtained [16]. Oxy- and deoxy-hemoglobin differ in their absorption of near infrared light, making them suitable to measure simultaneously.

In 2010, Pizza et. al [17] conducted a study to analyze the impact of different types of respiratory events on the brain hemodynamics in people with varying degrees of severity of sleep disordered breathing of the obstructive type. Nineteen patients were assessed and it was concluded

that the cerebral blood flow shows a distinct behavior for different respiratory events. During obstructive apneas, a decrease in oxygenated hemoglobin (Hb) is mirrored by an opposing deoxygenated Hb increase, and an opposite slight increase of total Hb. Relative changes on peripheral and cerebral oxygen saturation, and deoxygenated Hb were higher during OSA events than during hypopneas [17].

Transcranial Doppler (TCD) is used to determine cerebral blood flow velocity (CBFV). TCD allows for the blood flow to the brain to be recorded continuously throughout the night. To see the changes in cerebral hemodynamics during sleep, Furtner et. al [18] conducted a study in 2009 on seven subjects with severe OSA using TCD during overnight polysomnography. It was observed that CBFV increases during respiratory events, despite the type of event experienced (apnea or hypopnea). A loss of vasoreactivity and increase of arterial stiffness was indicated by CBF hyporeactivity and pulse transit time reduction during back-to-back respiratory events [18].

1.5   Structural Changes in the Brain Due to Sleep Apnea

Patients who have been diagnosed with sleep apnea can suffer from lost neurons, consequently showing flaws in their learning, reasoning, impulse control and attention [19], [20]. A study in 2001 subjected rats to low levels of oxygenation (i.e. a simulated apnea). They

were shown to have a loss of neurons in the cerebral cortex, hippocampus, and impairments of learning and memory [21].

1.5.1 Effect on Gray and White matter

Gray matter in the brain is present in three major regions—the basal ganglia, which controls movement, the cerebral cortex, and the limbic system. The limbic system surrounds the brain stem and is involved in emotions and cognitive reasoning while making decisions. Gray matter consists of unmyelinated nerve cell bodies and is associated with the higher functions of the brain. White matter is found mostly on the inner portions of the brain and serves as a connection between all of the various regions of gray matter [15]. White matter is composed mainly of myelinated axons and connects difference regions of the central nervous system via tracts [15].

A study was conducted in 2002 by Macey et. al [20] on 21 male patients with OSA and 21 healthy male controls. A technique of voxel-based morphometry (VBM) was used for imaging. This method finds the changes of volume in gray matter in the whole-brain. Significantly lower volumes of gray matter were seen among OSA patients, and more loss was apparent with a more severe diagnosis. Differences in gray matter volume between different regions ranged from 2-18%.

Morrell et. al [22] also found significant changes in brain morphology in the left hippocampal gray matter concentration. Seven subjects newly diagnosed OSA (moderate-severe AHI) and seven control subjects participated in this study. After exploring brain gray matter concentration between apneic subjects and controls via voxel based morphometry (VBM), Morrell and colleagues found a 6% change in concentration of the left hippocampal gray matter and concluded that the hippocampus is a fundamental area for higher level cognitive processing, and more information may be able to be extracted with a higher sampling size, or higher levels of OSA syndrome severity.

1.5.2 *Mammillary Bodies*

Mammillary body injury has been studied with OSA. Mammillary bodies have two nuclear groups, the medial and lateral, and project to the anterior thalamus and are responsible for recollective memory [23]. The medial mammillary bodies play a role in spatial memory and prefrontal function, while the lateral have a small influence on spatial tasks and other spatial memory aspects.

In 2008, Kumar et. al [24] studied mammillary volume in 43 newly diagnosed, untreated OSA patients and 66 control subjects. MRI studies were performed after an overnight PSG. Visual mammillary body loss was apparent in OSA patients in the right, left, and overall volumes, while

similar deficiencies are seen in Korsakoff's syndrome. Korsakoff's syndrome is linked to anterograde memory loss and other neuropsychological losses [24]. Although the mechanism for the structural change is unknown, Kumar et. al indicated it may contribute to memory deficits.

1.6   Cognitive Impairments Associated with Obstructive Sleep Apnea

Although the origins of cognitive impairments in OSA may still be unclear, neuropsychological impairments exist, including, but not limited to: vigilance impairments, attentional lapses, memory flaws, and even decreased motor coordination [25]. Several studies have investigated OSA and cognitive function, as well as the role of sleep fragmentation and hypoxia. Gagnon et. al [26] conducted a review on cognitive function of OSA in the areas of executive function, psychomotor speed, fine coordination, episodic memory, and attention. Executive function in OSA was reported to be significantly impaired in the areas of working memory, with overall impairments noted through delayed processing speed, increased perseverative responses/behaviors, impulsivity, and difficulty with problem solving.

1.6.1 Sleep Fragmentation and Cognition

In 2010, Bianchi et. al [27] studied the sleep architecture of people with obstructive sleep apnea and found that the sleep structure had

decreased temporal stability for non-REM and REM sleep. Minimal sleep fragmentation and episodes of being aroused from sleep are important in aspects of memory consolidation. In 2012, Djonlagic and colleagues [28] concluded that sleep fragmentation, as induced by OSA can affect off-line learning improvement on a motor sequence learning task.

1.6.2 Areas of the Brain Associated with Memory

The hippocampus is an important structure of the brain in learning and memory. The prefrontal lobes are involved in a specialized type of short-term memory called working memory. Other types of memory also include recall from the amygdala and cerebellum [15].

In order to show that structural changes showed cognitive deficits, Mueller et. al [29] conducted a study looking at the amount of gray matter and the lesions of white matter. A major finding as a result of their study showed that cognitive function was determined largely by lobar gray matter volume.

1.6.3 Short and Long Term Memory

Short-term memory (STM) is memory of events that have just occurred, while long-term memory (LTM) is made of events of past times. The two differ in capacity with STM lasting several minutes. However, LTM has a capacity that is vast and difficult to approximate [30].

One of the first to explore short and long-term memory with OSA was Kales and colleagues [31]. Fifty subjects diagnosed with OSA participated in the study and of those, 46% of patients had deficits in short-term memory whereas 32% exhibited long-term memory impairments. Later, studies showed that impairment of short-term memory, especially with immediate and a 30-minute delayed recall of verbal and visual memory was common in OSA subjects.

In 1995, Naegele et. al [32] also found in 17 subjects with OSA that short-term memory, despite the nature of it being visual or verbal, was impaired and long-term memory deficits were attributed to frontal lobe dysfunction.

Among others, Greneche and colleagues [33] directed research on short-term memory after a 24-hour period of sustained wakefulness in patients who had sleep apnea. The research utilized findings from 12 subjects with OSA and 10 healthy controls. Working and immediate memory were studied through tasks of short-term memory. Not only was excessive daytime sleepiness a prevalent issue, but also short-term memory and working memory deficits were observed when compared to healthy controls.

1.6.4 Attention and Vigilance

Being able to pay attention to a certain task or to keep that attention for a long time is a part of cognition that can be affected by OSA. Sleep disorders may compromise an individual's aptitude to maintain alertness over longer periods of time [10]. The daytime sleepiness that comes along with the syndrome can prevent those affected from having the extended attentional abilities. Various tests measure attention and vigilance in those affected by apneic episodes. The test battery for attentional performance (TAP), Wechsler memory scale (WMS3), psychomotor vigilance test (PVT), and Oxford Sleep Resistance test (OSLER) are just a few of the various methods that gauge the subject's attention and vigilance [1], [25].

In 2006, Nowak et. al [1] reviewed previous studies regarding daytime sleepiness and neurodegeneration in OSA subjects, which involved use of neuroimaging to determine the underlying cause for daytime sleepiness. When looking at the combined changes in mood, brain morphology, cerebral blood flow and oxygenation due to OSA, it was found that excessive daytime sleepiness was prominent, in addition to decreased vigilance and attentional capacity. Visual and verbal retrieval was also delayed [1].

1.6.5 Working Memory and Executive Function

Working memory is defined as the way we accumulate information while we are actively using and working with it [30]. For delayed responses, a common recall used in working memory tests, the prefrontal cortex is activated.

A study by Yaouhi and colleagues [25] in 2009 found that apneics performed more poorly than controls on a few tests of working memory. The TAP test for attentional performance, and three subtasks of WMS3 were used to assess working memory for 16 OSA patients and 14 healthy control subjects. Executive function was gauged using a verbal fluency test and two subtasks of the TAP. Gray matter changes were seen in the patients with OSA, in addition to a decline in vigilance. Although executive function was not significantly different, functional impairments were found in other areas of memory and motor function.

In 2011, similar findings of reduced working memory were found in 12 untreated patients with OSA. All of these subjects had moderate to severe apnea [33].

A study by Lee et. al [34] in 1999 evaluated executive function in 17 OSA subjects who were matched with 16 healthy controls for gender, age, IQ, and education level. Although no significant changes in working memory were found, OSA patients appeared to be impaired in retrieval of

information as well as making more perseverative errors—showing impairments in executive function.

1.6.6 Alzheimer's Disease and OSA

OSA is also linked to Alzheimer' disease—a cognitive impairment that affects daily interactions and quality of life. In 2010, Mueller and colleagues [29] conducted a study regarding gray and white matter and the effects on cognition and mood. Ninety-four subjects were studied, 42 of whom were elderly and cognitively intact, 21 cognitively impaired because of subcortical cerebrovascular disease, 11 with a type of mixed dementia or subcortical cerebrovascular dementia, and 20 with Alzheimer's Disease. A major finding of this study was that lobar gray matter structures determined cognitive function, but white matter lesions did not. In addition to this, with the collected lobar brain measurements, they were able to test the associations between lobar volumes and various cognitive domains.

1.7   Significance of the Study

Although many studies have examined the association between cognitive functions in apnea patients, structural changes in the brain, and the apnea severity based on AHI, few have looked at other parameters of apnea severity [10], [22], [24], [29], [32], [34]. AHI measures the severity of apnea through the frequency of events, but durations of events and the

levels of hypoxia have not been correlated with cognitive function. This study focuses on, not only, characteristics of sleep quality, but metrics related to apnea duration and the hypoxia in relation to cognition.

Apnea duration has also been explored in this study. Percentages of sleep time spent in apnea or hypopnea, along with percentages of sleep time spent in OSA, as well as durations of individual events were investigated. Previous studies have not investigated the length of OSA events.

Studies related to hypoxia have taken metrics such as number of episodes with a drop of greater than 4% and mean oxygenation throughout the night [35]. In this study, the method for the analysis of desaturation of oxygenation is taken for each OSA event and, therefore, the minima for each event is observed. The greatest drop in oxygenation throughout the night, as well as the average of the minima. Future sections will explain in depth the methodologies employed in the study.

1.8   Research Study Aims

In this research study, the goals are to explore whether there exists a relationship between cognitive function and the severity of apnea. Specifically, the duration and the frequency of apnea events, concomitant with the drop in the level of systemic oxygen are explored. It is hypothesized that systemic oxygen desaturation can be greater with

longer or more frequent apnea episodes, and this association between hypoxia and apnea duration may be associated with cognitive dysfunction.

Chapter 2

Methods and Means

In this chapter, the protocols and tools used to carry out the study will be described. This study involves the measurement of cognitive function and severity of apnea. Cognitive function was measured using a neurocognitive testing battery and the severity of apnea by NPSG.

2.1 Experimental Setup

2.1.1 *Subjects*

For this research, an Institutional Review Board (IRB) approval was obtained. A total of fifteen subjects, who were suspected of having apnea, participated. Ten males and five females, untreated for OSA with mean AHI of 60±28.3, BMI of 34.3±7.0, and age of 53±6.9 years (range: 39-77) were studied. The Epworth Sleepiness Scale (ESS) is a self-reported questionnaire that gauges the severity of daytime sleepiness of subjects on a scale of 0-24, with 24 being the most severe daytime sleepiness. Fourteen of the fifteen subjects had completed ESS scores prior to their sleep studies with scores of 11±6 (range: 4-23). Five of the fifteen also reported secondary insomnia, and two subjects had anxiety/depression. The subjects provided informed consent before participation. The sleep latency observed for the subjects was 15.9±20.8 minutes (range: 0-78.4

mins) and wakefulness after sleep of 124.5±75 minutes (range: 48.0-326.1 mins).

Many of the subjects also had extensive medication lists. Medications for comorbidities such as diabetes mellitus, hypothyroidism, hyperlipidemia, hypertension, heartburn/ acid reflux, emphysema, rhinitis/ sinusitis, coronary artery disease, and cardiomyopathy were in use by multiple patients. In addition to prescribed medications, some subjects were also taking over the counter vitamins, as well as pills such as Tylenol, Advil, Excedrin, and ibuprofen. Recently in 2015, Lal et. al [36] conducted a study on the impact of medications on cognitive functions in patients with OSA. Charts of diagnosed OSA adults older than 18 (and not undergoing CPAP) were reviewed and, using Mail-In Cognitive Function Screening Instrument (MCFSI), analyzed. It was found that medications including antidepressants, narcotics, antipsychotics, and statins correlated with OSA cognition. Multivariate analysis uncovered that Epworth Sleepiness Scale and the use of antipsychotics, narcotics, and anxiolytics correlated with higher MCFSI scores, while statin use was linked to improved cognition.

