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Sustaining Breaths for Restorative Rest: A Preliminary Evaluation of Sleep, Mental Health, and Cognitive Function Following Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

by

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Abstract

Introduction: Obstructive sleep apnea (OSA) is a sleep-related breathing disorder that produces repetitive obstruction or collapse of the upper airway. Positive airway pressure (PAP) therapy is the gold standard treatment for OSA. Hypoglossal nerve stimulation (HNS) is considered an alternative treatment for patients who are unable to tolerate PAP therapy. The purpose of the study was to examine sleep, mental health, and cognitive health outcomes before and after HNS to determine its viability as an alternative treatment.

Methods: The study utilized a single-group, pretest-posttest design. Objective and subjective sleep was measured using actigraphy, sleep diary, and questionnaires. Objective and subjective cognitive health was measured using paper-and-pencil tests and questionnaires. Lastly, questionnaires were used to obtain data pertaining to mental health. Data were analyzed using two-tailed dependent samples *t*-tests and reliable change indices (RCI).

Results: Eleven middle-aged and older adults participated in the study. There was no significant difference in objective or subjective sleep, objective cognitive function, daytime sleepiness, depression, or anxiety between pre- and post-HNS. Participants showed significant improvement in sleep disturbance, insomnia severity, subjective cognitive function, and anger following treatment. Largest improvement was shown for subjective cognitive function, anger, and insomnia severity during RCI analyses.

Discussion: The results suggest longer follow-up periods that include post-operative care and titration visits are necessary for enhancing the effectiveness of HNS. Discrepancies between objective and subjective data suggested participants perceived just-noticeable improvement in sleep and cognition in the context of cumulative non-significant change.

Keywords: Obstructive sleep apnea, cognitive function, mental health

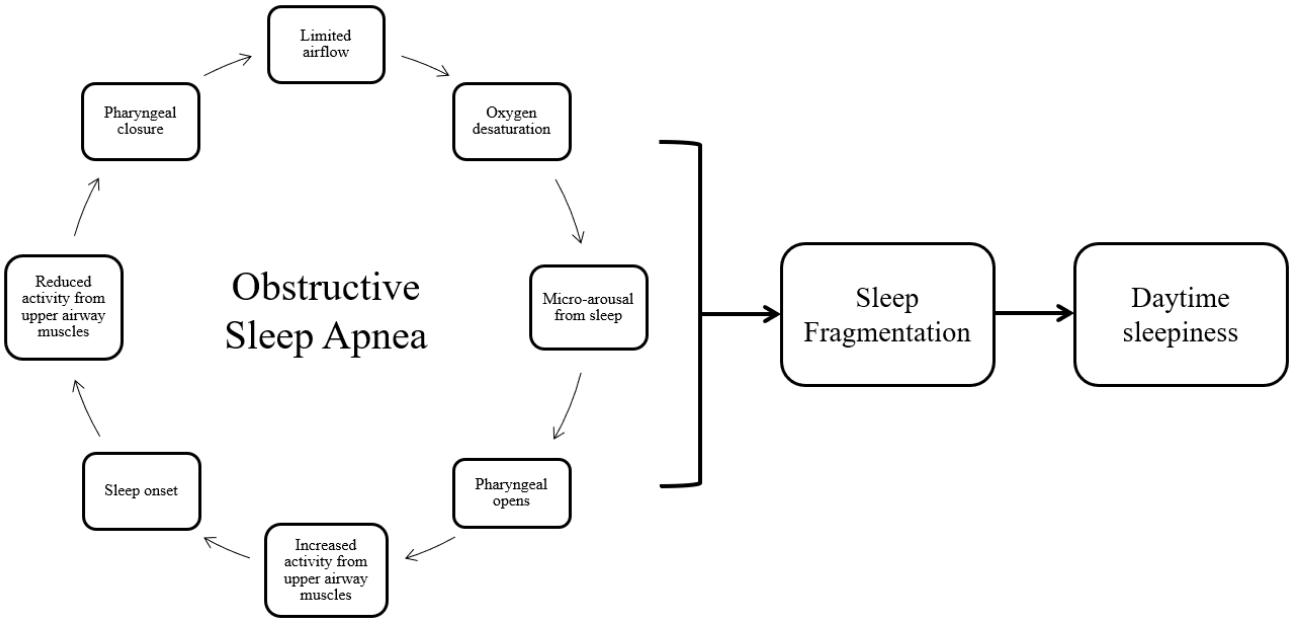
Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder that affects 9-38% of the adult population (Senaratna et al., 2017). Despite the high prevalence of OSA, a recent report from the American Academy of Sleep Medicine suggests that only 20% of individuals with OSA, 5.9 million people, are diagnosed and treated (American Academy of Sleep Medicine, 2016). Under-recognition and untreated OSA is associated with a host of direct and indirect consequences for individuals and the US healthcare system. Annually, 12.4 billion dollars are used to aid in the detection and treatment of OSA; however, this costs rises to 149.6 billion when considering direct economic consequences (American Academy of Sleep Medicine, 2016), such as vehicle and workplace accidents and higher risk of developing comorbid health conditions including diabetes and hypertension (American Academy of Sleep Medicine, 2016; Knauert et al., 2015). These estimates cumulatively suggest the importance of allocating additional attention and education towards the identification and treatment of OSA.

OSA is characterized by repetitive, partial, or complete obstruction or collapse of the upper airway during sleep that result in reductions in airflow (Chang et al., 2020; Gottlieb & Punjabi, 2020). Partial reductions in airflow for at least 10 seconds are considered hypopneas and near complete cessation in airflow for at least 10 seconds are considered apneas. During obstructive respiratory events, the back of the throat collapses and causes micro-arousals, oxygen desaturation, or both, which in turn produces fragmented sleep (Rundo, 2019). Physiologically, manipulation of the upper airway is controlled and maintained by upper airway dilator muscles (Kuna & Sant'Ambrogio, 1991). During normal sleep, the upper airway muscles maintain phasic activity during inhalation, and are responsible for dilating and stiffening the airway to maintain patency, or an unobstructed airway (Kuna & Sant'Ambrogio, 1991). Reduced upper airway

muscle activity during sleep relative to the pressure produced by respiratory pump muscles (e.g., chest wall muscles) leads to pharyngeal (throat) closure and limited airflow. The pharyngeal reopens during micro-arousals from sleep and restores upper airway muscle activity. This process repeats again upon sleep onset whereby upper airway muscle activity is reduced, pharyngeal closure occurs, limited airflow is present, the individual is aroused from sleep, and upper airway muscle activity is increased (Kuna & Sant'Ambrogio, 1991). Figure 1 provides a visual depiction of this nighttime sleep process. While there are other health factors (e.g., obesity, diabetes) and personal characteristics (e.g., alcohol consumption) that may add additional nuance or complexity to the obstructive respiratory event, this description briefly characterizes the common physiological process of individuals with OSA.

Figure 1: Nighttime sleep process with Obstructive Sleep Apnea



Note: Adapted with permission from Sleep Disorders in the Elderly. (Dzierzewski, Rodriguez, et al., 2022). In C. Durso, M. Fiatarone-Singh, L. Mosqueda & D. Swagerty (Eds.), *Reichel's Care of the Elderly, 8th Edition.* Cambridge University Press.

OSA is diagnosed based on criteria delineated in the third edition of the International Classification of Sleep Disorders (ICSD-3) and the fifth edition of the Diagnostic Statistical Manual of Mental Disorders (DSM-5) (American Academy of Sleep Medicine, 2014; American Psychiatric Association, 2013). According to the ICSD-3 and DSM-5, diagnostic criteria for OSA are met when there is evidence of at least five predominantly obstructive respiratory events (hypopneas or apneas) per hour of sleep, along with insomnia, daytime sleepiness, cognitive dysfunction, or other associated medical or psychiatric conditions (American Academy of Sleep Medicine, 2014; American Psychiatric Association, 2013; Sateia, 2014). Alternatively, diagnostic criteria for OSA can also be met if there is evidence of 15 or more obstructive respiratory events per hour regardless of the presence of disturbances or additional sleep and daytime symptoms. Diagnostic confirmation of OSA is completed with overnight testing (Gottlieb & Punjabi, 2020). Laboratory-based polysomnography is considered the gold-standard approach to testing; however, at home sleep apnea testing has been increasingly used (Gottlieb & Punjabi, 2020). The number of apnea or hypopnea events per hour, known as the Apnea-Hypopnea Index (AHI), is typically used as an indication of the severity of OSA. The occurrence of 0-5 apnea or hypopnea events per hour is considered within normal range, 5-15 apnea or hypopnea events is considered mild, 15-30 apnea or hypopnea events is considered moderate, and more than 30 apnea or hypopnea events is considered severe OSA (American Academy of Sleep Medicine, 2014; American Psychiatric Association, 2013).

Risk For Obstructive Sleep Apnea

Health status and demographic characteristics significantly elevate risk for OSA. Extensive evidence supports weight as a significant risk factor for the development of OSA (Gottlieb & Punjabi, 2020; Jehan, Zizi, et al., 2017; Senaratna et al., 2017). Relative to adults

within normal weight range, OSA is 2 times more common among overweight adults with a BMI between 25 and 30, and 4 times more common among obese adults with a BMI over 30 (Gottlieb & Punjabi, 2020). Overweight and obese adults experience additional obstruction in the upper airway due to the accumulation of fatty tissue, which in turn increases the likelihood of repeated obstructive respiratory events (Jehan, Zizi, et al., 2017). Overweight and obese individuals may also be predisposed to OSA due to structural changes in neck circumference and lung volume, in addition to reduced functioning of upper airway neuromuscular control (Schwartz et al., 2008).