2.1.2 Overnight Sleep Lab Study

Multiple methods are utilized for data collection during sleep studies. The main component of the sleep studies is the overnight

nocturnal polysomnography. Before the sleep study, subjects completed a computerized neurocognitive test. Then he/she is fitted for the transcranial Doppler mold, which measures the blood flow to the brain. Following, the sleep lab technician secured equipment to the subject; afterwards, the necessary equipment for this research study was connected to the subject. This included functional near infrared spectroscopy—measuring brain oxygenation—blood pressure, blood oxygenation, and carbon dioxide.

2.1.3 Overnight Polysomnography

In an accredited sleep lab, a nocturnal polysomnography (NPSG), which is the gold standard method of diagnosing and assessing sleep apnea, is used to collect various physiological parameters to detect the presence of apneic episodes. Electrodes are used for the measurement of electrocardiography (ECG) for heart rate and rhythm, peripheral leg movements via electromyography (EMG), eye movements via electrooculography (EOG), and electroencephalography (EEG). A chest and abdomen strain gauge was used to detect the presence of diaphragm movements. In addition to the aforementioned parameters, blood oxygen saturation levels were collected by pulse oximetry, and respiratory flow and respiratory rate were collected via thermistor and pressure transducer

(Bernoulli) [37]. A certified sleep specialist who is blind to the objective of this study completes scoring of the data.

2.1.4 Cognitive Function Measurement

In order to test cognitive function, CNS Vital Signs (CNSVS) was utilized. This is a computerized testing battery that consists of multiple parts, designed to gauge different cognitive measures. Gualtieri and Johnson [38] studied the validity of this measurement technique in 2006. A total of 1069 subjects ranging in ages of 7-90 were tested for the normative database. The test-retest reliability (TRT) was evaluated in 99 subjects on an average of 62 days in between. To validate the tests, the researchers studied 180 patients who had mild cognitive impairments and dementia, post-concussion syndrome, severe traumatic brain injury, ADHD, and depression for comparison. It was confirmed that the tests in the CNSVS test were parallel with conventional neuropsychological batteries that are typically used. That is, CNSVS test is a good screening instrument, but that it is not an replacement for formal neuropsychological testing. It is not a diagnostic assessment, but rather a serial assessment measure. A serial assessment is one that can be taken as a follow-up, again, for comparisons over time.

Before each section of the test is started, there is a set of written instructions on the screen. Subjects are asked to read the instructions, are

allowed to ask the proctor if they have any questions, and then move on either to a practice session that may be provided, or to the actual test. Using the outcome of these tests, a PDF file is then output to the tester's computer showing scores for different main domains based on test performance. The main domains are: neurocognitive index, composite memory, verbal memory, visual memory, psychomotor speed, reaction time*, complex attention*, cognitive flexibility, processing speed, executive function, working memory, sustained attention, simple attention, and motor speed[1]. These main domains also have subset component domain scores that compose of the following: verbal memory- correct hits immediate, verbal memory- correct hits delay, visual memory- correct hits immediate, visual memory- correct hits delay, commission errors and omission errors, and correct responses. A complete list of the scoring domains and components that are used to calculate their scores can be found in Appendix B.

For the report, the scores are color coded from above average (bright green) to very low (red) based on comparison to normal, healthy subjects who are of the subject's gender and age-range. The following sections will cover the different testing segments of CNSVS utilized during

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[1] Domain scores marked with an asterisk (*) denote that a lower raw score is better. Otherwise, a higher raw score yields a better standardized score.

the NPSG studies. The subjects do not see their score sheet after the test is finished. The test is taken only one time and results are only available to the research team for review.

2.1.4.1 Verbal memory

The verbal memory test (VBM) shows the subject a list of 15 simple words, presented one-by-one every two seconds. This whole test takes approximately three minutes. The subject is supposed to memorize these words so that they can pick them out of a list of twice the amount immediately following, as well as at the very end of the entire CNSVS test. These tests are known as the "immediate" and "delayed" verbal memory tests. For recall, when the subject recognized one of the words that they were supposed to memorize, they were instructed to tap the spacebar on the keyboard.

2.1.4.2 Visual memory

Much like the VBM, the visual memory test (VIM) also lasts approximately three minutes and uses the exact same format for testing, but instead of words, it contains geometric shapes such as stacked squares of varying sizes, embedded circles, a square on the left and circle on the right. These geometric shapes will be nested among a set of 30 shapes, which may be reversed and shifted, the subject will hit the spacebar when they recognize a shape they memorized. The VIM test will

be repeated twice, once immediately after the memorization for the "immediate" test, and once repeated as the very last examination on the cognitive battery for the "delayed" portion. In both the VBM and VIM tests, immediate and delayed test correct hits scores are measured.

2.1.4.3 Finger tapping

For the finger tapping test (FTT) portion, the subject will use the right index finger to continuously tap the space bar as fast as possible for 10 seconds. To conduct the test, first there is a practice session. Then, the test is repeated three times for the right index finger. After the right index finger is completed, three runs of the left index finger are recorded. This test is useful because by measuring the average of taps from the right and left index fingers, measurements contributing to motor speed, fine motor control, and psychomotor speed are obtained. This test lasts around two minutes.

2.1.4.4 Symbol digit coding

The symbol digit coding (SDC) gauges complex attention, complex information processing speed, visual-perceptual speed, and information-processing speed. The subject is given a session that explains the format and then allows the subject to try the test as practice. The SDC test runs continuously for two minutes and contains a key of symbols that correspond different symbols with numbers 1-9. The test key contains

symbols with blank spaces that the subject must fill in by using the given key. Subjects are instructed not to memorize the key of given symbols. They can only use the numbers on the top row of they keyboard and cannot backspace their answer if they make a typo or mistake. With the associated practice test, the SDC lasts approximately four minutes from start to finish. Figure 2-1 shows the SDC testing format.
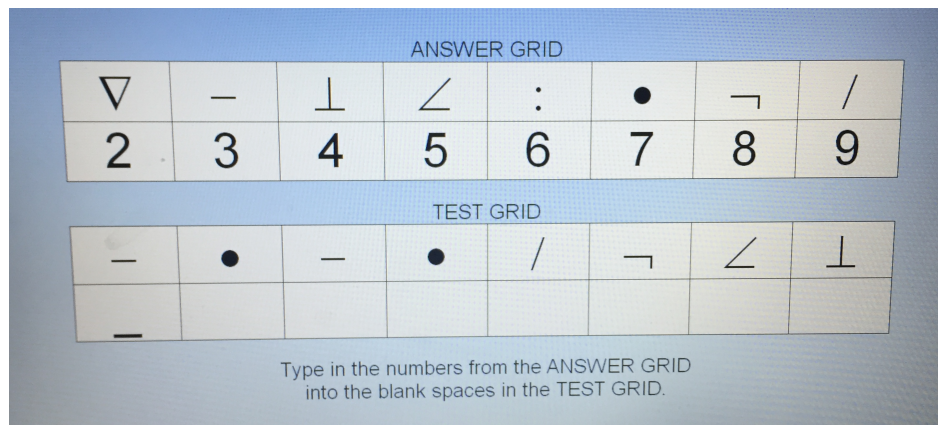
Figure 2-1 Symbol digit coding test

2.1.4.5 Stroop test

The Stroop[2] test (ST) is made up of three parts. For all portions of the test, words will be the names of colors and will flash on the screen (ex: RED, BLUE, GREEN, YELLOW). In the first part, anytime a word pops up on the screen, the user must hit the spacebar right away.

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[2] Named after John Ridley Stroop for his work in identifying the Stroop effect, which says that naming a color painted in its own color (ex: "RED" is painted in red ink) is easier than naming the color when it is painted in a different color (ex: "RED" painted in green ink).

For the second portion, when the word that flashes on the screen matches the color of the word, the user must hit the spacebar. For example, when "YELLOW" flashes on the screen and is filled in yellow, the subject would hit the spacebar, but if the word "YELLOW" flashed on the screen and was filled with green, the subject would not take any action.

For the third part, which is the last portion of the ST, the subject does the exact opposite of portion two, hitting the spacebar when the word and the color *do not* match. These tests, all together, last 4-5 minutes and are measured by Stroop reaction time (ms), simple and complex reaction time (ms), and processing speed (ms) by using inhibition/ disinhibition, and executive skills.

2.1.4.6 Shifting attention test

The shifting attention test (SAT) lasts roughly 2.5 minutes and asks the subject to shift their attention from one set of instructions to another set. A practice session is conducted before the actual SAT so that the subject can get acquainted to how they must go about with the changing instructions. At the top of the screen, there will either be a circle or square that will be filled in with either red or blue. The instructions above the shape that appears will either say "MATCH SHAPE" or "MATCH COLOR." The right and left shift key of the keyboard are used by the test subject and are either a square or a circle, and in either red or blue, mixed

randomly but staying consistent throughout the test. The subject will hit the left or right shift key depending on the rule and trying their best not to mix them up. Figure 2-2 shows the SAT test format. This test measures executive function, reaction times (ms), and shifting sets according to different categories through rapid decision-making.
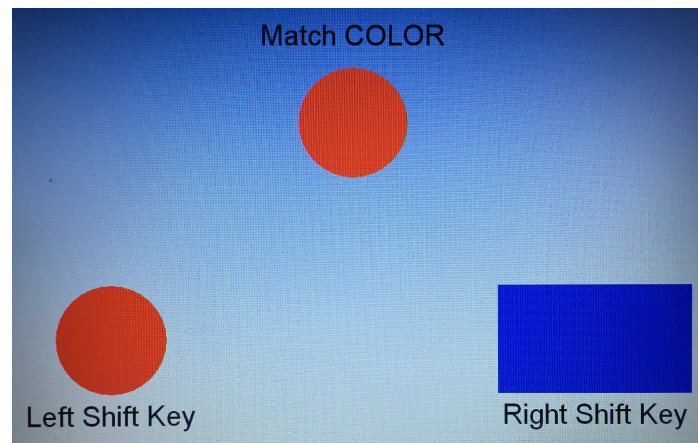
Figure 2-2 Shifting attention test

2.1.4.7 Continuous performance test

The continuous performance test (CPT) measures sustained attention, choice reaction time (ms), and impulsivity. For 5 minutes straight, letters of the alphabet will flash on the computer screen one-by-one. All letters will be capitalized and the user is asked to hit the spacebar every time a "B" flashes on the screen.

2.1.4.8 Four-part continuous performance test

The last test before the VBM and VIM "delayed" recall is the four-part continuous performance test (FPCPT), measuring sustained attention and working memory. This testing portion is the longest part of the CNSVS testing battery and lasts around 7 minutes.

Part one is a simple reaction time (ms) test. Various geometric shapes will appear on the screen in different colors. The participant should hit the spacebar as soon as they see the shape appear. Figure 2-3 shows a patient taking this portion of the test.
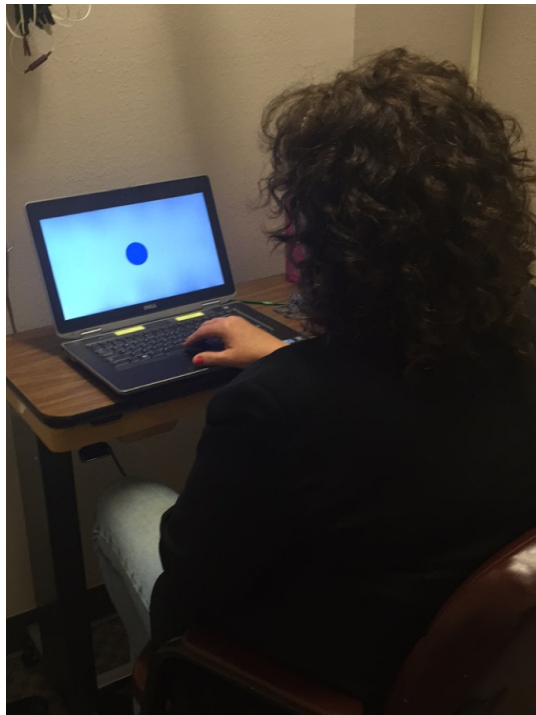
Figure 2-3 Patient taking part 1 of the FPCPT

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Part two is a variant of the continuous performance test, and asks the subject to hit the spacebar when a particular shape in a particular color pops up. For example, the user is asked to hit the spacebar every time a RED STAR is presented on the screen. Any other colored stars and any other shapes should be passed and ignored.

Part three is a "one back" CPT. The subject has to respond to a figure only if the figure immediately preceding was the same. Sometimes, it can be more than just two in a row. The color and shape of the objects must match.

Part four is a "two-back" CPT, in which every other object of the same color and shape must match. This means that two of the same shape in the same color will be separated by a different shape or color. For example, a red circle will flash on the screen in between the appearance of two yellow squares. The second yellow is the correct time for the user to hit spacebar. There may be another yellow square separated by another shape after that as well, resulting in another correct hit of the spacebar.

2.1.4.9 Domain scoring calculation

After the completed neurocognitive test, the software completes a scoring that is done based on various calculations. For example, composite memory is calculated as the combination of VBM correct hits

immediate, VBM correct passes immediate, VBM correct hits delay, VBM correct passes delay, VIM correct hits immediate, VIM correct passes immediate, VIM correct hits delay, and VIM correct passes delay[3]. A complete list of the scoring can be found in Appendix B.