Overall risk is significantly higher among men than women, and age of onset is typically earlier for men (Fietze et al., 2019; Senaratna et al., 2017). Although the causes and mechanisms are still unclear and under investigation, sex differences in risk for OSA are suspected to be associated with sleep architecture and arousal, differences in upper airway anatomy and physiology, respiratory control stability, differential aging effects, and under-recognition of OSA in women who are often misdiagnosed with insomnia or depression (Lin et al., 2008). Sex differences are also suspected to be due to the presence of specific sex hormones. While overall evidence is mixed, some studies suggest that lower rates of testosterone in men and lower rates of progesterone and estrogen in women may elevate risk of OSA (Netzer et al., 2003; Ruchała et al., 2017; Shahar et al., 2003). Changes in progesterone and estrogen during aging have been considered a contributing factor to significant elevations in risk for OSA among perimenopausal women (Dancey et al., 2001; Jehan et al., 2015).

Differential risk for OSA has also been linked to race. Available evidence, while limited for some racial/ethnic groups, indicate that Black, Latinx/Hispanic, and Native American people are at higher risk of developing OSA compared to White and Asian adults (Dudley & Patel, 2016). Risk for OSA in Asian adults has appeared to be similar to or lower than White adults

(Dudley & Patel, 2016). However, risk may also vary according to the specific ethnic identity. For example, among Latinx/Hispanic groups, Cubans having the highest risk for OSA relative to other Latinx/Hispanic ethnic groups (Dudley & Patel, 2016). Research is very limited on Native Americans; however, current evidence suggests that Native Americans are 1.7 times more likely than White adults to develop moderate to severe OSA (Dudley & Patel, 2016). Differential risk for OSA also changes during the lifespan. Compared to White young adults, Black young adults are approximately 88% more likely to develop OSA (Dudley & Patel, 2016). Differential risk is present, but to a lower extent in middle-aged adulthood than young adulthood; however, in older adulthood, differential risk increases again such that while Black and White older adults share similar prevalence rates of OSA, black older adults are approximately 2 times more likely to have severe OSA (Dudley & Patel, 2016).

Several factors have been implicated in differential risk for OSA among racial/ethnic groups. First, craniofacial shapes differ among racial groups. Skeletal features, such as the maxillary-mandibular shape, and soft tissue features, such as the size of the tongue and pharyngeal walls may influence susceptibility to OSA (Dudley & Patel, 2016). For instance, an enlarged tongue area is associated with higher risk of OSA among Black adults, while the position of the maxilla is associated with higher risk among Latinx/Hispanic and Asian adults (Dudley & Patel, 2016). Moreover, skull shape is predictive of OSA risk among White adults while length and position of the mandible is predictive of OSA risk among Asian adults. An additional theory is that differential racial risk for OSA is related to obesity. Black adults are 51% more likely to develop obesity compared to other racial/ethnic groups after accounting for key demographics including age, sex, comorbidities, and socioeconomic factors (Dudley & Patel, 2016). Native American and Latinx/Hispanic adults also have significantly higher obesity

rates compared to White adults. Obesity rates, however, are significantly lower among Asian adults which may be related to comparable prevalence rates to White adults. Lastly, socioeconomic status (SES) may be an additional mechanism linking race and elevated risk for OSA (Guglielmi et al., 2019). While systematic reviews have documented the association between SES and risk for OSA (Etindele Sosso & Matos, 2021; Guglielmi et al., 2019), one appears to suggest that after controlling for obesity, SES, and other comorbidities, the direct association between race and risk for OSA diminishes (Guglielmi et al., 2019). This underscores the critical need for evaluating psychosocial and environmental factors contributing differential risk.

Prevalence rates of OSA significantly increase over the lifespan (Fietze et al., 2019; Senaratna et al., 2017). Among adults 18 years and older, middle-aged and older adults had significantly higher rates of OSA, defined as an AHI of 5 or more (Senaratna et al., 2017). Moreover, an AHI of 15 or more was present in 6-17% of adults over 18 years of age, but as high as 36% in late middle-age and older adults. From middle-age to older adulthood there is an additional 2-3 fold increased risk for OSA (Gaspar et al., 2017; Senaratna et al., 2017). Higher risk among middle-aged and older adults have been attributed to physiological and anatomical changes in the upper airways that increase susceptibility to pharyngeal airway collapsibility. These factors include increased pharyngeal fat deposition, structural changes in the soft palate, and reduced ability to produce negative pressure, which enables the upper airway muscles to adapt to airway collapse and maintain patency (Gaspar et al., 2017; Malhotra et al., 2006).

Consequences of Obstructive Sleep Apnea

OSA is associated with a range of deleterious sleep outcomes including fragmented sleep, poor sleep quality, poor sleep efficiency, less total sleep time, and excessive daytime sleepiness

(Frangopoulos et al., 2021; Gottlieb & Punjabi, 2020). Furthermore, there is a high rate of comorbidity between OSA and insomnia disorder (Zhang et al., 2019). Recent meta-analytic evidence suggests 36% of individuals diagnosed with OSA also report insomnia complaints and 38% of individuals meet criteria for insomnia disorder (Zhang et al., 2019). Prevailing theoretical conceptualizations of comorbid OSA and insomnia suggest that OSA may be a precursor for insomnia given that the presence of respiratory events lead to repeated awakenings during the night, and in turn, lead to difficulty maintaining sleep (Ong & Crawford, 2013). Indeed, subjective complaints of difficulty maintaining sleep and early terminal awakening were more frequently reported insomnia symptoms than falling asleep among patients with OSA (Chung, 2005). Furthermore, subjective complaints pertaining to sleep maintenance insomnia were associated with more severe daytime sleepiness and elevated AHI than those reporting sleep-onset insomnia. However, these differences did not translate to significant differences in objective sleep characteristics such as wake after sleep onset (WASO) or sleep efficiency (Chung, 2005). An alternative conceptualization of comorbid OSA and insomnia is that awakenings caused by respiratory events may activate the sympathetic nervous system and increase hyperarousal, making it difficult to fall back asleep (Ong & Crawford, 2013). However, additional investigation is needed, as some longitudinal studies have been unable to find a temporal relationship between OSA and insomnia and some evidence suggesting OSA may contribute to acute insomnia, not chronic insomnia (Ong & Crawford, 2013).

Among individuals with OSA there are higher rates of mental health symptoms (Ejaz et al., 2011; Garbarino et al., 2020). Individuals with OSA are at greater risk of developing depression than those without OSA (Edwards et al., 2020), and the presence of OSA or depression alone is associated with an 18% elevation in risk of developing the other disorder

(Jehan, Auguste, et al., 2017). Individuals with OSA or depression alone both also report similar symptoms of daytime sleepiness, poor concentration, irritability, and fatigue (Ejaz et al., 2011). Ongoing research is aimed at identifying the nature of the association between OSA and depression and the mechanisms involved. The literature has been limited to cross-sectional studies and high variability in study methodology (Edwards et al., 2020; Ejaz et al., 2011). However, several hypotheses have gained attention and support. One theory suggests that sleep fragmentation and hypoxia produced by OSA creates neurophysiological arousals that contribute to disturbance in the sleep-wake cycle, and subsequent daytime sleepiness and depressive symptoms (Ejaz et al., 2011). Alternatively, abnormal neurotransmission of serotonin, a neurotransmitter implicated in depression and upper airway neurons in the hypoglossal nucleus, may limit upper airway patency and elevate risk for depression. Lastly, another theory suggests pro-inflammatory substances and cytokines, such as interleukin 6 and tumor necrosis, may mediate the relationship between OSA and depressive symptoms (Ejaz et al., 2011). While ongoing research continues to investigate these hypotheses and delineate the relationship between OSA and depression, it is clear that OSA and depression are significantly associated and need to be considered in the screening and treatment for OSA.

OSA is also significantly associated with a higher risk of anxiety symptoms and anxiety disorder (Diaz & Brown, 2016; Garbarino et al., 2020; Gupta & Simpson, 2015). Evidence suggests that greater somatic arousal in anxiety disorder elevates experiences of sleepiness and fatigue in individuals with OSA, but may not necessarily increase severity of OSA symptoms (Akberzie et al., 2020; Broderick et al., 2014; Gold et al., 2016). Research delineating the potential pathogenesis of the association between anxiety disorder and OSA is even more limited than the literature on depression and OSA. Similar to depressive symptoms, anxiety symptoms

may develop in response to sleep fragmentation produced directly by apnea/hypopneas and subsequent arousals; however, it is also plausible that anxiety symptoms and OSA may be mediated by other factors such as biological dysregulation (e.g., inflammation, neurotransmitter imbalances) or metabolic dysregulation (e.g., diabetes, obesity, cardiovascular disease; Gupta & Simpson, 2015). It is also plausible that anxiety symptoms may produce cascading effects on the central nervous system that lead to metabolic dysregulation and greater sleep fragmentation.

Individuals diagnosed with OSA often report cognitive complaints. While there is clear, demonstratable evidence of cognitive impairment for individuals with OSA (Bucks et al., 2013, 2017; Olaithe et al., 2018), additional study is needed to clarify the domains most impacted. Consensus exists among meta-analyses and reviews that executive function, attention, memory, and visuospatial/constructional abilities are particularly susceptible to OSA (Bucks et al., 2013; Olaithe et al., 2018; Stranks & Crowe, 2016). According to the most recent meta-review, a small-sized effect was observed for global cognitive ability and medium-sized effects were observed for attention, memory, executive function, and visuospatial abilities (Olaithe et al., 2018). Within the domain of memory, both meta-reviews found that delayed verbal and visual memory were particularly salient. The two meta-reviews differed on the susceptibility of language and psychomotor function. Bucks and colleagues (2013) did not find sufficient evidence of impairment in language and psychomotor domains among individuals with OSA; however, Olaithe et al. (2018) and colleagues found a small-sized effect for language and both Olaithe et al. (2018) and Stranks and Crow (2016) found a large and medium-sized effect for psychomotor function, respectively. Within older adults specifically, OSA is associated with impaired executive function, attention, episodic and declarative memory, verbal and non-verbal memory, and processing speed (Dzierzewski, et al., 2022). However, vigilance, executive function, and

memory are most frequently reported in community-based and clinic-based population studies with various neuropsychological tests. Longitudinal evidence is limited to differing methodological approaches; however, some evidence suggests that OSA is associated with decline in global cognitive ability over 15 years and attention over 8 years (Dzierzewski, Perez, et al., 2022).

Two broad theories exists that explain the relationship between cognitive functioning and OSA (Bucks et al., 2017). One theoretical model suggests that cognitive impairment associated with OSA is a short-term, reversible consequence of poor nighttime sleep (Bucks et al., 2017). This perspective suggests that poor nighttime sleep contributes to daytime sleepiness and/or daytime attention problems and impaired executive function and higher level memory are considered to be the direct result of sleepiness and/or daytime attention impairment (Bucks et al., 2017). The second theoretical model posits that chronic intermittent hypoxia leads to long-term changes in the brain via vascular changes, neural damage, and cell death. These structural and functional changes are implicated in the association between chronic intermittent hypoxia and impaired cognitive function (Bucks et al., 2017). Other mechanisms implicated in this second theoretical model include blood-gas abnormalities and cerebral homeostatic changes. Available evidence suggest that both may be critical processes involved in disease burden, impact, and treatment refractoriness (Bucks et al., 2017).

Beyond specific OSA and cognition theoretical models, other global sleep and cognition theories may explain the association between OSA and cognition (Dzierzewski, Perez, et al., 2022). The Neuropsychological hypothesis suggests that poor sleep in older adults may incur negative effects on domain-specific cognitive abilities that are mediated by the prefrontal cortex (Dzierzewski, Perez, et al., 2022; Jones & Harrison, 2001). Moreover, the cognitive impairment

observed in individuals with OSA is beyond what is expected to be accounted for by attention, vigilance, sleepiness, and arousal alone. Alternatively, the Vigilance/Arousal hypothesis proposes that impaired cognitive function is due to a reduced capacity for sustained attention which is critical for adequate performance on cognitive tasks (Bonnet & Arand, 1995; Dzierzewski, Perez, et al., 2022). Moreover, the impact of sustained attention on cognitive tasks is directly mediated by limited arousal and vigilance following poor sleep. Another critical hypothesis, the Controlled Attention hypothesis, posits that cognitive tasks that are monotonous or less intrinsically motivating are more susceptible to the cognitive consequences of poor sleep because greater emphasis is placed on top-down control processes for sustaining attention (Dzierzewski, Perez, et al., 2022; Jaussent et al., 2012). In contrast, cognitive tasks that are more complex and difficult are more intrinsically motivating and involve greater emphasis of bottom-up processes. As noted with specific OSA and cognition theories, all global sleep and cognition theories may not be mutually exclusive (Dzierzewski, Perez, et al., 2022) and may all be involved in similar or different aspects of the association between OSA and cognitive function in middle-aged and older adults.

Treatment Options for Obstructive Sleep Apnea

Oral appliances are an effective treatment option for adults with mild-to-moderate OSA severity (Gottlieb & Punjabi, 2020; Ramar et al., 2015). Oral appliances are a set of plates that are made to fit the upper and lower teeth and can be adjusted to move the lower mandible forward in order to increase airflow volume. Oral appliances are tolerated well among patients including those who are not tolerant to continuous positive airway pressure treatment (Gottlieb & Punjabi, 2020). Objective and subjective measurement of adherence rates for oral appliances at 1-year follow-up is over 80% (Dieltjens et al., 2013; Sutherland et al., 2021). However, oral

appliances are less effective than positive airway treatment in most patients, especially those within severe OSA symptoms (Gottlieb & Punjabi, 2020). General behavioral recommendations may also be provided to adults managing sleep apnea symptoms including abstinence from alcohol, regular exercise, and/or weight loss (Gottlieb & Punjabi, 2020). Sleeping on a side or prone position is recommended to individuals with positional OSA.

Surgical modification is an alternative treatment option for patients who have been unable to tolerate positive airway pressure (PAP) treatment or for whom an oral appliance would be ineffective (Gottlieb & Punjabi, 2020). Surgical consultation is also recommended by the American Academy of Sleep Medicine (AASM) for individuals who are unable to tolerate PAP treatment (Kent et al., 2021). There are many types of upper airway surgical procedures that may minimize anatomical obstruction of the airway during sleep and are typically identified according to the target, such as the nasal (e.g., septoplasty and nasal valve), oral/palatal (uvulopalatopharyngoplasty), hypopharyngeal (ablation of the tongue), and other sites (tracheostomy; Lee & Sundar, 2021). For example, an uvulopalatopharyngoplasty (UPPP) is a surgical procedure in which there is an excision of the upper airway soft tissues including the soft palate and tonsils, and the tonsillar pillars are closed (Caples et al., 2010; Sutherland et al., 2014). Multi-level surgeries, which include more than one surgical approach, are performed when there at multiple sites of airway collapse (Lee & Sundar, 2021).

Recently, hypoglossal nerve stimulation (HNS) has emerged as an alternative, efficacious treatment modality for individuals with moderate or severe OSA who are intolerant of PAP treatment (Mashaqi et al., 2021). Individuals interested in pursuing HNS treatment undergo a comprehensive health history screen, sleep comorbidities, overnight diagnostic polysomnography (PSG), and BMI (Mashaqi et al., 2021). Furthermore, individuals complete a

drug-induced sleep endoscopy which is designed to investigate tongue base and palate collapse. During an outpatient surgical procedure lasting 90-180 minutes, a generator is inserted under the skin in the upper right chest. A hypoglossal nerve stimulator is a device that uses the generator inserted in the chest to produces electrical impulses that travel through a tunneled lead that ends at a cuff electrode surrounding the hypoglossal nerve (Mashaqi et al., 2021). The HNS procedure operates by providing electrical stimulation to the genioglossus muscle, which in turn, produces protrusion of the tongue and stiffens the pharyngeal wall (Eastwood et al., 2011). Of the hypoglossal nerve stimulator devices tested in clinical trials, only the Inspire Medical Systems device is currently approved by the Federal Drug Administration (FDA) for the treatment of OSA. The Inspire system contains several components. The generator placed in the upper right chest generates the electrical impulse that travels to the hypoglossal nerve (Mashaqi et al., 2021). The generator contains two ports. One port contains a respiratory sensing lead that is programmed to detect respiratory efforts via mechanical signals and converts the mechanical signals into electrical signals. The second port, the stimulation lead, transmits the electrical signals to the hypoglossal nerve through electrodes located in the inner surface of the cuff (Mashaqi et al., 2021). The device is activated after the patient has been provided sufficient time to heal and rest after the surgical procedure, typically four weeks. Patients are also provided with a remote they can use to turn device on or off, set on pause during nighttime awakenings, and modify the strength of the electrical stimulation (Mashaqi et al., 2021).

PAP therapy is the gold standard treatment for OSA and is effective for individuals with OSA at any severity level, level of airway collapse, or body weight (Gottlieb & Punjabi, 2020). PAP provides normal oxygenation to individuals during sleep through a mask worn over the nose, or over the nose and mouth. Despite the clinical effectiveness of PAP treatment, its utility

is undercut by low adherence rates (Rotenberg et al., 2016). PAP intolerance is defined as the inability to use PAP for five nights per week or more, for four hours per night or more (Mashaqi et al., 2021). Moreover, intolerance is characterized by patients who are unwilling to use PAP after discontinuing its use. Non-adherence rates have not significantly improved in the last 15 years and have remained between 30-40% (Rotenberg et al., 2016). Some cited reasons for PAP intolerance include nasal discomfort, congestion, mask leak, dermatitis, rhinitis, and claustrophobia (Virk & Kotecha, 2016).

Clinical Outcomes for Obstructive Sleep Apnea Treatment

A recent systematic review and meta-analysis of 184 studies on treatment outcomes for OSA following PAP treatment was published by the AASM (Patil et al., 2019). High quality evidence from the meta-analysis shows that PAP treatment for OSA is associated with clinically significant reductions in OSA severity and subjective reports of excessive daytime sleepiness (Patil et al., 2019). Moreover, OSA severity was reduced by up to 86% following PAP treatment. In terms of specific sleep characteristics, 6 months of PAP treatment was associated with significantly improved objective sleep quality, sleep duration, and sleep consolidation (Quan et al., 2018). While both non-surgical options, oral appliance therapy and PAP therapy, improve OSA severity, evidence from 11 studies show that AHI scores improve significantly more in PAP treatment than oral appliance therapy and a greater proportion of patients experience completion resolution of OSA in PAP treatment (Iftikhar et al., 2017; Sutherland et al., 2014). Furthermore, nearly double the number of patients experience a complete response to PAP treatment than oral appliance therapy, which was defined as less than 5 obstructive respiratory events per hour (Sutherland et al., 2014).

Extensive research on treatment outcomes for OSA also suggest cognitive benefits for patients who undergo PAP treatment. After one month of PAP treatment, Rosenzweig et al. (2016) found significant improvement in patients' episodic memory, working memory, executive function, processing speed, and attention. After 3 months of PAP treatment, significant improvement was observed for global cognitive function (Castronovo et al., 2014; Kanbay et al., 2017), attention and processing speed (Barnes et al., 2004; Castronovo et al., 2014), short-term visual and verbal memory (Castronovo et al., 2014; Turner et al., 2019), and working memory (Castronovo et al., 2014; Turner et al., 2019). Furthermore, a meta-analysis performed by Olaithe and Bucks (2013) revealed significant improvement among patients in five separate domains of executive function following PAP treatment. Medium-sized effects were noted for shifting and inhibition abilities and small-sized effects for updating, fluid reasoning, and generativity (Olaithe & Bucks, 2013). One recent narrative review also found evidence supporting the cognitive benefits of OSA treatment in older adults (Dzierzewski, Perez, et al., 2022). Review of the literature indicated significant improvement among older adults for episodic learning and memory, short-term memory, executive function, working memory, attention, psychomotor speed, and nonverbal delayed recall following 3 months of PAP treatment (Dzierzewski, Perez, et al., 2022).