2.1.5 Blood Oxygenation

Using the Nellcor™ N-600x Pulse Oximetry Monitor with OxiMax™ Technology (Covidien, Dublin, Ireland), blood oxygen saturation was continuously and non-invasively monitored throughout the night. The monitor and finger sensor can be seen in Figures 2-4 and 2-5. The saturated oxygenation waveform is collected using analog to digital conversion at a sampling rate of 1000 Hz. The program was designed to save the information every 30 minutes. A Dell (Dell, Round Rock, Texas) laptop was used along with a LabVIEW (National Instruments, Austin, Texas) program. The presence of an alarm management system allowed for monitoring without the subject's sleep to be disrupted.

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[3] This information was retrieved from the CNSVS webpage, visited on September 15, 2015 [45].
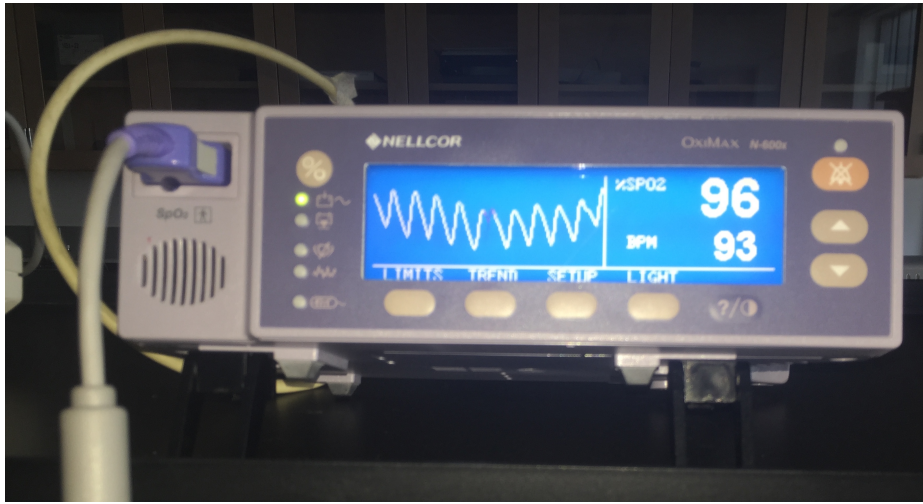
Figure 2-4 Nellcor™ Pulse Oximetry monitor
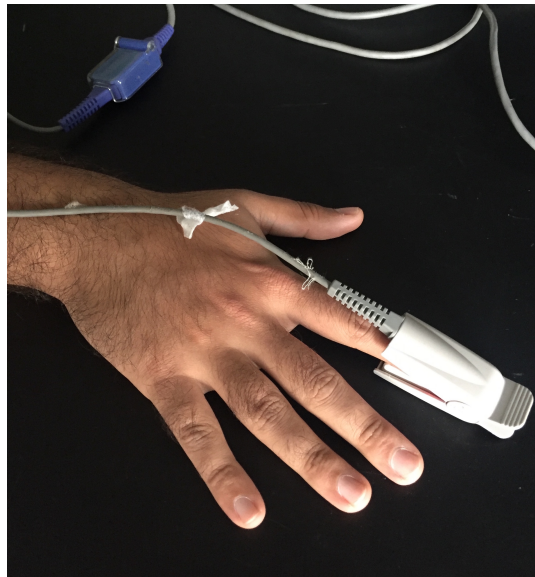
Figure 2-5 Finger sensor

2.2 Data Analysis

2.2.1 Quantification of the Severity of Apnea

For each subject's NPSG study at Sleep Consultants Inc., a sleep study report is put together and contains a slew of information. The

globally accepted metric used for measuring apnea severity is the apnea-hypopnea index (AHI). The AHI is calculated by dividing the number of apneas and hypopneas throughout the night of study by the total sleep time in adults. A score from 0-4 is considered normal, 5-14 is mild, 15-29 is moderate, and scores of 30 or over are considered to be severe cases. A certified sleep specialist, who is blind to the purpose of this study, completes the scoring for the sleep study and sends it to be reviewed by a physician.

2.2.1.1 Sleep study report utilization

From the report obtained by the sleep lab, several elements were used during analysis. BMI was the only physical parameter used for correlational studies; however, gender and age were also extracted. The total sleep time (T_{ST}), in minutes, from the report was used in several ways. Total sleep time is defined as the time from the onset of sleep until the subject woke up. The percentage of total sleep time spent in OSA (T_{OSA}) and percentage of total sleep time in any type of apnea-hypopnea (AH) (T_{AH}) were calculated, as well as obstructive apnea event time (in minutes) (T_o). In addition to this, the percentage of apnea time spent in only OSA (A_{OSA}) was considered—this is the ratio of time the subject spent in the obstructive apnea (in minutes) out of all types of apnea and

hypopnea events (in minutes). Sleep study parameters are represented by the equations shown below:

$$T_{OSA} = \frac{T_O}{T_{ST}} * 100\%$$

$$T_{AH} = \frac{T_E}{T_{ST}} * 100\%$$

$$A_{OSA} = \frac{T_O}{T_E} * 100\%$$

In the equations above T_o is the time spent in obstructive apnea (in minutes), T_{ST} is the total sleep time (in minutes), and T_E is the total amount of time spent in any event (in minutes).

From the scoring, percentages of total sleep time spent in N1 (T_{N1}), N2 (T_{N2}), N3 (T_{N3}), and REM (T_{REM}) stages of sleep are readily available and utilized. Moreover, sleep efficiency percentage, counts of REM periods, awakenings throughout the night, total number of arousals, the arousals from respiratory and snoring events—called the respiratory disturbance index (RDI), and stage shifts are also used.

2.2.2 Feature Extractions

2.2.2.1 Apnea feature extraction

A scored marker signal obtained from the Sandman (Natus Medical Incorporated, Pleasanton, California) system allows for analysis to be done on any signal while simultaneously viewing the duration of an apneic

episode. Sandman is diagnostic software that collects the data from the polysomnography. The marker signal can be layered on a typical plot of data using MATLAB (Mathworks, Natick, Massachusetts) and viewed, as shown in Figure 2-6. The signal is associated with a marker on a scale from 0-10. When the marker dips down on the scale to 1, an obstructive apnea event is denoted. A marker score of 2, 3, and 4 are mixed, central, and hypopnea events, respectively. A marker score of 10 is normal breathing. In Figure 2-6, the green marker with varying depths shows the apnea type and duration, the blue waveform is the saturated oxygenation (SaO_2); the red dots are representative of the maxima of the SaO_2 waveform, while the purple dots are the minima.
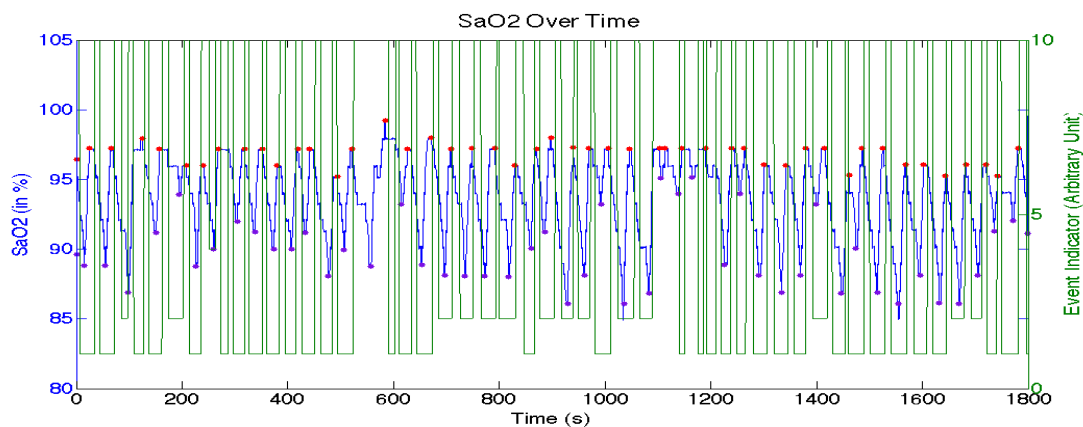
Figure 2-6 A thirty minute clip of various apnea events

For this study, OSA and some hypopnea events were taken into consideration. The reason that central or mixed apneas were not

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considered in the analysis was because they were less prominent in the subject subset when compared to the occurrence of OSA. As mentioned above in section 2.2.1.1, T_{AH} and A_{OSA} utilized the duration of hypopneas. After the apneic event types were separated, an important feature taken into consideration from the obstructive events was their duration (in minutes).

2.2.2.2 Cognitive study feature extraction

The files containing scoring reports provided by CNSVS were imported and sorted for each of the 15 subjects. In order to see which cognitive measures had the most variations between subjects, the number of scores that were categorized as lower than average were counted across all subjects. Every measure was reviewed for the number of subjects that had below average scores, as categorized by the CNSVS report based on gender and age. Most domains contained 3 or less. Any measure that had five or more subjects with a score lower than average was considered as a parameter of interest that would be analyzed, this number was representative of a third of subjects; however, domains with four subjects below average were also considered for assurance. The following is a list of those measures with five or more below average subjects: composite memory, verbal memory, verbal memory- correct hits immediate, verbal memory- correct hits delay, Stroop test- commission

errors, part 2 of the FPCPT- average incorrect response time. Furthermore, the correct responses and omission errors of part 4 of the FPCPT were included. The Stroop test commission error score was one that was higher when there was a corresponding lower amount of errors.

Despite the criteria for 5 or more subjects being below average, the components of the FPCPT part 2 average incorrect response time could not be used in analysis because subjects who did not have any incorrect responses did not have a score for this domain. Those that did have a score, however, were all below average.

2.2.2.3 Saturated oxygenation measure extraction

The saturated oxygenation (SaO_2) waveform was collected from the right hand of the subject and measured the oxygenation of the periphery. The data was saved digitally using a customized LabVIEW (National Instruments, Austin, Texas) program at 1000 Hz. Due to the nature of the SaO2 signal, there were movement artifacts that needed to be accounted for. The signal was filtered in MATLAB using a low-pass finite-impulse response (FIR) equiripple filter, accommodating for zero phase-shift using a forward-backward filtering command [39]. The filter was a 10th order filter with a pass band frequency of 1 Hz and stop band frequency of 2 Hz. The frequency response of the filter can be seen in Appendix E. More information regarding FIR filter design can be found in chapter 10 of

Digital Signal Processing: Principles, Algorithms, and Applications (4th Edition) by John G. Proakis and Dimitris G. Manolakis [40].
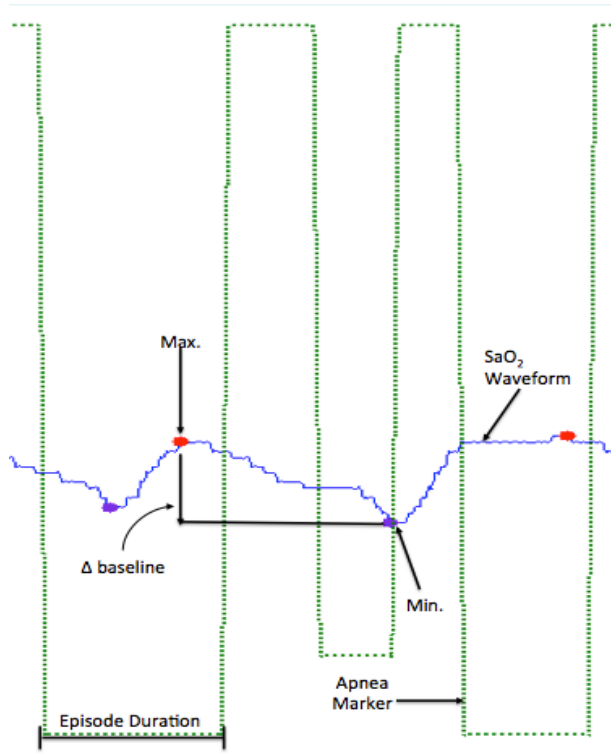
Figure 2-7 SaO$_2$ waveform features

After a cleaner signal was extracted after the noise filtration, custom codes ran peak detection algorithms to find maximums and minimums of the waveforms. The maxima and minima can be seen above in Figure 2-7 by the red and purple dots, respectively. These were visually checked and manually corrected if any mistakes in detection were found. For the extraction of a baseline measure for each subject, at least 200-300 seconds of steady SaO$_2$ measurements were taken and averaged. The

baseline across all subjects was 96%±2%. This time frame was when the subject was laying down in the bed, awake, and not experiencing any apnea. If the subject fell asleep and experienced apneic events immediately, a period of 200-300 seconds of baseline was taken while the subject was not experiencing any episodes as close to the onset of sleep as possible.

Data points for the detected minima, as well as the baseline number for each subject, were tabulated. In addition to investigating the minimum values of oxygen desaturation, values for the change with respect to the baseline for each event were obtained by calculating the minimum SaO_2 value for each apneic event. The changes with respect to the baseline were found using the average baseline that was computed using the initial uneventful, with respect to apneas, 200-300 seconds. The delta baseline representation can also be found in Figure 2-7. A detailed MATLAB code that shows how the SaO_2 was filtered, along with peak detection and the manual correction of peaks, are found in Appendix A.

2.3   Statistical Analysis

The relationships between cognitive function measures with sleep quality metrics, sleep physiology parameters, and SaO_2 wave metrics were examined. Averages, absolute values, and percentages of time were regressed with cognitive scores. These associations were initially explored

using linear regression and the linear R^2 value—this was to determine if there was any linear correlation. Normality was tested using the Kolmogorov–Smirnov test (KS test) and yielded non-normal distributions for all cognitive parameters at α=0.05. The check for the distribution of normality for the 11 measures of cognition used for analysis in this study can be found in Appendix C. Since the distribution was not normal, MATLAB was used and Spearman's ρ and corresponding p-values were obtained in order to show whether the relationships were statistically significant. The level of significance was set to 0.05 a priori.