Treatment for obstructive sleep apnea has also been shown to lead to significant improvement in mental health symptoms, particularly anxiety and depression. Patients who complete 3 months of PAP treatment demonstrate significantly improved depressive symptoms (Canessa et al., 2011) that is maintained after 6 months of PAP treatment (Lee et al., 2017). Anxiety symptoms following OSA treatment have been studied to a lesser degree than depressive symptoms; however, anxiety symptoms have also been shown to improve after 6

months of PAP treatment (Lee et al., 2017). These findings are bolstered by systematic reviews indicating significantly improved anxiety symptoms, depressive symptoms, and quality of life following PAP treatment for OSA (Aftab et al., 2021; Gupta et al., 2016).

A recent systematic review and meta-analysis indicates that HNS is associated with long-term benefits in daytime sleepiness and OSA severity (Certal et al., 2015; Costantino et al., 2020). HNS has been linked to significant reduction in OSA severity after 1 year, and the effects were durable, persisting between 3 to 5-years post-baseline. Moreover, 75% of participants showed greater than 50% reduction in OSA severity at 5-year follow-up (Woodson et al., 2018). There is little research available on mental health outcomes following the HNS procedure; however, some data suggests that patients who complete HNS also report significant improvement in depressive symptoms at 1-year follow up (Pascoe et al., 2022).

Only one study to date has reported preliminary neurocognitive outcomes following HNS (Grieco et al., 2021). The pilot study was a single group, pretest-posttest design that investigated intelligence, expressive vocabulary, communication, working memory, attention, and processing speed in a sample of pediatric patients between the ages of 10 and 21 who were diagnosed with Down Syndrome and had severe residual OSA. Nine participants completed cognitive and behavioral testing prior to HNS and approximately 6.5 months following the procedure. Greico et al. (2021) found significant improvement on tests of intelligence, communication, and attention; however, no significant improvement was found for expressive vocabulary, working memory, or processing speed. Given that HNS treatment is considered an effective, alternative treatment for individuals intolerant to PAP treatment for OSA, further research is needed to determine whether mental health and cognitive benefits obtained from PAP treatment are also present for patients who undergo HNS treatment.

Current Investigation Aims and Hypotheses

Despite the promise of HNS as a novel approach to OSA treatment, few studies have examined the mental health benefits of this treatment approach, and none have examined objective cognitive outcomes in adults. Moreover, very few studies have examined subjective sleep outcomes following HNS. This gap in the literature is an important area to explore as HNS is considered a viable alternative to the gold standard treatment, PAP therapy. The purpose of the study was to fill these gaps in the literature by examining the sleep, mental health, and cognitive outcomes of middle-aged and older adults with OSA before and after HNS treatment.

Figure 2 contains a conceptual model for the anticipated benefits of HNS on sleep, mental health, and cognitive outcomes based on evidence garnered from the literature. First, patients who undergo HNS have shown significantly improved apnea severity (Certal et al., 2015; Costantino et al., 2020; Woodson et al., 2018). Thus, as it has been shown with PAP treatment (Quan et al., 2018), improved sleep apnea severity was expected to lead to reduced sleep fragmentation, and in turn, improved sleep quality. Improved sleep consolidation and sleep quality were also expected to lead to reduced daytime sleepiness (Certal et al., 2015; Costantino et al., 2020). Preliminary data showed HNS may be associated with improved depression (Pascoe et al., 2022), and several studies showed evidence of improved depressive symptoms (Canessa et al., 2011; Lee et al., 2017) and anxiety symptoms (Gupta et al., 2016; Lee et al., 2017) following PAP treatment. Therefore, improved sleep apnea severity was hypothesized to lead to reductions in depression, anxiety, and anger directly. Depressive symptoms may have also been benefitted from improved sleep quality, and the reverse, reduced depressive symptoms may have translated to improved sleep quality. This was predicted due to the bi-directional relationship between sleep and depression (Bao et al., 2017; Fang et al., 2019). While there is some evidence of a bi-

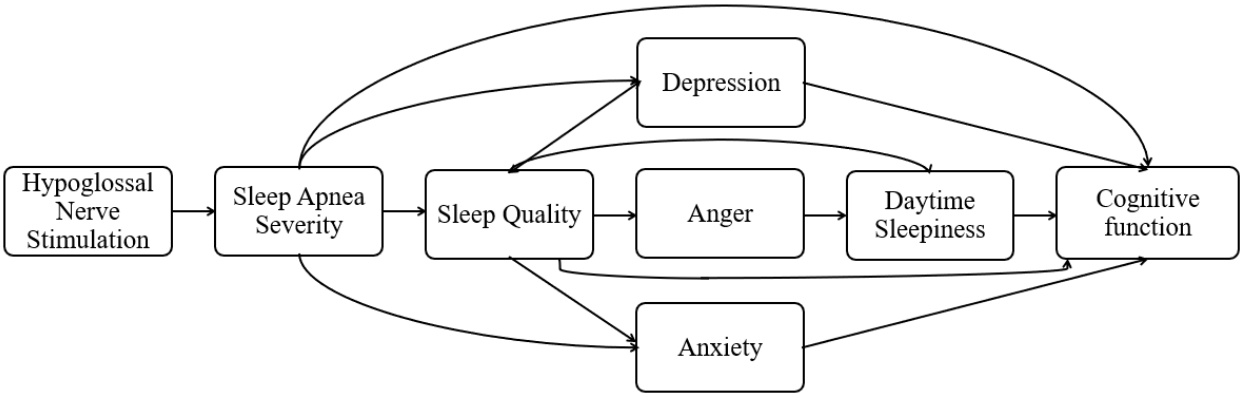
directional association between sleep and anxiety (Jansson-Fröjmark & Lindblom, 2008) the evidence is weaker than the literature on sleep and depression, with most studies showing longitudinal precedence for improved sleep leading to improved anxiety (Lee et al., 2017; Scott et al., 2021). Thus, sleep quality was predicted to lead to improved anxiety symptoms. Evidence regarding changes in anger after OSA treatment has been sparse. The study aimed to contribute additional information to the literature regarding anger and OSA treatment. Finally, some cognitive benefit was found for HNS in a pediatric population (Grieco et al., 2021), and extensive evidence showed cognitive benefits following PAP treatment (Castronovo et al., 2014; Dzierzewski, Perez, et al., 2022; Olaithe & Bucks, 2013; Rosenzweig et al., 2016; Turner et al., 2019). Given theoretical models suggesting cognitive impairment from OSA may be due to the short-term reversable impact of poor sleep quality and daytime sleepiness (Dzierzewski, Perez, et al., 2022; Ejaz et al., 2011), improved sleepiness was expected to lead to improved cognitive function. Furthermore, cognitive improvement was also anticipated following improved sleep quality (Dzierzewski, Perez, et al., 2022; Miyata et al., 2013; Nebes et al., 2009), depressive symptoms (McDermott & Ebmeier, 2009) and anxiety symptoms (Beaudreau & O'Hara, 2008), factors that are independently associated with poor cognitive function.

The current study had four aims and hypotheses:

Aim 1: To confirm evidence from the literature regarding improved objective and subjective sleep, including total sleep time, number of nighttime awakenings, total wake after sleep onset, sleep efficiency, and sleep quality from pre-to-post HNS for middle-aged and older adults.

Hypothesis 1: Objective and subjective measures of total sleep time, number of nighttime awakenings, total wake after sleep onset, sleep efficiency, and sleep quality will show significant improvement following HNS treatment.

Figure 2: Conceptual model of Hypoglossal Nerve Stimulation (HNS) and predicted direct and indirect clinical outcomes.



Note: Sleep quality includes sleep consolidation, sleep characteristics, and insomnia symptoms. Cognitive function includes global cognitive function, attention, memory, visuospatial abilities, processing speed, and executive function.

Aim 2: To assess changes in self-reported sleepiness, insomnia severity, and sleep disturbance before and after the HNS procedure.

Hypothesis 2: Patients who undergo HNS treatment will report significant improvement in sleepiness, insomnia severity, and sleep disturbance.

Aim 3: Investigate changes in objective and subjective global cognitive function as well as individual cognitive domains before and after HNS treatment.

Hypothesis 3: HNS treatment will be associated with significant improvement in objective and subjective global cognitive function and individual cognitive domains of executive function, memory, visuospatial/constructional abilities, and attention.

Aim 4: To investigate changes in self-reported depression, anxiety, and anger from pre-to-post HNS treatment.

Hypothesis 4: Patients who undergo HNS treatment will report significant improvement in depression, anxiety, and anger following HNS treatment.

Methods

Participants

Participants were recruited from the Virginia Commonwealth University Healthcare System (VCUHS). In order to be eligible, participants must have been: 1) 50 years or older, 2) diagnosed with OSA, 3) eligible for INSPIRE (HNS) and provided consent to complete the procedure, 4) able to speak and read English for brief cognitive assessments and questionnaires, and 5) possess the cognitive capacity to provide consent. Patients are eligible for INSPIRE if they are over 22 years old, have moderate to severe OSA, and have been unable to use PAP continuously for five nights or more per week for four hours or more per night or are unwilling to use PAP again after discontinuation (Mashaqi et al., 2021). Eligibility for INSPIRE is contraindicated in patients with central sleep apnea, sleep-related hypoxia or hypoventilation, complete concentric collapse of the palate during apneas or hypopneas, or a body mass index of 32 kilograms or more (Mashaqi et al., 2021). Cognitive capacity for consent was determined using the Mini Mental Status Exam (MMSE; Folstein et al., 1975), a brief screening instrument designed to provide an estimate of overall cognitive ability in adults. Participants with a total raw score of 22 or above were considered eligible to participate in the study and provide consent for participation. Evidence suggests this score yields sufficient classification accuracy for dementia in diverse older adults (Pedraza et al., 2012).

Measures

Demographics. A demographic form was completed by all participants enrolled in the study. The demographic form contained questions pertaining to age, height, weight, gender, race, marital status, highest level of education, employment status, and household income.

Daily Sleep. Wrist actigraphy was used to obtain nightly objective sleep information before and after the HNS procedure. Actigraph devices were worn by participants for one week at both timepoints concurrent with their completion of online or physical daily sleep diaries. Actigraph devices are similar in form to wristwatches, and are worn on the non-dominant wrist to record movement and estimate sleep characteristics based on algorithms contained within the actigraph software (Martin & Hakim, 2011). A report published by the AASM recommended the use of actigraphy for the measurement and evaluation of sleep and sleep disorders including obstructive sleep apnea (Smith et al., 2018). Furthermore, it is recommended for characterizing sleep, circadian patterns, and treatment responses in older adults who may have difficulty with traditional sleep monitoring. Actigraphy has been shown to have high sensitivity (96.5%), the ability to detect sleep states, but low specificity (33.3%), the ability to detect wake states within sleep periods when compared to polysomnography in a sample of older adults (Marino et al., 2013). Test-retest reliability is stable over time with previous data showing correlations within acceptable to excellent range for sleep duration (.76), sleep efficiency (.90), and sleep latency (.93; Knutson et al., 2007). Outcome measures were total sleep time, number of nighttime awakenings, total wake after sleep onset, and sleep efficiency.

The Consensus Sleep Diary (CSD) is a standardized self-monitoring tool that was used to measure nightly subjective sleep information before and after the HNS procedure (Carney et al., 2012). Participants completed the online sleep diary daily for one week at both timepoints.

Online sleep diaries were administered using VCU Redcap, a software application designed to facilitate online data collection and management. Online sleep diaries were emailed every morning to participants at 6am. If no response was recorded by 2pm on any day of sleep monitoring, participants were called and reminded of their sleep diary entry for that day.

Sleep diaries are widely used and accepted instruments for measuring subjective sleep information (Buysse et al., 2006; Trauer et al., 2015; Tu et al., 2021; van der Zweerde et al., 2019). These self-monitoring tools ask participants to answer questions pertaining to waketime, bedtime, sleep latency, total sleep time, total nighttime awakenings, total wake time, and sleep quality. Waketime, bedtime, and total sleep time information provided by participants on the sleep diary also enable the calculation of sleep efficiency. Sleep efficiency is a metric frequently used to indicate the percentage of time an individual spends asleep in bed out of the total amount of time they spend in bed. Data obtained from sleep diaries demonstrated good concurrent validity with subjective reports of sleep disturbance and actigraphy-measured sleep (Maich et al., 2018). Sleep diary has also been shown to be a reliable measure of subjective sleep with reliability increasing with the number of consecutive days recorded (Borba et al., 2020). Reliability for seven consecutive days of self-monitoring with sleep diary generates adequate reliability ($\alpha = .70$). Outcome measures for the sleep diary were total sleep time, number of nighttime awakenings, total wake after sleep onset, and sleep quality.

Daytime Sleepiness. The Epworth Sleepiness Scale (ESS) is an 8-item instrument that is frequently used to measure level of daytime sleepiness (Johns, 1991). The ESS was used to measure participants' level of daytime sleepiness before and after the HNS procedure. Participants rate their level of sleepiness in eight situations during the past week. Each item is scored on a scale from 0, indicating "No chance of dozing" to 3, "High chance of dozing." Total

scores on this scale range from 0 to 24 with higher scores indicating a higher level of sleepiness. A systematic review of 35 studies evaluating the psychometric properties of the ESS suggest the internal consistency of the scale is within the good range (.73-.86) and has moderate support for test-retest reliability (Kendzerska et al., 2014). The outcome measure for ESS was the total sleepiness score.

Sleep Disturbance. The PROMIS Sleep Disturbance short form is a brief 8-item measure that is designed to assess the presence and severity of sleep-wake problems during the past week (Yu et al., 2011). Participants completed the Sleep Disturbance short form before and after the HNS procedure. The short form was developed by reducing the number of items on the longer 16-item version (Buysse et al., 2010). The longer version was developed using literature reviews, qualitative item review, focus groups, cognitive interviewing, and psychometric testing methods that include classical test theory and item response theory. Participants were asked to indicate how often each of the following symptoms occurred during the past week. Responses to each item ranged from "1" indicating "Not at all" to 5 "Very much." Total raw scores range from 8 to 32 with higher scores suggesting greater sleep disturbance. These scores can also be converted to T-scores for additional descriptive interpretation. T-scores less than 55 suggest "None to slight" sleep disturbance, 55 to 59 suggest "Mild," 60 to 69 suggest "Moderate," and 70 and above suggest "Severe" sleep disturbance symptoms. The reliability of the sleep disturbance short form was excellent with a reliability coefficient at .90 (Yu et al., 2011). Moreover, the short form version of the scale was highly correlated to the full bank of items on the original scale at .98. The outcome measure for the PROMIS Sleep Disturbance short form was the total raw score.

Insomnia Symptoms. The Insomnia Severity Index (ISI) is a 7-item instrument measuring the presence and severity of insomnia symptoms during the past two weeks (Bastien

et al., 2001). Participants completed the ISI before and after the HNS procedure. The first three items on the scale ask participants to rate the severity of insomnia symptoms from "0" indicating "None" to "4" indicating "Very severe." The remaining questions on the measure ask participants to rate the level of distress, dissatisfaction, and consequences associated with insomnia symptoms. Responses to these items also range from "0" indicating "Not at all" or to "4" indicating "Very much." Total scores range from 0 to 28 with higher scores indicating greater severity of insomnia symptoms. Scores between 0 and 7 suggest "No clinically significant insomnia," 8 to 14 suggest "Subthreshold insomnia," 15 to 21 suggest "Clinical insomnia (moderate severity)", and 22 to 28 suggest "Clinical insomnia (severe)." Evidence indicates the ISI has excellent internal consistency in a clinical and community sample (Morin et al., 2011). Moreover, there is evidence of concurrent validity with measures of depression, anxiety, fatigue, and subjective and objective measures of sleep, and sensitivity to detecting changes after treatment (Bastien et al., 2001; Morin et al., 2011). The outcome measure for the ISI was the total ISI score.

***Repeatable Battery for the Assessment of Neuropsychological Status*.** The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al., 1998) is a brief neuropsychological test battery designed to identify and characterize cognitive deficits and decline. The battery is comprised of ten subtests that are used to compute scores for five cognitive domains and overall cognitive status. The five cognitive domains include: immediate memory, visuospatial/constructional ability, language, attention, and delayed memory. Immediate memory measures participants' ability to remember information immediately after presentation (Randolph, 2012). The Visuospatial/Constructional domain measures participants' ability to perceive spatial relationships and construct spatially accurate copies of designs. The

Language domain assesses the ability to verbally name and retrieve learned material (Randolph, 2012). The Attention domain examines the capacity to remember and manipulate visual and oral information in short-term memory. Lastly, the Delayed memory domain examines participants' anterograde memory capacity after a delay (Randolph, 2012).

The RBANS contains four equivalent forms, Forms A-D, which facilitates repeated testing over short time periods while limiting practice effects. Form A of the RBANS was administered before the HNS procedure and Form B was administered after the HNS procedure. The battery takes approximately 20-30 minutes to administer. RBANS normative information was developed from a representative sample of US participants between the ages of 20-89 years old. The battery was found to be a sensitive, valid, and reliable assessment for detecting cognitive impairment among adults from various age groups, as well as the detection and characterization of dementia (Randolph et al., 1998). Additional test-retest reliability data obtained from Duff et al. (2005) suggests the battery is reliable in a sample of older adults 65 years and above (r = .81-.83). Test-retest reliability coefficients for index scores ranged from .58 to .83 (Duff et al., 2005). Outcome measures for the RBANS were the total scale score and index scores for immediate memory, visuospatial/constructional, language, attention, and delayed memory.

Trail Making Test (TMT). The Trail Making Test (TMT) is a brief, frequently administered neuropsychological task that contains two subtests (Reitan, 1958). Participants completed the Trail Making Test before and after the HNS procedure. On the first subtest, Trails A, participants were asked to draw lines connecting numbered circles scattered on a single page in numerical order "as fast you can." Trails A is primarily a measure of complex visuo-motor scanning and tracking, attention, and processing speed (Arbuthnott & Frank, 2000; Lezak et al.,

2012). The second subtest, Trails B, presents numbered and lettered circles. Trails B asked individuals to alternate between drawing lines connecting numbered circles in numerical order and lettered circles in alphabetical order scattered on a single page "as fast as you can." Trails B is viewed as a measure of visual-motor scanning and tracking, as well as executive function, particularly cognitive flexibility, inhibition, and task-switching ability (Arbuthnott & Frank, 2000; Kortte et al., 2002; Lezak et al., 2012). Meta-analytic data suggest test-retest reliability for the TMT is adequate for Trails A (r = .66) and good for Trails B (r = .77; Calamia et al., 2013). The outcome measure for Trails A and Trails B was completion time. Shorter completion times on Trails A and B indicate better performance on these tasks and suggest better visual-motor scanning and tracking, processing speed, attention, and executive function.