2.3.1 Linear Regression

Initially, linear regression values were found using Excel. Linear regression is found by the following formula:

$$a = \bar{y} - b\bar{x}$$

$$b = \frac{\Sigma xy - n\overline{xy}}{\Sigma x^2 - n(\bar{x})^2}$$

Where $\bar{x}$ is the mean of data x and $\bar{y}$ is the mean of data y. Following this method of statistical analysis were Spearman's rank correlation calculations.

2.3.2 Spearman's Analysis

Spearman's rank correlation coefficient was the nonparametric correlational coefficient utilized in this study. Spearman's analysis uses

rank to show statistical correlation and ρ as a measure. Spearman's ρ is defined by:

$$\rho = 1 - \frac{6 \sum\limits_{i=1}^{n} d_i^2}{n(n^2 - 1)}$$

Where d_i is defined as the difference between the ranks of the two comparisons and n is the number of subjects in the sample.

2.3.3 Apnea Duration Histograms

OSA events were analyzed with histograms. Placing individual OSA event durations in 5-second bins allowed for a visual interpretation of where the frequency of events was most for each patient. Two-second bins showed similar sensitivity as the 5-second bins, when considering the shape of the distribution. Analysis of histograms with 10-second bins did not have enough sensitivity. Following the histograms of OSA for each subject, the centroids of the histograms were calculated with the following equations:

$$\bar{x} = \frac{\int_A \tilde{x}\, dA}{\int_A dA}$$

$$\bar{y} = \frac{\int_A \tilde{y}\, dA}{\int_A dA}$$

Where $\tilde{x}$ and $\tilde{y}$ are the centroid coordinate locations of each bar in the histogram and are integrated over total area. For each histogram, an ($\bar{x}, \bar{y}$) centroid location was found. In this case $\bar{x}$ represents the duration centroid while $\bar{y}$ represents the frequency.

Chapter 3

Results

This chapter presents correlation coefficients and linear regressions of metrics derived from sleep, physiological measurements, and cognitive measures. Many correlational studies were done to find the significance of the relationships between various cognitive parameters with sleep and apnea metrics. The cognitive parameters that were taken into consideration were those that had five or more patients with below average scores. The scoring parameters taken from the CNSVS computerized neurocognitive test included some main domain scores as well as subset domain scores, as mentioned in section 2.1.4. Visual memory and its components were checked even though the number of subjects who scored below average was less than five. This was done because composite memory is composed of verbal and visual memory combined, and the composite memory did have low values in six subjects.

3.1 Relationship Between Cognitive Measurements with Sleep and Breathing Metrics

The cognitive measure main domain scores and components mentioned in section 2.2.2.2 were correlated against all of the features extracted from the overnight sleep study reports, and apnea events as mentioned previously in sections 2.2.1.1 and 2.2.2.1. The Spearman

correlation values that were found to be significant can be seen in Table 3-1. A complete list of cognitive measures and their correlational studies with various sleep and breathing metrics can be found in Appendix D.

Table 3-1 Statistically significant values (p<.05)

Cognitive Measure	Sleep/ Physiology Parameter	R^2 Value	Spearman's ρ Value	P-Value
Composite Memory	T_{AH}	0.4303	-0.6589	0.0076
Composite Memory	AHI	0.4735	-0.7216	0.0024
Composite Memory	Arousals	0.5184	-0.5998	0.0181
Composite Memory	Total Number of Events	0.5509	-0.6052	0.0168
Composite Memory	T_O (mins)	0.3756	-0.5735	0.0254
Composite Memory	RDI	0.4005	-0.6224	0.0132
Verbal Memory	AHI	0.3669	-0.6386	0.0104
Verbal Memory-Correct hits immediate	AHI	0.1879	-0.5314	0.0415
Verbal Memory-Correct hits immediate	BMI	0.3145	0.5368	0.0391
Stroop Test-Commission errors*[4]	T_{REM}	0.1984	0.6830	0.0050
Visual Memory-Correct hits immediate	Total Number of Events	0.0783	-0.5139	0.0501

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[4] Cognitive measures marked with an asterisk (*) denote that a lower score is better. Otherwise, higher is better.

A component that was found to be significant between various cognitive measures more than once was the AHI value. Composite memory proved one of the measures of cognition that showed statistically significant relationships with multiple metrics of sleep and apnea physiological metrics.

Although the T_{OSA} events did not prove to show any significant correlation with composite memory, it was seen that the percentage of total sleep time (T) while experiencing any type of apnea or hypopnea (T_{AH}) was significant. Figure 3-1 shows the linear regression of this relationship. Similarly, OSA time in minutes (T_O) proved to be statistically significant when compared with composite memory.
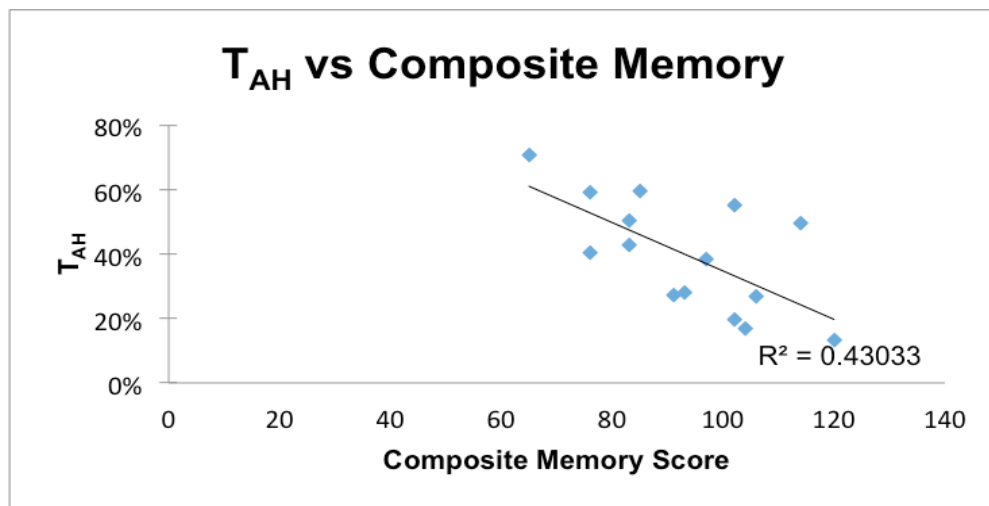
Figure 3-1 T_{AH} versus composite memory scores (N=15, ρ=-0.6589, p=0.0076)

The highest significance level (p-value= .0024) was observed for correlation between AHI and composite memory. The linear regression of this relationship can be seen in Figure 3-2.

In addition to the AHI values exhibiting significant relationships with some measures of cognition, the total number of events experienced throughout the night also showed reasonable correlation with composite memory score, and the correct hits immediate portion of visual memory (Table 3-1).
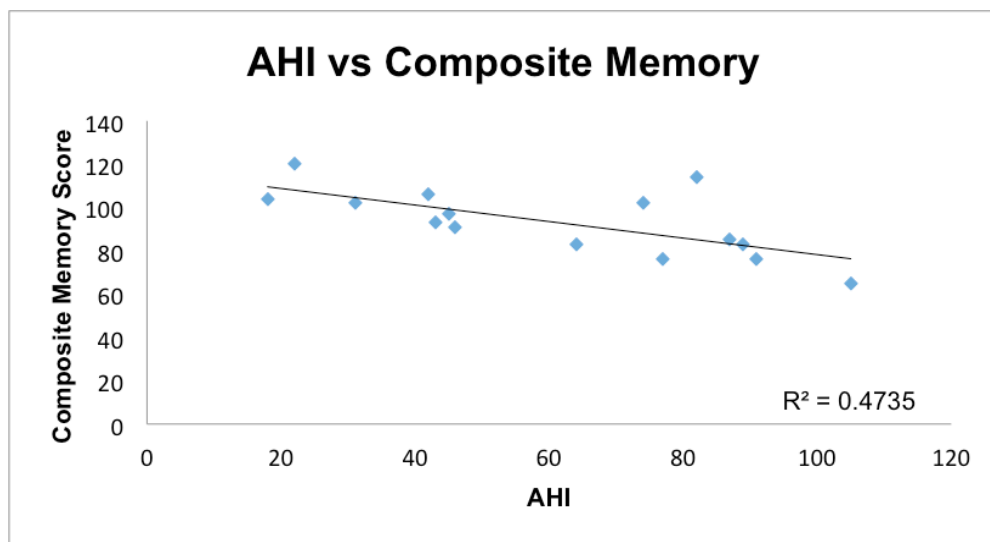
Figure 3-2 AHI values versus composite memory scores (N=15, ρ=-0.7216, p=0.0024)

Several cognitive metrics, sleep apnea metrics, and sleep physiology metrics were found that had lower correlation coefficients and

near statistically significant levels. They are shown in Table 3-2 for reference. The components of visual memory- correct hits immediate are also included. Each of the linear regressions for the remaining significant relationships between cognitive measures and sleep/physiology parameters can be seen in Figures 3-3 through 3-11.
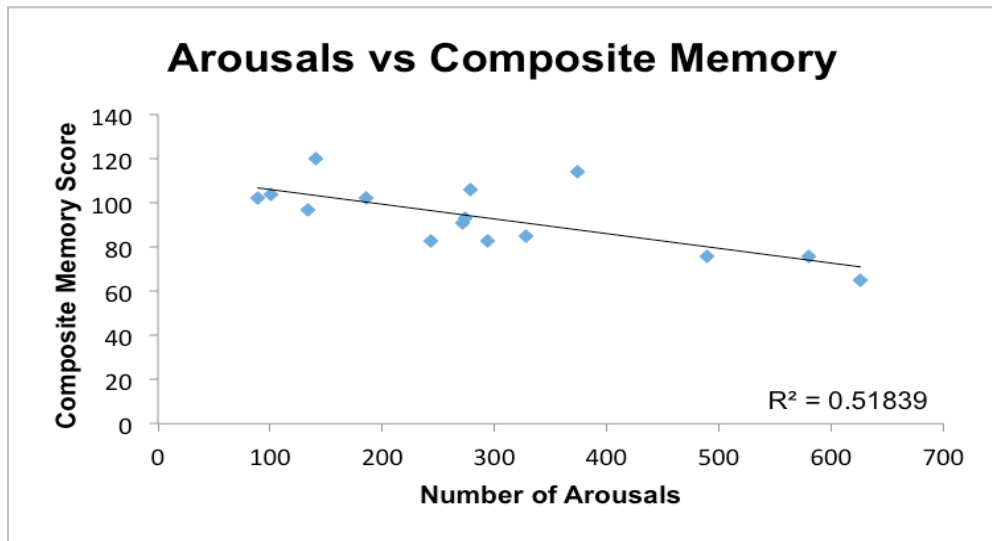
Figure 3-3 Number of total arousals versus composite memory scores

(N=15, ρ=-0.5998, p=0.0181)
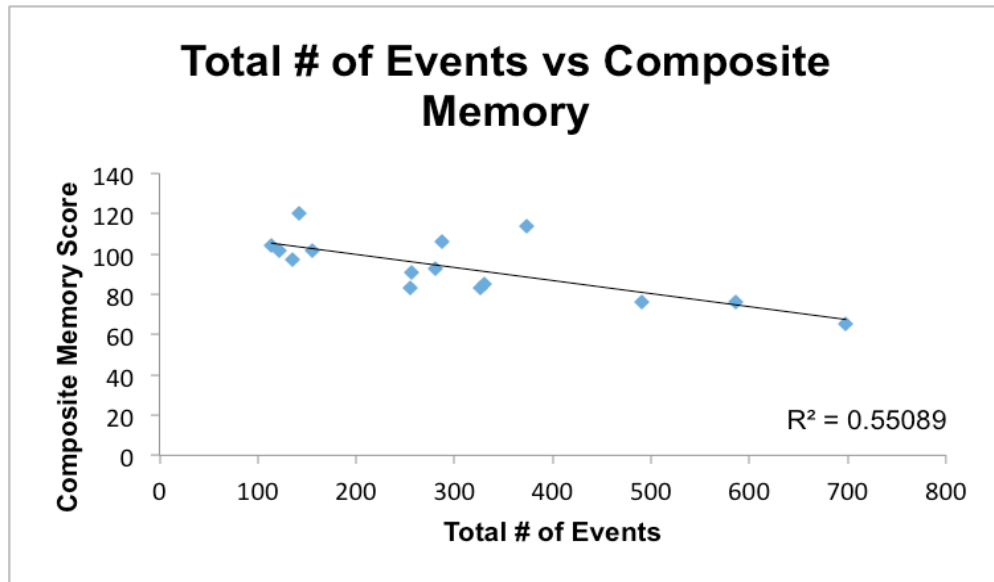
Figure 3-4 Total number of events (apneas+hypopneas) versus composite

memory scores (N=15, ρ=-0.6052, p=0.0168)
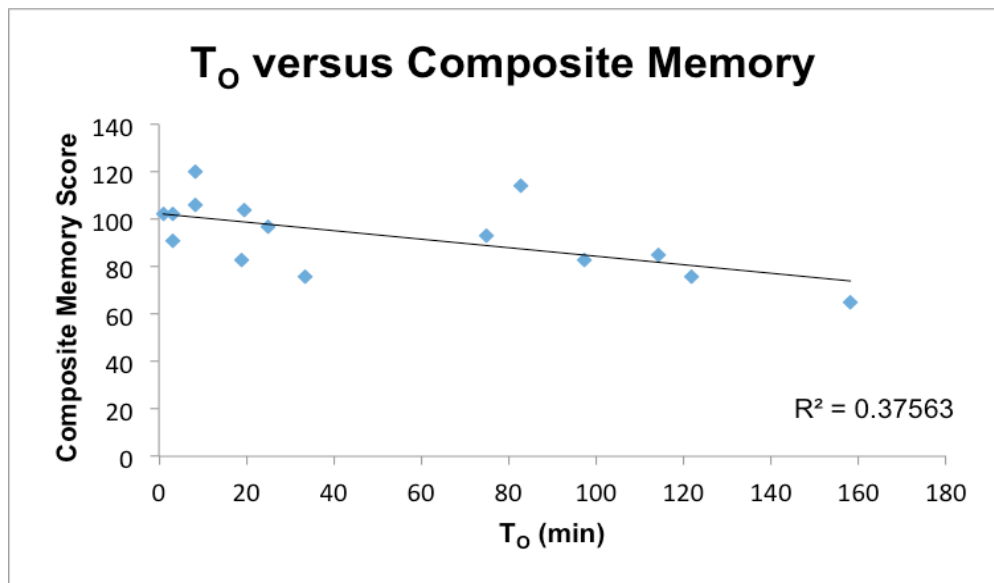
Figure 3-5 Time in OSA (in minutes) versus composite memory scores

(N=15, ρ=-0.5735, p=0.0254)
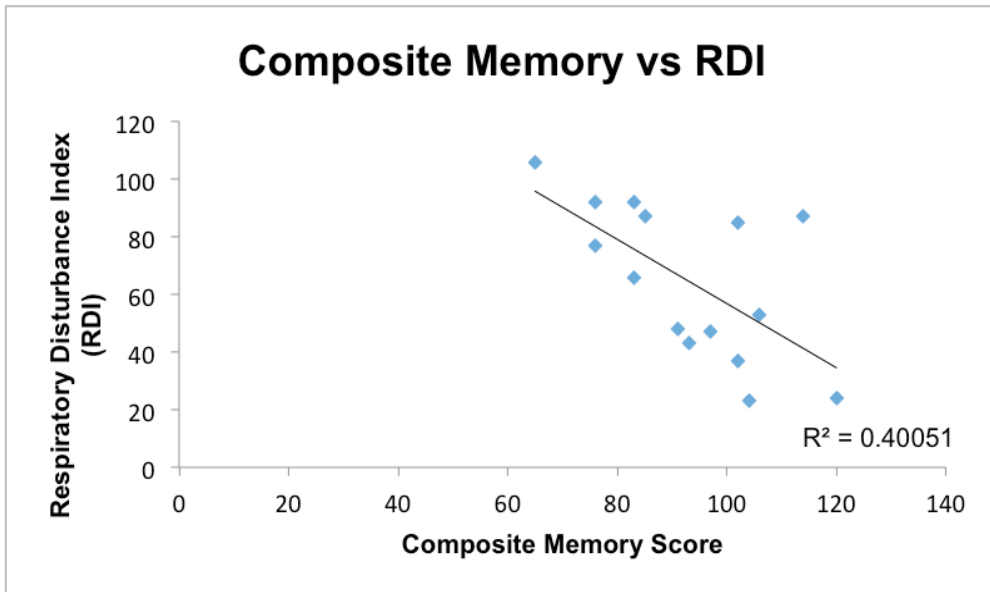
Figure 3-6 Composite memory score vs respiratory disturbance index

(RDI) (N=15, ρ=-0.6224, p=0.0132)
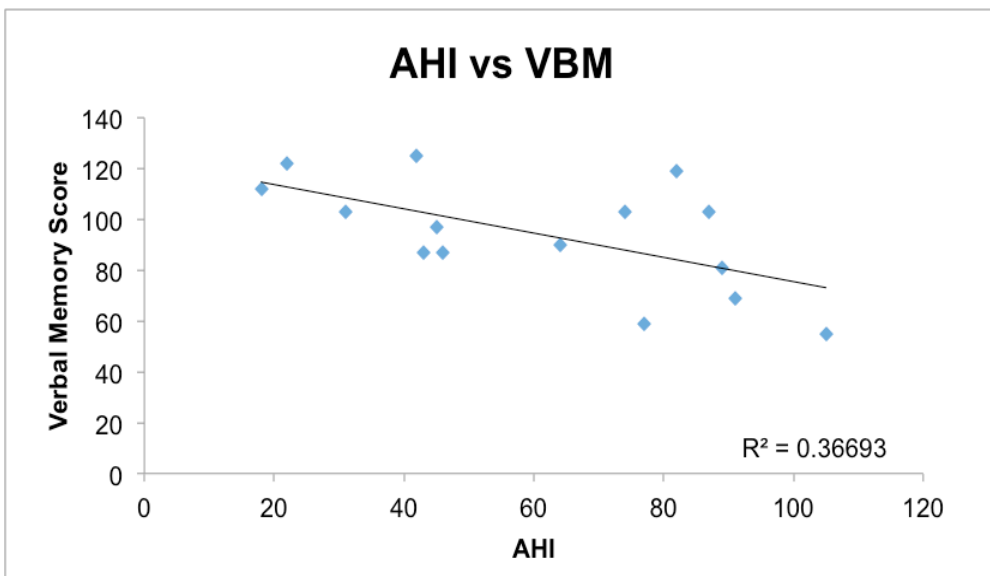
Figure 3-7 AHI versus verbal memory scores (N=15, ρ=-0.6386,

p=0.0104)
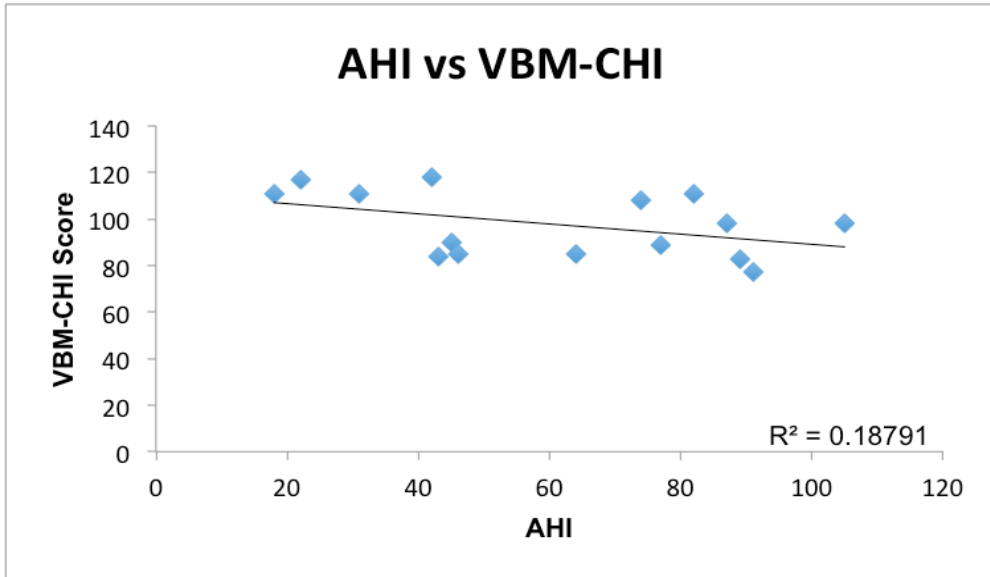
Figure 3-8 AHI versus verbal memory-correct hits immediate scores

(N=15, ρ=-0.5314, p=0.0415)
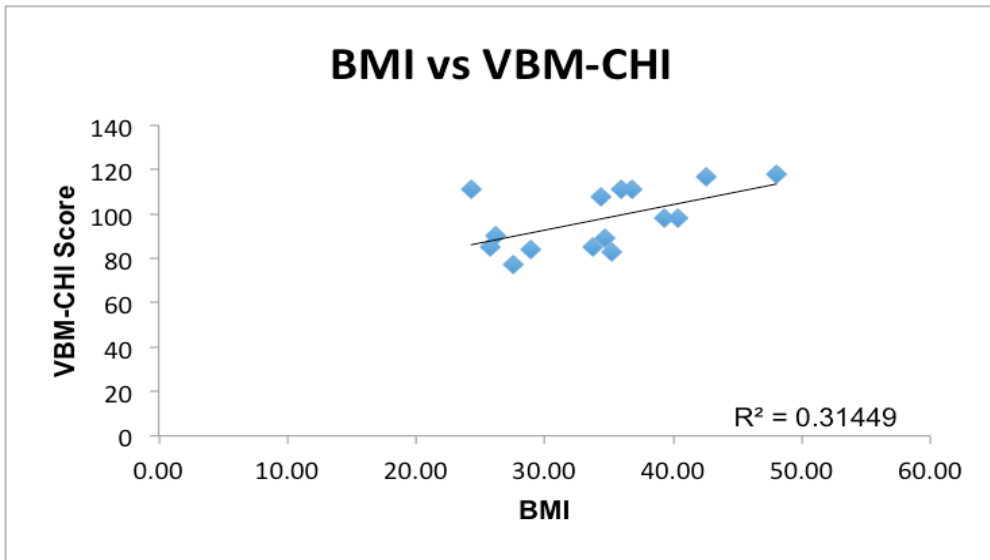
Figure 3-9 BMI versus verbal memory- correct hits immediate scores

(N=15, ρ=0.5368, p=0.0391)
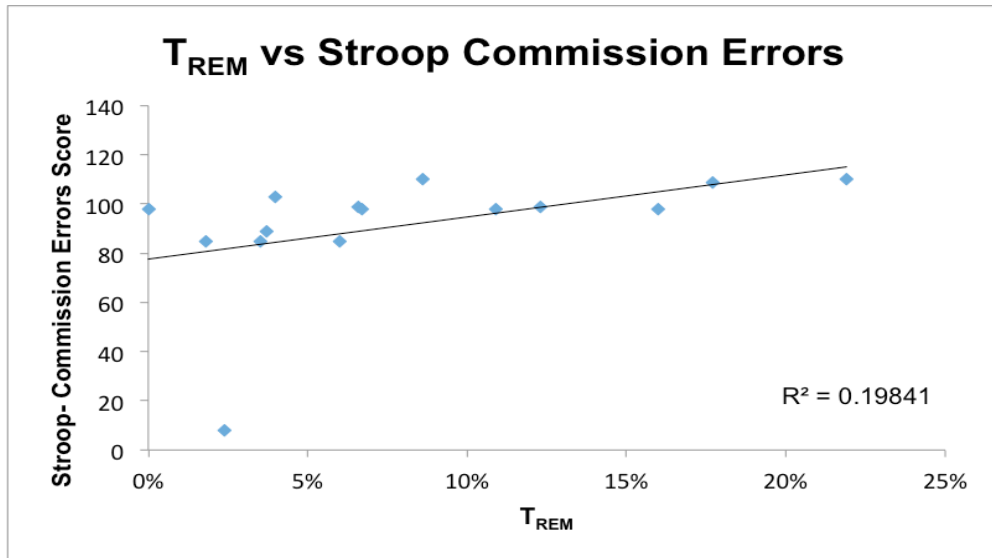
Figure 3-10 T_{REM} versus Stroop- commission errors scores (N=15,

ρ=0.6830, p=0.0050)
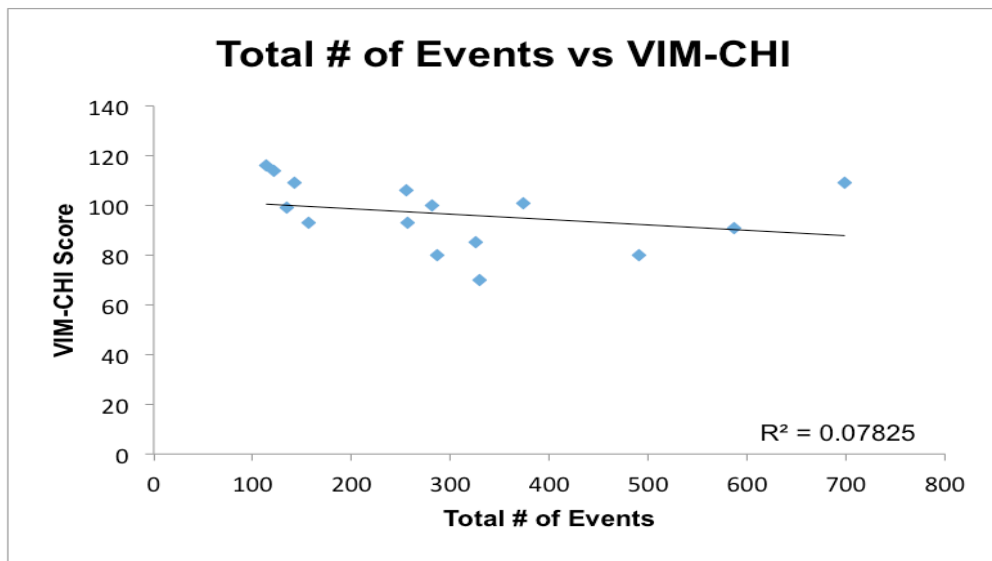
Figure 3-11 Total number of events versus visual memory-correct hits

immediate scores (N=15, ρ=-0.5139, p=0.0501)

Table 3-2 Cognitive components with borderline significance levels

Cognitive Measure	Sleep/ Physiology Parameter	Spearman's ρ Value	P-Value
Verbal Memory	T_{AH}	-0.5112	0.0515
Verbal Memory	Total Number Events	-0.4933	0.0617
Verbal Memory	Arousals	-0.4861	0.0662
Visual Memory-Correct hits immediate	# REM Periods	-0.4939	0.0613
Visual Memory-Correct hits immediate	Arousals	-0.5103	0.0519

For the cognitive measures of visual memory seen in Table 3-2, higher scores were indicative of better performances.