Subjective Cognitive Function. The 6-item PROMIS Cognitive function short form was used to assess participants' perceived cognitive function during the past 7 days (Lai et al., 2014). The PROMIS Cognitive function was completed before and after the HNS procedure. Participants rate how often they have had problems with various cognitive skills and abilities including attention, memory, and processing speed. Responses to each item are rated on a five-point Likert scale ranging from "1" indicating "Never" to "5" indicating "Very Often (Several times a day)." Total raw scores on the scale range from 6 to 30. Raw scores were converted to T-scores in order to facilitate interpretation. Higher raw scores and T-scores indicate better perceived cognitive function while lower raw scores and T-scores suggest poorer perceived cognitive function. The PROMIS Cognitive Function short form had excellent internal consistency (α = .94) in a large sample of adults 18 to 99 years old (Iverson et al., 2021). Construct validity was bolstered by significant associations with similar and related constructs. In a sample of older adults, the longer version of the PROMIS Cognitive function scale was

correlated with the Saint Louis University Mental Status (SLUMS; Tariq et al., 2006) and MMSE (Howland et al., 2017). Furthermore, 1-year changes in perceived cognitive function were associated with 1-year changes in total scores on the MMSE.

Depression. The presence and severity of depressive symptoms during the past week was assessed using the 8-item short form of the PROMIS Depression short form before and after the HNS procedure (Pilkonis et al., 2011). Participants indicated on the form how often they have been bothered by a set of depressive symptoms during the past 7 days, such as feelings of worthlessness, failure, and helplessness. Responses to each item are rated on a five-point Likert scale ranging from "1" indicating "Never" to "5" indicating "Always." Total raw scores on the scale range from 8 to 40. Raw scores may be converted to T-scores in order to facilitate descriptive score classifications. Similar to the PROMIS Sleep Disturbance short form, T-scores less than 55 indicate "None to slight" depressive symptoms, 55 to 59 indicate "Mild," 60 to 69 indicate "Moderate,", and 70 and above indicate "Severe" depressive symptoms. Internal consistency of the short form was excellent ($\alpha = .95$) and the item-total correlation was good at .83 (Pilkonis et al., 2011). The short form measure was also highly correlated with the longer, full item bank version of the PROMIS Depression form. Prior research also found very little differential item functioning across racial/ethnic, educational, age, gender, and language groups (Teresi et al., 2016). The outcome measure for the PROMIS Depression short form was the total raw score.

Anxiety. The presence and severity of anxiety symptoms during the past week was assessed using the 7-item short form version of the PROMIS Anxiety short form before and after the HNS procedure (Pilkonis et al., 2011). The PROMIS Anxiety short form is structured and is scored in a similar fashion to the PROMIS Depression short form. Participants were asked to

indicate how often they are bothered by a list of symptoms associated with anxiety, such as feeling worried, anxious, and/or tense. Responses to each item ranges from "1" indicating "Never" to "5" indicating "Always." Total raw scores range from 7 to 35 with higher scores indicating greater symptom severity. Raw scores may also be converted to T-scores to obtain descriptive classifications. Descriptive classification of T-score ranges for the PROMIS Anxiety is identical to classification for PROMIS Sleep Disturbance and PROMIS Depression scales. Internal consistency for this scale is also excellent ($\alpha = .93$) with good item-total correlations at .79 (Pilkonis et al., 2011). The short form anxiety scale was also highly correlated (.96) with PROMIS full item banks for anxiety. The outcome measure for the PROMIS Anxiety short form was the total raw score.

Anger. Anger was measured before and after HNS using the 5-item PROMIS Anger short form (Pilkonis et al., 2011). The PROMIS Anger short form is also structured similarly to the PROMIS Depression and Anxiety short-forms. Participants rated how often they were "bothered by feeling irritated, grouchy, or angry" during the past week. Responses to each item ranged from "1" indicating "Never" to "5" indicating "Always." Total raw scores range from 5 to 30 with higher scores indicating more anger and lower scores indicating less anger. T-scores were also obtained to facilitate descriptive classification which were also identical to other PROMIS measures. The PROMIS Anger short-form had excellent internal consistency ($\alpha = .90$) and was highly correlated to the full scale PROMIS Anger scale (.95; (Pilkonis et al., 2011). Moreover, the short-form was moderately correlated ($r = .52$) with the anger and verbal aggression subscales of the Aggression Questionnaire (Buss & Perry, 1992). The outcome measure for the PROMIS Anger short form was the total raw score.

Study Design and Procedure

The study was a single-group, pretest-posttest design that compares cognitive status, mental health, and sleep prior to HNS and 2-3 months following the HNS procedure. Patients with OSA who are not adherent to PAP treatment were seen for consultation for the HNS procedure by a licensed physician in otolaryngology specializing in medical and surgical management of the ear, nose, and throat. The physician uses several sources of information, including a drug-induced sleep endoscopy (DISE), to determine candidacy for the HNS procedure. The physician met with patients for a follow-up appointment to discuss the results of the DISE, share clinical impressions, and discuss treatment options. If the patient was considered a good candidate for the INSPIRE treatment and the patient provided consent to obtain treatment, patients were contacted about their interest in participating in the proposed study.

The study entails four in-person appointments; two before the HNS procedure and two after the procedure. Please see Figure 3 below for a visual depiction of the proposed study procedures and timeline. Upon providing consent, participants completed their first study visit either at the clinical setting directly after their follow-up appointment with their provider or at a research lab at VCU following telephone contact. The MMSE was completed following the provision of consent to participate. If eligible, participants completed a brief demographic form and were provided with wrist actigraphy and instructions for completing an online sleep diary. A link to the sleep diary questions was emailed every morning at 6am to participants via VCU Redcap. After one week of wrist actigraphy and daily sleep diary, participants met with research staff for their second study visit. At the second visit, participants completed the RBANS, TMT, and questionnaires assessing mental health, sleep, and cognitive function. The first two visits provided a baseline representation of current cognitive, mental health, and sleep functioning

prior to HNS. Cognitive and mental health assessment occurred one week after sleep assessment in order to establish a temporal relationship between variables whereby sleep precedes mental health and cognitive function.

Usual care guidelines for the HNS procedure recommend four weeks for patients to heal from the surgical procedure and address adverse events (Mashaqi et al., 2021). The HNS generator is inactive during this time period. Typically, four weeks after the procedure, patients meet with a sleep technician to activate the generator. Approximately 2-3 months after the HNS procedure has been completed, participants met with their provider to assess current functioning and OSA severity. Participants were contacted after this medical appointment to schedule their third and fourth study visits. The third study visit repeated the procedures of the first study visit with the exception of the demographic questionnaire and brief cognitive screener. Participants received wrist actigraphy and instructions for using actigraphy and completing sleep diary questions. One week after the third appointment, participants completed their fourth and final study visit. The final visit replicated the procedures of the second study visit with the assessment of cognitive and mental health functioning. During the final visit, Form B of the RBANS and a reversed TMT was administered.

Data Analysis

Two-tailed dependent samples *t*-tests were used to detect significant differences in sleep, mental health, and cognitive function before and after the HNS procedure using the Statistical Package for the Social Sciences (SPSS). A power analysis for the proposed aims using G-power indicated a sample size of 199 participants was needed in order to detect a small effect size or larger (.20) at a 5% error rate. However, given that the average length of time needed for participants to complete all study visits lasted approximately 4-6 months and study data

collection lasted approximately one year, the ability to obtain the desired sample size was limited. Therefore, sample size estimates for successful detection of small-medium and medium effect sizes were also computed to provide a range of sample sizes. A sample size of 52 participants was needed to detect a small-medium effect (.40) at a 5% error rate and a sample size of 34 was needed to detect a medium effect (.50) or larger with a 5% error rate. Therefore, the study attempted to enroll between 34-52 participants to maximize power to detect medium to small-medium effect sizes, respectively.

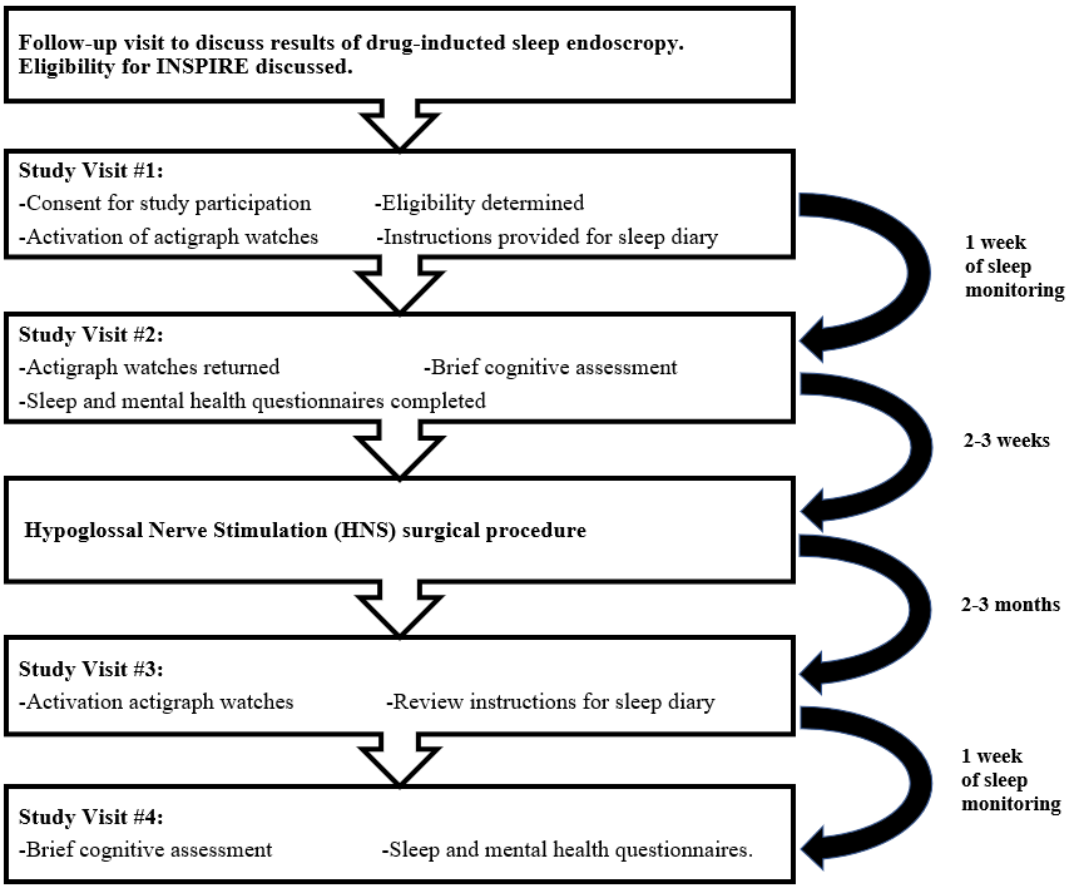
A Reliable Change Index (RCI) was used to determine whether the magnitude of the change before and after the HNS procedure is statistically reliable (Jacobson & Truax, 1991). The RCI is designed to account for measurement error and is calculated as the individual pre-test score minus the individual post-test score. The difference between the two scores is then divided by the standard error of measurement of the difference score. RCI scores equal to or greater than 1.96 indicate a statistically significant change in functioning. An RCI of 1.96 is equivalent to the 95% confidence interval and indicates that the difference between pre- and post-test scores is at least two times greater than the standard error of the difference scores. RCI analyses were performed using parameters from the current sample, including standard deviation and test-retest reliability of the sample for each outcome variable. A summary of the analytic plan and the variables specified for each analysis is provided below.