To further investigate AHI, it was correlated against other metrics that were sensitive to composite memory. These correlations can be seen in Table 3-3 below.

Table 3-3 AHI with sleep and physiology parameters[5]

Apnea Severity	Sleep/ Physiology Parameter	Spearman's ρ Value	P-Value
AHI	Arousals	.6786	0.0069*
	BMI	.1000	0.7241
	T_{ST}	-0.2964	0.2827

---

[5] Asterisk (*) denotes significant values

3.2   Cognitive Measures with SaO_2 Metrics

Of the correlational studies performed on all 15 patients, none of the elements of cognitive function showed a statistically significant relationship with the proposed metrics derived from SaO_2 waveform. This included the delta from the baseline of oxygen saturation, the average change in baseline, the minimum SaO_2 experienced throughout the night during an OSA event, and the average of SaO_2 minimums across all events throughout the night. One metric of cognition, part 2 incorrect responses of the FPCPT test, was close to statistical significance (ρ value= -0.5108 and p-value= .0517) when correlated against the average delta baseline.

3.3   Apnea Durations with Centroid Calculation

When analyzing the centroids that were computed using patient histograms, it was found that the centroid-y, meaning the centroid in terms of frequency of events, was significantly correlated with composite memory (ρ value= -0.5264 and p-value= .0438). An example of a centroid, represented by a red circle, on its corresponding histogram with 5-second bins representing the durations of apnea can be seen in Figure 3-12. The y-axis represents the frequency of the amount of apneas in those bins.
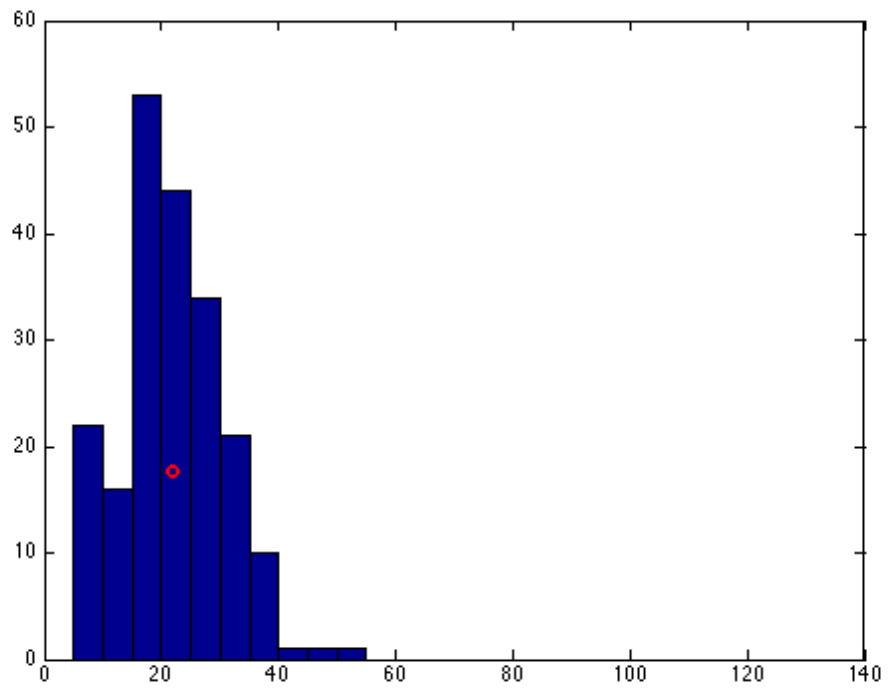
Figure 3-12 Centroid on histogram of subject's apnea durations

Chapter 4

Discussion and Conclusion

This chapter will discuss the results presented in chapter 3 to shed light on possible relationships between different aspects of apnea and cognitive functioning.

4.1 Cognitive Measures with Sleep and Breathing Metrics

Through statistical analysis, several sleep and breathing metrics showed reasonable correlation to various measures of cognition, as shown in Table 3-1. Although linear regressions did not show high R^2 values, Spearman's rank correlation clearly showed the correlational relationships between the metrics of interest; this is because the data is not within a normal distribution.

With AHI as the currently established method of measuring apnea severity, it appears that it correlates well with composite memory, verbal memory, and verbal memory-correct hits immediate. This is important because it implies that the current standard of quantifying the severity of apnea, AHI, accurately represents the OSA syndrome. In addition to investigating the relation of AHI with cognition, the total number of events throughout the night was also considered.

When computing the AHI, the certified technician who scores the sleep study divides the total count of apnea and hypopnea events by the

total sleep time (in hours). AHI shows significant correlations with more cognitive metrics than the total number of events throughout the night. AHI reflects the frequency of events occurring, as opposed to the totality of events, hence revealing new information about the severity by giving the rate. Depending on how long the subjects slept, their AHI scores can vary, even with similar amounts of events. For instance, subjects 13 and 8 have 114 and 122 events of apnea and hypopnea, respectively. However, their AHI scores are 18 and 74, despite their 8-event difference. In addition, the total sleep times for subjects 13 and 8 are 332 mins and 55.5 mins, respectively.

The duration of apnea is of interest in assessing its possible effect on cognition. When comparing the cognition metrics with the different duration of apneas, there were four metrics that were considered: AT in OSA (in mins) (T_O), T_{OSA}, T_{AH}, and A_{OSA}, as mentioned in section 2.2.1.1. For composite memory, the T_{OSA} did not show statistically significant correlation yielding a p-value of .0830 and A_{OSA} generated a p-value of .2021. However, the time in OSA without normalizing with respect to total sleep time returned a p-value of .0254.

When we normalize a metric with respect to another, we actually obtain a new metric that reflects a relative value, rather than the absolute measure. Some cognitive metrics were more sensitive and showed

correlation with absolute values while others with relative values. Although different subjects may have had durations of time spent in OSA, their total sleep time or total time in apnea may have completely differed.

For example, subjects 9, 12, and 13 have total OSA durations of 18.79 minutes, 25.08 minutes, and 19.62 minutes, respectively. Their A_{OSA}, however, is 26.8%, 36.3%, and 35.1%, respectively. While there is not much of a difference in the amount of time between subjects 9 and 13, there is a difference of 8.3% in A_{OSA}. For patients 12 and 13, there is only a difference of 1.2%, but the time spent in apnea is 5.46 minutes longer for subject 12. As it is evident, this normalization process does give an overview about the nature of apnea for the total events, but shields other information that may be pertinent in predicting cognitive function. Therefore, it is important to investigate both the rate of apnea through percentage values, as well as the absolute values of time or event counts.

Even though the T_{OSA} was not significant, it was interesting to see that percentage of total sleep time (T) in any event was statistically significant with composite memory. This implies that a wider scope of inspection may be needed to see the effects that the cessations of breath may have on memory function. Hypopneas, though not a complete cessation of the breath, may be important in their impact factor because of their prevalence.

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Arousals are significant to sleep apnea because they cause the subject to go from a deeper stage of sleep to a lighter stage of sleep. When frequent arousals are occurring, it makes getting to REM stage sleep less likely, thus negatively impacting sleep architecture. Specifically, an ideal amount of uninterrupted sleep is necessary in aiding memory consolidation [28].

Reinforcing this concept, the effects of higher rates of arousals throughout the night are seen in correlation with lower composite memory scores. The number of arousals also affected visual memory-correct hits immediate and verbal memory domains, albeit not statistically significant (p-value=0.0519 and p-value=0.0662, respectively). The RDI is of particular interest because it is the combined index score of respiratory and snore arousals, which is used to characterize the apnea arousals. This was also statistically significant with composite memory (ρ=-0.6224, p=0.0132). There were several components of visual and verbal memory that were close to having a p-value of <.05. These values contribute to the significance in the composite memory scoring because of the way the score is obtained—the scoring of composite memory can be referred to in Appendix B.

An interesting finding is that the correlation between BMI and the verbal memory-correct hits immediate cognitive component is significant.

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When correlating AHI and BMI, there was no statistical significance found (Table 3-3). This was the only parameter that had a physical basis. Ahbab et. al found correlations between BMI and AHI, however the same findings were not confirmed in this study [5]. Although previous studies have reported BMI and cognitive function with sleep apnea, the relationship between BMI and cognition has not been investigated in adults. A study was conducted on 351 children by Spruyt et. al [41]. They concluded that since increased weight predicts increases sleep disordered breathing, and increased sleep disordered breathing had adverse effects on cognition, then children who had weight problems in lieu of sleep disordered breathing would have a significant increase in cognitive functioning. The researchers also suggested that the affected children have continuous monitoring to prevent future learning deficits [41].

From the Stroop testing—which is used to measure reaction time, complex attention, and cognitive flexibility—it was shown that the percentage of sleep time spent in REM stage sleep was positively correlated. Commission errors for this section are scored where a lower amount of errors yields a higher functioning score. This means, the more percentage of sleep time spent in REM, the less errors the subjects made on their Stroop portion of the test.

When comparing the centroids for each subject, with respect to duration and frequency, it was found that there was sensitivity with the frequency centroid when correlated with composite memory. This finding helps to validate the AHI, since frequency of events is an integral part of obtaining the value. In addition to centroids, AHI was correlated with some measures that were responsive to cognitive measures. When correlated with the number of arousals experienced by subjects throughout the night, a ρ value of .6786 and p-value of .0069 was obtained. The relation between these two metrics shows that cognitive functioning is sensitive to arousals, also.

4.2   Cognitive Function with SaO_2

In the case of SaO2 parameters and cognitive function metrics, there were no significant correlations that were found. The cognitive function may not have been sensitive to the levels of hypoxia as measured by the proposed metrics in these subjects.

Since apnea deprives the body of oxygen and the brain requires a significant level of O_2, it may be beneficial in future research to examine the relationship between cognitive function and oxygen saturation of the brain tissue using functional near-infrared spectroscopy (fNIRS) instead of O_2 in the periphery.

In addition to breathing metrics—like AHI, apnea duration, and time in OSA—sleep parameters such as arousals, sleep efficiency, the number of awakenings, and T_{REM} were considered in this study. Cognitive measures seem to show correlation to measures from both sleep and respiration. Since obstructive sleep apnea has so many physiological and structural consequences on the subjects' health, it was presumed that some areas of cognition would be affected. Although AHI is the standard used to quantify the severity of apnea, there was a suspicion about the duration of apnea being a good predictor of the severity.

While the longer T_O did show sensitivity to lower scores in composite memory, it was found that the normalized scores of T_{OSA} and A_{OSA} were not sensitive. As mentioned before, when normalizing scores with respect to other metrics, a rate of events is gained. In order to investigate every aspect, it is important to also consider the absolute values of events, like time spent in the events or the number of events.

When considering the entire night, instead of time in OSA (T_O), T_{AH} did show associated drops in composite memory scores. This is consistent with previous findings [42]. Consequently, the duration of any degree of breathing cessation may be a more sensitive indicator of cognitive dysfunction. With this in mind, it may be important to take a wider-scope approach and consider the night as a whole with parameters

such as hypoxia and duration, as opposed to analyzing individual OSA events.

Arousals throughout the night causing intermittent periods of interrupted sleep also proved to be significant with the composite memory of the subjects. Most of the subjects in this study did not enter sleep stages N3 and had very little of their total sleep time spent in REM stage sleep. Of the fifteen subjects in the study, twelve experienced less than 13% of their T_{REM} stage of sleep.

4.3 Conclusions

This present study showed that there is a high correlation between the severity as measured by AHI and composite memory. The durations of apnea and the level of hypoxia did not characterize the severity of apnea better than the AHI at this time. While the rates of OSA throughout the night were not sensitive to cognitive measures, the absolute values of time spent in OSA did show relationships with composite memory. The total number of events and the number of arousals also had good correlations, implying that sleep fragmentation is an important factor to proper cognitive function. In addition, composite memory seemed to be a good measure of cognition because it combined scores of visual and verbal memory. The centroid method of examining duration and frequency also proved to be significant when correlated with composite memory.

When comparing the findings in this study to those of previous investigations, deficits in short-term memory were consistent through visual and verbal memory tests, as well as their score as a whole (composite memory). However, no deficits in executive function, working memory, or attention and vigilance were found. Scores across the 15 subjects did not show sensitivity for either of these cognitive domains that would allow for analysis showing the potential impact of OSA and its accompanied hypoxia, sleep fragmentation, or other characteristics. Although other studies had explored the relationship between severities of apnea and cognition, the importance and novelty of this present study was the investigation of the impact that the duration of time spent in apnea would have on the cognitive function—which later proved to be significant. In any exploratory study of this type, there are certain inherent limitations that can be noted. For example, with sleep apnea, it is impossible to pinpoint the onset of the syndrome. In future studies, it would be helpful to quantify how long subjects' had been experiencing OSA so as to have a better understanding of how long they may have been experiencing the consequences of it. For instance, it may be possible that a patient with a very high AHI could have just begun to experience the OSA and, therefore, have higher cognitive scores; another subject may have a similar AHI value, but has had apnea for 5-10 years, has below average

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scores. Without being able to isolate the onset, it is unknown how long patients have had OSA, and by simply measuring cognitive function, it is difficult to predict the effects caused by the syndrome. One possible way to assess the effect of time on cognition is to establish a method with imaging techniques and, perhaps, perform serial assessments of cognition to monitor any cognitive decline that may result.

The study could also be improved by increasing the number of subjects studied in order to increase statistical power. Also, in order to provide a more accurate representation of the sets of data and cognition, it may be beneficial to have a control group of non-OSA subjects. Cognitive measures may show a relationship with some of the sleep metrics, such as the percent of sleep time spent in REM or the number of arousals.

Finally, when making multiple comparisons between cognitive measures and physiological parameters, an α level of .05 may have been too liberal because correlational analyses between 11 cognitive measures and 26 measures of sleep quality, duration, and hypoxia were conducted. Two alternatives could have been considered. For example, one would be to use a more conservative α of .01, thus decreasing the possibility of Type I errors. In so doing, the relationships between composite memory and T_{AH} and AHI, as well as the association between Stroop-commission errors and the $T_{REM,}$ would still be significant. Alternatively, an even more

conservative Bonferroni correction could have used. This type of correction assumes that pairs are separate and independent [43]. If this correction was used, one would have to divide the α by 26, yielding a new required α of 0.0019. If this alpha value was used, none of the associations between cognition and physiological parameters would have been statistically significant. This might then be viewed as increasing Type II errors, and potentially overlooking important new information yet to be reported in the scientific literature. Therefore, because this was a preliminary study of potentially important new relationships, it was decided to use the more liberal 0.05 α level for determining statistical significance in order to stimulate future clinical research in this important area.

4.4   Future Studies

The longer durations of obstructive sleep apnea events with their simultaneous systemic oxygen desaturation did not predict outcomes of cognitive function. Although the parameters of saturated oxygen did not prove to be significant with any of the examined cognitive parameters, further inspection of oxygenation to the brain may be pertinent to gaining more insight. The injured brain needs more oxygen to repair [44] and, therefore, may shed more light on the adverse effects currently associated with apnea.

Appendix A

MATLAB Codes

MATLAB code to filter the SaO$_2$ waveform and perform peak detection. This code also contains the code for the manual peak correction:

```matlab
clear all; close all; clc;
 [c, pathc]=uigetfile({'C:\Users\ndm4733\Documents\MATLAB\SLEEP DATA
2013\Synchronized Fnirs-DAQ-Sandman Final Files'},'Select SaO2 file:');
file=[pathc c];
savedata=importdata(file);

%%
%The following designs the lowpass FIR filter:
   HD = fdesign.lowpass('Fp,Fst,Ap,Ast',1,2,1,80,100);% signal output from
monitor is at every 2s giving a freq of 0.5hz. so fp is chosen as 1
   D= design(HD,'equiripple');
   sao2 = filtfilt(D.Numerator,1, savedata(:,8));%% filtered sao2 with no phase
shift
   time=savedata(:,1);
   mark=savedata(:,15);

%This calls the function to find the peaks and valleys of the sao2 signal
   [v1,v2, t1, t2]= tcdpeakdet(sao2, time, 0.02);

   h(1)=gcf;

marker_round=round(mark); % rounding the marker to nearest integer. 1=OSA;
4=hypopnea etc.
 m=1; ind=0;
for i=2:1:length(mark)-1
   if marker_round(i)<marker_round(i-1)&&marker_round(i)==1 ||
marker_round(i)<marker_round(i+1)&&marker_round(i)==1
      ind(m)=i;  %% finding the index where marker =1 (OSA)
      m=m+1;
   end
end
if ind==0
   display ('NO OSA in this file')
   marker_matrix=[];
else
   pks=mark(ind); tpk=time(ind);  % values corresponding to the index obtained.
   %plot(tpk,pks,'*r');

   marker_matrix=horzcat(tpk,pks,ind');
```

```
end

%plots the peaks and valleys, and also allows for manual peak and valley
detection
 [v1,t1,v2,t2]=fixtcd(v1,t1,v2,t2,h(1));
delete (gcf);
figure(h(1));
hold on;
plot(time,sao2);
plot(t1,v1,'r*');
plot(t2,v2,'g*');
hold off;


% %% how to plot a graph with a Right handed-y axis label- useful for printing
graphs for poster presentation, as well.
% X = [0:10]; Y = X;
% A = plotyy(time,sao2*100,time,mark);
% set(A(2),'ytick',[],'yticklabel',[]);
% ylabel(A(1),'SaO2 (in %)')
% ylabel(A(2),'Event Indicator')
% set(A(2),'ytick',[0,5,10],'yticklabel',[0,5,10])
```

Appendix B

Cognitive Function Scoring Guide

Formulas for Calculating the Neurocognitive Domain Scores:

BRIEF- CORE Clinical Domains	Domain Score Calculations: 1600+ norms, ages 7-90
Neurocognition Index	NCI Average of five domain scores: Composite Memory, Psychomotor Speed, Reaction Time, Complex Attention , and Cognitive Flexibility ; representing a form of a global score of neurocognition
Composite Memory	VBM Correct Hits Immediate + VBM Correct Passes Immediate + VBM Correct Hits Delay + VBM Correct Passes Delay + VIM Correct Hits Immediate + VIM Correct Passes Immediate + VIM Correct Hits Delay + VIM Correct Passes Delay
Verbal Memory	VBM Correct Hits Immediate + VBM Correct Passes Immediate + VBM Correct Hits Delay + VBM Correct Passes Delay
Visual Memory	VIM Correct Hits Immediate + VIM Correct Passes Immediate + VIM Correct Hits Delay + VIM Correct Passes Delay
Psychomotor Speed	FTT Right Taps Average + FTT Left Taps Average + SDC Correct Responses
Reaction Time	(ST Complex Reaction Time Correct + Stroop Reaction Time Correct) / 2
Complex Attention	Stroop Commission Errors + SAT Errors + CPT Commission Errors + CPT Omission Errors
Cognitive Flexibility	SAT Correct Responses - SAT Errors - Stroop Commission Errors
Processing Speed	SDC Correct Responses - SDC Errors
Executive Function	SAT Correct Responses - SAT Errors
Simple Attention	Continuous Performance (CPT) Correct Responses minus CPT Commission Errors
Motor Speed	Finger Tapping Test Right Taps Average + Finger Tapping Test Left Taps Average

Clinical Domains	Domain Score Calculations: 700+ Norms, Ages 7 to 90
Working Memory	(4PCPT Part 4 Correct Responses) - (4PCPT Part 4 Incorrect Responses)
Sustained Attention	(4PCPT Part 2 Correct Responses + 4PCPT Part 3 Correct Responses + 4PCPT Part 4 Correct Responses) – (4PCPT Part 2 Incorrect Responses + 4PCPT Part 3 Incorrect Responses + 4PCPT Part 4 Incorrect Responses)

Abbreviations: VBM – Verbal Memory Test; VIM – Visual Memory Test; SDC – Symbol Digit Coding Test; SAT –Shifting Attention Test; FTT - Finger Tapping Test; ST – Stroop Test; CPT – Continuous Performance Test; 4PCPT – Four Part CPT

Appendix C

Checking for the Normality of Distribution

MATLAB code using KS test to check distribution of cognitive metrics:

Composite memory:
```
[h, p]=kstest(C)
h =
    1
p =
   1.2678e-14
```

Verbal memory:
```
[h, p]=kstest(VBM)
h =
    1
p =
   1.2678e-14
```

Verbal memory-correct hits immediate:
```
[h, p]=kstest(VBMCHI)
h =
    1
p =
   1.2678e-14
```

Verbal memory-correct hits delayed:
```
[h, p]=kstest(VBMCHD)
h =
    1
p =
   1.2678e-14
```

Visual memory:
```
[h, p]=kstest(VIM)
h =
    1
p =
   1.2678e-14
```

Visual memory-correct hits immediate:
```
[h, p]=kstest(VIMCHI)
h =
    1
p =
   1.2678e-14
```

Visual memory- correct hits delayed:
[h, p]=kstest(VIMCHD)
h =
    1
p =
   1.2678e-14

Part 2- incorrect responses:
[h, p]=kstest(P2IR)
h =
    1
p =
   1.2678e-14

Part 4- correct responses:
[h, p]=kstest(P4CR)
h =
    1
p =
   1.2678e-14

Part 4- omission errors:
[h, p]=kstest(P4OE)
h =
    1
p =
   1.2678e-14

Stroop- commission errors:
[h, p]=kstest(StroopCE)
h =
    1
p =
   1.2678e-14

Appendix D

Cognitive Component Correlational Relationships with Various Sleep and

Breathing Metrics

Correlations with Composite Memory		
Metric	Rho	P-Value
Average delta BL	0.1826	0.5147
Max delta BL	-0.0289	0.9185
%TST in AH	-0.6589	***0.0076
%TST in OSA	-0.4620	0.0830
%AT in OSA	-0.3492	0.2021
Time in OSA (mins)	-0.5735	***0.0254
Average Duration	-0.0854	0.7621
Max OSA Duration	-0.2274	0.4150
Max AH Duration	0.3169	0.2498
Min OSA SaO2	0.0985	0.7270
Average Min SaO2	0.0143	0.9596
Total Number Events	-0.6052	***0.0168
AHI	-0.7216	***0.0024
N1 TST%	-0.1826	0.5147
N2 TST%	0.1397	0.6196
N3 TST%	-0.0869	0.7582
REM TST%	0.2292	0.4113
REM Periods	-0.0600	0.8318
Awakenings	-0.3049	0.2691
Arousals	-0.5998	***0.0181
Stage Shifts	0.1146	0.6843
Sleep Efficiency	0.0125	0.9646
RDI	-0.6224	***0.0132
Centroid Duration	-0.1432	0.6106
Centroid Frequency	-0.5264	***0.0438
BMI	0.2131	0.4458

Correlations with Verbal Memory		
Metric	**Rho**	**P-Value**
Average delta BL	0.1327	0.6372
Max delta BL	-0.0145	0.9591
%TST in AH	-0.5112	*0.0515
%TST in OSA	-0.3211	0.2433
%AT in OSA	-0.2368	0.3955
Time in OSA (mins)	-0.4632	0.0821
Average Duration	0	1
Max OSA Duration	-0.1381	0.6235
Max AH Duration	0.2816	0.3092
Min OSA SaO2	0.0233	0.9343
Average Min SaO2	-0.0269	0.9241
Total Number Events	-0.4933	*0.0617
AHI	-0.6386	***0.0104
N1 TST%	-0.1184	0.6743
N2 TST%	0.0915	0.7458
N3 TST%	-0.1680	0.5496
REM TST%	0.1238	0.6603
REM Periods	-0.0432	0.8785
Awakenings	-0.2399	0.3891
Arousals	-0.4861	*0.0662
Stage Shifts	0.2529	0.3631
Sleep Efficiency	-0.0484	0.8639
RDI	-0.5103	0.0519
Centroid Duration	-0.0251	0.9292
Centroid Frequency	-0.4413	0.0997
BMI	0.2816	0.3092

Correlations with VBM Correct Hits Immediate		
Metric	Rho	P-Value
Average delta BL	0.2980	0.2806
Max delta BL	0.185	0.5093
%TST in AH	-0.4363	0.1040
%TST in OSA	-0.2460	0.3769
%AT in OSA	-0.2154	0.4406
Time in OSA (mins)	-0.2983	0.2802
Average Duration	-0.0397	0.8884
Max OSA Duration	-0.0377	0.8939
Max AH Duration	0.2747	0.3218
Min OSA SaO2	-0.2029	0.4684
Average Min SaO2	-0.3351	0.2221
Total Number Events	-0.3106	0.2599
AHI	-0.5314	***0.0415
N1 TST%	-0.0108	0.9696
N2 TST%	-0.0359	0.8989
N3 TST%	-0.1620	0.5640
REM TST%	-0.1221	0.6647
REM Periods	-0.1541	0.5834
Awakenings	-0.0162	0.9543
Arousals	-0.3034	0.2716
Stage Shifts	0.3178	0.2484
Sleep Efficiency	0.0916	0.7455
RDI	-0.4002	0.1394
Centroid Duration	-0.1077	0.7024
Centroid Frequency	-0.2837	0.3056
BMI	0.5368	***0.0391

Correlations With VBM Correct Hits Delay		
Metric	Rho	P-Value
Average delta BL	0.0645	0.8193
Max delta BL	-0.0787	0.7803
%TST in AH	-0.3029	0.2725
%TST in OSA	-0.1129	0.6887
%AT in OSA	-0.1057	0.7076
Time in OSA (mins)	-0.2834	0.3060
Average Duration	0.1431	0.6109
Max OSA Duration	-0.0323	0.9091
Max AH Duration	0.2652	0.3394
Min OSA SaO2	0.0466	0.8690
Average Min SaO2	0.0547	0.8465
Total Number Events	-0.3781	0.1646
AHI	-0.4301	0.1095
N1 TST%	0.1022	0.7172
N2 TST%	-0.0806	0.7751
N3 TST%	-0.2709	0.3287
REM TST%	0.0287	0.9192
REM Periods	-0.1088	0.6995
Awakenings	-0.1526	0.5872
Arousals	-0.3656	0.1802
Stage Shifts	0.2115	0.4493
Sleep Efficiency	-0.1237	0.6606
RDI	-0.3007	0.2761
Centroid Duration	0.1523	0.5878
Centroid Frequency	-0.267	0.336
BMI	0.2007	0.4732