Aim 1 Analytic Plan

Dependent *t*-test. Independent variable was Time (1, 2). Dependent variables were objective and subjective total sleep time, subjective sleep onset, number of nighttime awakenings, total wake after sleep onset, sleep efficiency and subjective sleep quality.

Reliable Change Index. The RCI was completed using sleep characteristics pre-HNS minus sleep characteristics post-HNS.

Figure 3: Study Procedures and Timeline



Aim 2 Analytic Plan

Dependent *t*-test. Independent variable was Time (1, 2). The dependent variables were total ESS score, ISI score, and PROMIS Sleep Disturbance score.

Reliable Change Index. The RCI was completed using total scores pre-HNS minus total score post-HNS.

Aim 3 Analytic Plan

Dependent *t*-test. Independent variable was Time (1, 2). The dependent variables were RBANS total scale score and index scores for immediate memory, visuospatial/constructional, attention, language, and delayed memory. PROMIS Cognitive function, and the completion times for Trails A and B were also dependent variables.

Reliable Change Index. RCI was completed using RBANS total score pre-HNS minus RBANS total score post-HNS, index scores pre-HNS minus index scores post-HNS, Trails A and B time pre-HNS minus Trails A and B time post-HNS, and PROMIS Cognitive Function pre-HNS minus PROMIS Cognitive Function post-HNS.

Aim 4 Analytic Plan

Dependent *t*-test. Independent variable was Time (1, 2). The dependent variables were total scores for PROMIS Depression, PROMIS Anxiety, and PROMIS Anger scales.

Reliable Change Index: The RCI was performed using total scores for PROMIS Depression, Anxiety, Anger pre-HNS minus total scores for PROMIS Depression, Anxiety, Anger post-HNS.

Results

Sample Demographics

Participant demographics, means, and standard deviations for all variables are presented in Table 1. One participant was excluded during the study screening process. Eleven participants were recruited to participate in the study. One participant stated they were no longer interested in pursuing surgery and was lost to follow-up. The final sample at post-assessment consisted of 10 participants. Trail making test data was missing for one participant. Two participants had missing data for actigraphy post-HNS. Finally, sleep onset latency data was not captured with actigraphy during pre-HNS and post-HNS due to data corruption. Participants were middle-aged

and older (*M* = 64.73, *SD* = 7.38). Most participants identified as white (90.9%), male (63.6%), and were married (72.7%). The highest level of education among participants was a bachelor's degree (36.4%) and most participants were retired (45.5%). Household income ranged widely from $25,001 to $200,000 (72.7%).

Prior to surgery participants total MMSE score (*M* = 28.27, *SD* = 2.10) and RBANS score (*M* = 92.45, *SD* = 18.10) suggested they were within average cognitive range. Immediate memory (*M* = 95.45, *SD* = 25.30), visuospatial/constructional abilities (*M* = 90.82, *SD* = 18.08), language (*M* = 97.36, *SD* = 10.08), attention (*M* = 92.82, *SD* = 18.69), and delayed memory (*M* = 94.91, *SD* = 17.27) were all within average range. Trails A (*M* = 46.94, *SD* = 13.00) and Trails B (*M* = 92.07, *SD* = 28.97) performance at baseline suggested low average processing speed and average executive function, respectively. PROMIS Cognitive function scores also suggested that participants viewed their current cognitive status as low average (*M* = 16.45, *SD* = 5.92). Participants rated anxiety symptoms (*M* = 13.27, *SD* = 5.71), depressive symptoms (*M* = 13.45, *SD* = 5.92), and anger (*M* = 12.09, *SD* = 4.74) within normal range.

Participants reported mild sleep disturbance (*M* = 27.18, *SD* = 6.08), higher normal daytime sleepiness (*M* = 7.50, *SD* = 5.52), and moderate insomnia symptoms (*M* = 15.55, *SD* = 5.47). With respect to subjective sleep, participants generally obtained slightly under 406 minutes (7 hours) of sleep per night (*M* = 405.96, *SD* = 67.24) and reported fairly good sleep efficiency (*M* = 78.58, *SD* = 8.95). Participants indicated on average it took slightly under 30 minutes to fall asleep (*M* = 28.70, *SD* = 22.83). Furthermore, participants woke approximately 3 times per night (*M* = 2.82, *SD* = 2.15) and remained awake during the night for approximately 30 minutes (*M* = 29.49, *SD* = 20.34). Sleep quality was generally viewed as fair (*M* = 2.92, *SD* = .59). HNS device adherence data was available for eight participants. On average, participants

used the HNS device approximately 93% of the nights between activation and their next post-care visit. Furthermore, participants used the device for approximately 7.5 hours per night.

Aims 1-2: Sleep Health

Subjective sleep. Table 2 contains means, standard deviations, *t*-statistics, *p*-values, and observed power for all paired samples *t*-tests. Paired sample *t*-tests revealed no significant differences between pre-HNS and post-HNS subjective sleep efficiency, $t(9) = -.39$, $p = .71$, subjective total sleep time, $t(9) = -.28$, $p = .78$, subjective sleep onset, $t(9) = -.45$, $p = .66$, number of nighttime awakenings, $t(9) = .09$, $p = .93$, and subjective WASO, $t(9) = 1.85$, $p = .10$. However, there was a significantly large improvement between pre-HNS and post-HNS sleep quality, $t(9) = -3.03$, $p = .014$, $g = -.88$. Table 3 contains RCI scores for subjective and objective sleep characteristics. RCI analyses for subjective sleep characteristics indicated that one participant (10%) experienced significant improvement in sleep efficiency, and one participant (10%) experienced significant decline in sleep efficiency from pre-HNS to post-HNS. Total sleep time improved significantly for two participants (20%). One participant had significantly shortened sleep onset latency (10%) and another participant had significantly longer sleep onset latency post-HNS (10%). Significantly fewer nighttime awakenings, shortened WASO, and improved sleep quality were each shown by one participant (10%).

Objective sleep. No significant differences were detected between pre-HNS and post-HNS for objective sleep efficiency, $t(7) = -.40$, $p = .70$, objective total sleep time, $t(7) = -.46$, $p = .66$, objective WASO, $t(7) = .56$, $p = .59$, or number of nighttime awakenings, $t(7) = .75$, $p = .48$. RCI analyses indicated that one participant (10%) had significantly improved sleep efficiency post-HNS and one participant showed significantly reduced sleep efficiency. One participant

(10%) showed significantly increased total sleep time and reduced nighttime awakenings. No significant differences from pre-HNS to post-HNS were found for WASO.

Self-reported sleep. Participants reported significantly large improvement at post-HNS for sleep disturbance, $t(9) = 3.05$, $p = .014$, $g = .88$, and insomnia symptoms, $t(9) = 3.16$, $p = .012$, $g = .91$. There was no significant difference between pre-HNS and post-HNS daytime sleepiness, $t(9) = 1.24$, $p = .25$. Table 4 contains RCI scores for self-reported sleep and mental health outcomes. RCI analyses revealed two participants (20%) reported significantly reduced sleep disturbance post-HNS. Significantly reduced daytime sleepiness was reported by one participant (10%). Three participants (30%) reported significantly improved insomnia symptoms post-HNS.

Aim 3: Cognitive Health

RBANS. Paired samples *t*-tests did not reveal significant differences between pre-HNS and post-HNS RBANS total score, $t(9) = -.15$, $p = .88$, immediate memory, $t(9) = .70$, $p = .51$, visuospatial/constructional skills, $t(9) = -.15$, $p = .88$, language, $t(9) = -1.02$, $p = .33$, attention, $t(9) = -1.59$, $p = .15$, or delayed memory, $t(9) = .76$, $p = .47$. Table 5 contains RCI scores for cognitive outcomes. RCI analyses showed one participant (10%) had a significantly improved RBANS total score, immediate memory, language, and attention. Two participants (20%) had significantly improved visuospatial/constructional skills post-HNS. Delayed memory was significantly lower for one participant post-HNS (10%).

Trail Making Test. No significant difference was found between pre-HNS and post-HNS Trails A completion time, $t(8) = -.71$, $p = .50$. When an outlier was removed, there was still no significant difference in Trails A completion time, $t(7) = 1.11$, $p = .30$. Moreover, there was no significant difference in Trails B completion time between pre-HNS and post-HNS, $t(8) = -1.67$,

p = .13. RCI analyses indicated one participant (10%) showed significant decline in Trails A completion time at post-HNS. Furthermore, one participant had significantly reduced Trails B completion time, but two participants (20%) had significantly longer Trails B completion time.