Correlations with P2-Incorrect Reponses		
Metric	**Rho**	**P-Value**
Average delta BL	-0.5108	*0.0517
Max delta BL	-0.3701	0.1745
%TST in AH	-0.0848	0.7638
%TST in OSA	-0.1232	0.6619
%AT in OSA	0.0202	0.9431
Time in OSA (mins)	-0.1202	0.6695
Average Duration	0.1998	0.4753
Max OSA Duration	0.1777	0.5264
Max AH Duration	0.1777	0.5264
Min OSA SaO2	0.1191	0.6724
Average Min SaO2	-0.1273	0.6511
AHI	-0.2383	0.3925
Total Number Events	-0.2241	0.422
N1 TST%	-0.1434	0.6103
N2 TST%	0.1232	0.6619
N3 TST%	0.3827	0.1592
REM TST%	-0.0848	0.7638
REM Periods	0.0592	0.8340
Awakenings	-0.2771	0.3173
Arousals	-0.2241	0.4220
Stage Shifts	0.1959	0.4842
Sleep Efficiency	0.0626	0.8246
RDI	-0.2296	0.4104
Centroid Duration	0.1252	0.6567
Centroid Frequency	-0.1595	0.5701
BMI	-0.2847	0.3037

Correlations with P4- Correct Response		
Metric	**Rho**	**P-Value**
Average delta BL	0.0430	0.8790
Max delta BL	0.0986	0.7265
%TST in AH	0.1434	0.6102
%TST in OSA	0.3405	0.2143
%AT in OSA	0.2097	0.4532
Time in OSA (mins)	0.304	0.2706
Average Duration	0.3420	0.2121
Max OSA Duration	0.0771	0.7849
Max AH Duration	-0.0824	0.7702
Min OSA SaO2	-0.1398	0.6193
Average Min SaO2	-0.2027	0.4688
AHI	0.0842	0.7654
Total Number Events	0.2599	0.3496
N1 TST%	-0.0215	0.9394
N2 TST%	0.0125	0.9646
N3 TST%	-0.1112	0.6932
REM TST%	0.2115	0.4493
REM Periods	0.1407	0.6170
Awakenings	-0.2765	0.3185
Arousals	0.2724	0.3260
Stage Shifts	0.2133	0.4454
Sleep Efficiency	0.3029	0.2725
RDI	0.1311	0.6415
Centroid Duration	0.3979	0.1419
Centroid Frequency	0.3047	0.2696
BMI	0.0358	0.8991

Correlations with P4- Omission Errors		
Metric	Rho	P-Value
Average delta BL	0.0538	0.8489
Max delta BL	0.1159	0.6807
%TST in AH	0.1363	0.6281
%TST in OSA	0.3354	0.2216
%AT in OSA	0.2027	0.4688
Time in OSA (mins)	0.3007	0.2761
Average Duration	0.3351	0.2221
Max OSA Duration	0.0753	0.7896
Max AH Duration	-0.0753	0.7896
Min OSA SaO2	-0.1525	0.5875
Average Min SaO2	-0.2029	0.4684
AHI	0.0825	0.7700
Total Number Events	0.2619	0.3457
N1 TST%	-0.0197	0.9444
N2 TST%	0.0108	0.9696
N3 TST%	-0.1113	0.6929
REM TST%	0.2152	0.4410
REM Periods	0.1493	0.5954
Awakenings	-0.2794	0.3132
Arousals	0.2744	0.3222
Stage Shifts	0.2045	0.4648
Sleep Efficiency	0.3103	0.2603
RDI	0.1312	0.6412
Centroid Duration	0.3892	0.1516
Centroid Frequency	0.3067	0.2661
BMI	0.0323	0.9091

Correlations with Stroop Commission errors		
Metric	Rho	P-Value
Average delta BL	0.0326	0.9081
Max delta BL	0.1574	0.5754
%TST in AH	-0.2627	0.3442
%TST in OSA	-0.0888	0.7530
%AT in OSA	0.0181	0.9489
Time in OSA (mins)	-0.0979	0.7284
Average Duration	-0.2712	0.3283
Max OSA Duration	-0.1431	0.6108
Max AH Duration	0.1468	0.6017
Min OSA SaO2	0.1051	0.7094
Average Min SaO2	0.1324	0.6381
AHI	-0.1920	0.4929
Total Number Events	-0.0761	0.7875
N1 TST%	-0.3189	0.2467
N2 TST%	0.1920	0.4929
N3 TST%	0.1717	0.5406
REM TST%	0.6830	***0.005
REM Periods	0.3708	0.1736
Awakenings	-0.2931	0.2890
Arousals	-0.0924	0.7433
Stage Shifts	0.1468	0.6017
Sleep Efficiency	0.2392	0.3906
RDI	-0.1752	0.5324
Centroid Duration	-0.116	0.6807
Centroid Frequency	-0.0272	0.9234
BMI	-0.0960	0.7335

Correlations with Visual Memory		
Metric	Rho	P-Value
Average delta BL	0.1400	0.6186
Max delta BL	0.1287	0.6475
%TST in AH	-0.4237	0.1155
%TST in OSA	-0.3070	0.2657
%AT in OSA	-0.1759	0.5305
Time in OSA (mins)	-0.2695	0.3313
Average Duration	-0.2714	0.3278
Max OSA Duration	-0.1364	0.6278
Max AH Duration	0.2675	0.3351
Min OSA SaO2	0.0880	0.7552
Average Min SaO2	0.0934	0.7405
AHI	-0.3321	0.2265
Total Number Events	-0.2783	0.3152
N1 TST%	-0.0467	0.8688
N2 TST%	-0.1005	0.7215
N3 TST%	0.1256	0.6556
REM TST%	0.2262	0.4175
REM Periods	-0.0893	0.7517
Awakenings	0.0647	0.8187
Arousals	-0.2944	0.2868
Stage Shifts	-0.1741	0.5348
Sleep Efficiency	0.2029	0.4684
RDI	-0.3867	0.1545
Centroid Duration	-0.316	0.2512
Centroid Frequency	-0.2047	0.4643
BMI	0.0395	0.8889

Correlations with VIM Correct Hits Immediate		
Metric	Rho	P-Value
Average delta BL	0.1773	0.5274
Max delta BL	-0.2930	0.2893
%TST in AH	-0.1719	0.5402
%TST in OSA	-0.2202	0.4303
%AT in OSA	-0.3205	0.2442
Time in OSA (mins)	-0.2957	0.2846
Average Duration	-0.0791	0.7792
Max OSA Duration	-0.2990	0.2790
Max AH Duration	-0.1289	0.647
Min OSA SaO2	0.3868	0.1544
Average Min SaO2	0.1237	0.6606
AHI	-0.1665	0.5531
Total Number Events	-0.5139	***0.0501
N1 TST%	0.2990	0.2790
N2 TST%	-0.2256	0.4188
N3 TST%	-0.2121	0.4479
REM TST%	-0.1791	0.5232
REM Periods	-0.4939	*0.0613
Awakenings	0.1148	0.6837
Arousals	-0.5103	*0.0519
Stage Shifts	-0.2936	0.2881
Sleep Efficiency	-0.1737	0.5359
RDI	-0.1561	0.5786
Centroid Duration	-0.1629	**0.5618**
Centroid Frequency	-0.2829	0.3069
BMI	-0.1200	0.6702

Correlations with VIM Correct Hits Delay		
Metric	Rho	P-Value
Average delta BL	0.1828	0.5143
Max delta BL	-0.1376	0.6249
%TST in AH	-0.1039	0.7124
%TST in OSA	-0.0484	0.8640
%AT in OSA	0.0108	0.9697
Time in OSA (mins)	-0.1031	0.7145
Average Duration	0.0117	0.9670
Max OSA Duration	-0.0233	0.9343
Max AH Duration	0.0233	0.9343
Min OSA SaO2	0.0358	0.8991
Average Min SaO2	0.0682	0.8093
AHI	-0.0233	0.9343
Total Number Events	-0.2993	0.2785
N1 TST%	-0.0054	0.9848
N2 TST%	0.1183	0.6746
N3 TST%	0.1294	0.6458
REM TST%	-0.1470	0.6012
REM Periods	-0.0206	0.9418
Awakenings	-0.0566	0.8413
Arousals	-0.2796	0.3129
Stage Shifts	-0.4122	0.1268
Sleep Efficiency	-0.3136	0.2550
RDI	-0.0404	0.8863
Centroid Duration	-0.0573	0.8391
Centroid Frequency	-0.0394	0.8891
BMI	-0.2097	0.4532

Appendix E

Frequency Response of FIR filter

Magnitude Response (dB)
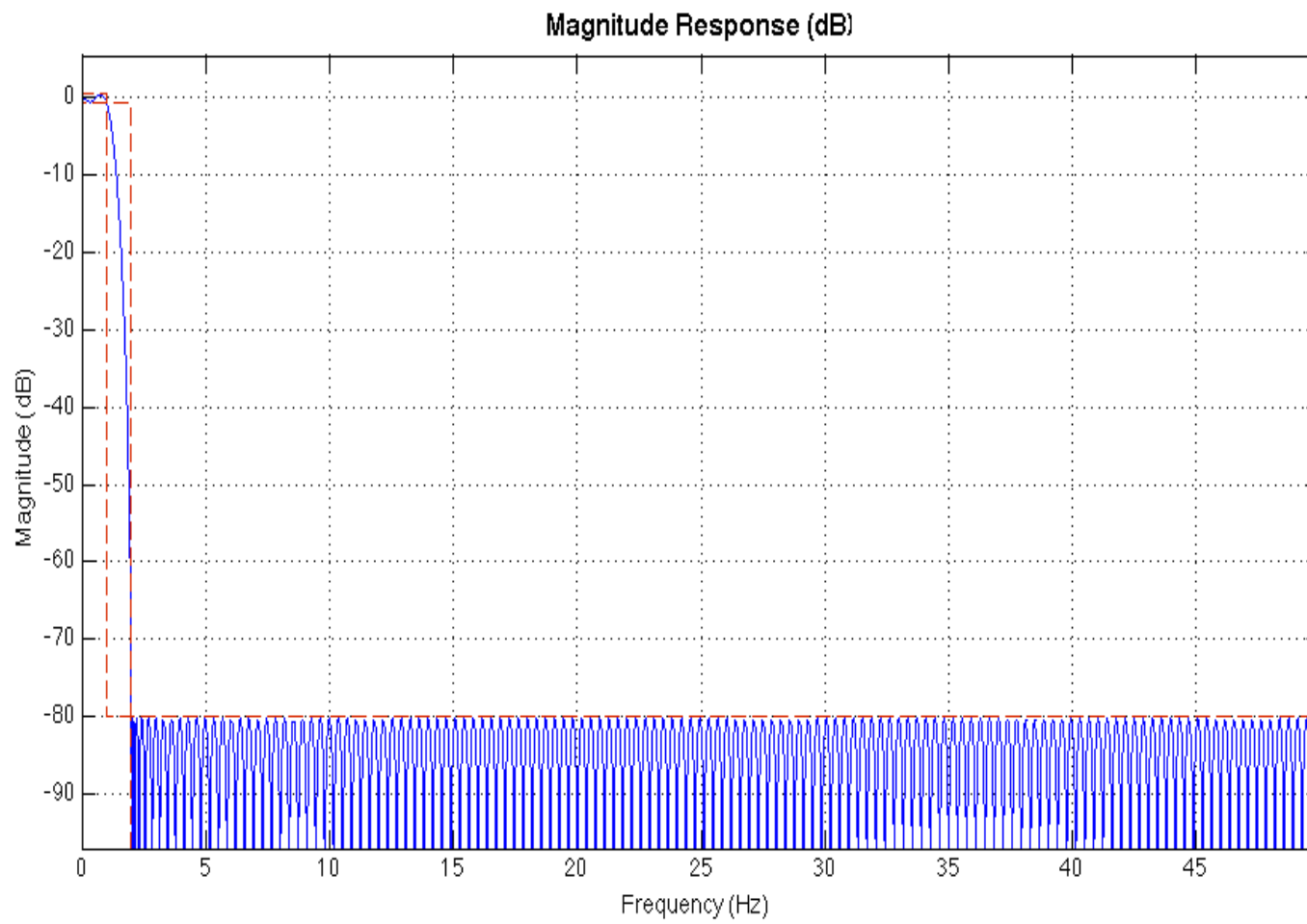
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Nazaneen Mousavi attended the University of Houston, double majoring in Biology and Psychology, and earned her Bachelor of Science in 2010. Combining her love for technology, medicine, and math Nazaneen decided to begin her Master of Science in Biomedical Engineering at the University of Texas at Arlington in 2012. She was privileged to join the dean of engineering, Dr. Khosrow Behbehani, in his lab in 2013 to further her knowledge of bioinstrumentation. Seeing the significance of sleep apnea on today's population compelled her to combine her psychology background with the current research. Nazaneen's research interests include cognitive functioning, apnea duration, and hypoxia as related to sleep apnea severity. Ms. Mousavi plans on a successful career in the marketing development, sales, and support of innovative biomedical devices and technology.