Subjective cognitive function. Participants reported significantly large improvement in subjective cognitive function from pre-HNS to post-HNS, $t(9) = -4.68$, $p = .001$, $g = -1.35$. RCI analyses indicated that four participants (40%) reported significantly improved subjective cognitive function.

Aim 4: Mental Health

There were no significant differences detected between pre-HNS and post-HNS anxiety symptoms, $t(9) = 1.44$, $p = .18$, or depressive symptoms, $t(9) = .11$, $p = .91$. However, there was a significantly large improvement in anger, $t(9) = 2.96$, $p = .016$, $g = .86$. Table 6 contains RCI scores for mental health outcomes. RCI analyses indicated two participants (20%) reported significantly improved anxiety symptoms. One participant (10%) reported significantly improved depressive symptoms, but two participants (20%) reported significantly worse depressive symptoms. Three participants (30%) reported significantly improved anger at post-HNS.

Discussion

The investigation aimed to evaluate changes in sleep, mental health, and cognitive functioning following hypoglossal nerve stimulation for OSA. While no significant change was detected for objective sleep, most subjective sleep, objective cognitive function, or depression and anxiety outcomes, participants demonstrated significant improvement in subjective sleep quality, insomnia severity, sleep disturbances, subjective cognitive function, and anger. The findings suggest that hypoglossal nerve stimulation is capable of providing clinical relief to OSA symptoms and increasing sleep satisfaction. The results also indicate that global indicators of

sleep and cognitive function may be more sensitive to hypoglossal nerve stimulation than individual sleep and cognitive parameters. Furthermore, large change in sleep, mental health, and cognitive function may be detected within 3 months of device activation; however, this timeframe may be insufficient for detecting smaller changes in functioning.

Post-Operative Care and Sample Characteristics

The short period between HNS device activation and post-assessment may have restricted the degree of clinical benefit that could be obtained from hypoglossal nerve stimulation. On average, participants completed post-assessment approximately 3 months after device activation and 4 months after surgery. Most of the literature evaluating post-HNS health outcomes found significant improvement in sleep and mental health outcomes at intervals of 6 months or longer (Costantino et al., 2020; Grieco et al., 2021; Woodson et al., 2018). Individuals evaluated at later timepoints may show more improvement due to periodic titration of the nerve stimulator that occurs as part of post-operative care. Following a sleep study, a provider uses an external programming device to customize stimulation parameters during post-operative care to strengthen the therapeutic effectiveness of the stimulator device and enhance patient comfort (Baptista et al., 2020). Post-operative titration visits contribute significantly to patient adjustment to the device and clinical improvement (Baptista et al., 2020; Bosschieter et al., 2022). Moreover, evaluations completed at later timepoints provide sufficient time to address potential adverse events that may arise after surgery and delay recovery and treatment (Bestourous et al., 2020). While significant improvement in outcomes have been shown in short, 3-month follow-up intervals for PAP treatment (Canessa et al., 2011; Kanbay et al., 2017), likely due to the non-surgical nature of the intervention, more studies have also shown greater improvement after longer follow-up periods (Aftab et al., 2021; Lee et al., 2017; Patil et al., 2019). Therefore, the

implementation of several, longer post-assessment timepoints that provide sufficient time to address adverse events and perform post-operative titration may have maximized the effectiveness of the intervention.

While most studies have evaluated health outcomes following hypoglossal nerve stimulation at 6 months or later, a few studies have reported significant clinical improvement in daytime sleepiness and depression outcomes 1 to 3 months post-HNS device activation (Certal et al., 2015; Pascoe et al., 2022). Clinical improvement was not found within a similar timeframe in this study; however, this may be in part due to the baseline characteristics of the samples. Relative to the sample included in Pascoe et al. (2022) and Certal et al. (2015), participants in the current study were within normal range for mental health symptoms, cognitive function, daytime sleepiness, and most objective and subjective sleep characteristics. The level of functioning at baseline may have imposed a ceiling effect for the intervention and restricted the amount of clinical benefit that may be gained with these specific symptoms. Relatedly, participants showed significant improvement on most health outcomes that were at least mildly impaired or below average at baseline. These observations lend support to the theory that therapeutic gain was more likely to occur in the context of some impairment or deficit. Additionally, the sample included in this study may reflect a subsample of individuals that have adapted to the symptoms of OSA and maintained high functioning and psychological well-being despite sleep difficulties. Thus, the recruitment of individuals with more severe sleep, mental health, and cognitive symptoms may yield more clinical data about the effectiveness of HNS for sleep, mental health, and cognitive outcomes among individuals with OSA in greatest need of intervention.

Only three studies to date have compared clinical outcomes between HNS and PAP therapy on various outcomes. Collectively, the findings suggested that HNS and PAP treatment

produced comparable improvement in OSA severity, insomnia severity, and functional status related to sleep after controlling for covariates (Heiser et al., 2022; Pascoe et al., 2022). Two of the three studies found that patients who underwent HNS treatment showed significantly greater reduction in daytime sleepiness than patients who completed PAP treatment (Heiser et al., 2022; Walia et al., 2020). Moreover, one study showed that patients in HNS treatment showed significantly greater improvement in depression severity than PAP treatment (Pascoe et al., 2022). While available literature is limited, the results appear to suggest that HNS is a viable alternative that provides similar clinical benefits to PAP treatment.

Insomnia and Sleep Disturbance

Participants reported a significant reduction in insomnia severity and sleep disturbance from baseline to post-assessment. These findings are consistent with previous research evaluating hypoglossal nerve stimulation for OSA (Pascoe et al., 2022) and PAP treatment (Björnsdóttir et al., 2013; Glidewell et al., 2014). While no AHI data was available to determine OSA severity and the frequency of micro-arousals, it can be surmised that pharyngeal muscle responsiveness may have been sufficiently addressed by hypoglossal nerve stimulation to increase the arousal threshold and reduce the number of larger arousals that result in awakenings during the night (Ong & Crawford, 2013; Ragnoli et al., 2021). In other words, participants perceived a noticeable improvement in their ability to maintain sleep during the night. Improved sleep continuity may have translated to alleviation of sleep maintenance difficulties, a core symptom of insomnia and source of sleep disturbance.

Residual subthreshold insomnia and sleep disturbance remained after hypoglossal nerve stimulation which may indicate the presence of sleep problems independent of OSA. Although data is limited, one study showed that after two years of PAP treatment, there was a 50%

reduction in sleep maintenance insomnia, but initiation insomnia maintained a significant presence (Björnsdóttir et al., 2013). Moreover, another study showed that despite improvement in OSA severity, daytime sleepiness and total sleep time, insomnia symptoms remained (Mendes & dos Santos, 2015). Collectively, these findings bolster support for the conceptualization of insomnia as an independent contributor to sleep disturbances in the context of comorbid OSA and insomnia, and suggest the consideration of cognitive behavioral therapy for insomnia (CBT-I) for residual insomnia symptoms. Individuals with OSA report dysfunctional beliefs and attitudes about sleep (Crönlein et al., 2014), engage in detrimental sleep behavior and hygiene practices (Jung et al., 2019), and also experience significantly improved sleep after CBT-I (Ong et al., 2020; Sweetman et al., 2017). Therefore, residual symptoms of insomnia and sleep disturbance may indicate a pivotal period in which individuals may benefit from full or modules of CBT-I to modify remaining behavioral sleep patterns before progression to chronic insomnia.

Obstructive Sleep Apnea and Anger

Very little research has focused on the association between anger and OSA, especially following treatment. The research available has documented the prevalence of anger among adults with OSA (Bardwell et al., 1999), and older adults seeking hypoglossal nerve stimulation treatment for OSA (Dzierzewski et al., 2021). This study found significantly improved anger following hypoglossal nerve stimulation which diverged from one other study that investigated this outcome. Turner et al. (2019) did not find significant change in anger after 3 months of CPAP treatment. The discrepant finding may have been due to the foci of the instruments measuring anger. The PROMIS anger questionnaire focused on the internal emotional experience of anger instead of the enactment or expression of aggressive behaviors captured in Turner et al. (2019). Inadequate sleep quality and duration are known factors associated with increased

activation of the amygdala (Saghir et al., 2018; Vandekerckhove & Wang, 2017). Activation of the amygdala enhances negative emotional reactivity to negative stimuli and weakens positive emotional reactivity to positive stimuli. Additionally, other studies suggest that insufficient REM sleep may also contribute to greater negative emotional reactivity (Rosales-Lagarde et al., 2012). This has been further supported by data showing that obtaining more REM sleep decreased negative emotional reactivity and improved emotion regulatory capabilities (Gujar et al., 2011). It is plausible that improved sleep quality may have led to lower susceptibility to negative emotional reactivity. Moreover, perceived improvement in sleep continuity reported among participants may have increased opportunities to obtain REM sleep and reduce anger.

Objective and Subjective Discrepancy

There were divergent findings between objective and subjective measures of sleep and cognitive function. While no significant improvement was observed for actigraphy and most sleep diary characteristics, participants' self-reported insomnia severity and sleep disturbance were significantly improved. This pattern also occurred for objective and subjective measures of cognitive function. Participants perceived subjective cognitive improvement despite non-significant objective improvement. These discrepancies are not uncommon in studies implementing multi-method approaches to sleep (Benz et al., 2023; Miller et al., 2015; Silva et al., 2007) and cognitive function (Burmester et al., 2016). The discrepant findings may potentially reflect the limitations associated with each measurement strategy such as the detection of wake states with actigraphy, recall or social desirability bias with self-report measures, or consistency and accuracy of sleep diary completion (Althubaiti, 2016; Halson, 2019). Furthermore, subjective improvement may have been influenced by internal expectations—a placebo effect (Petrie & Rief, 2019). Publicly available information about the

effectiveness of hypoglossal nerve stimulation for OSA, and the degree of time and energy participants personally invested in treatment may have strengthened expectations for improved functioning. Alternatively, change in higher-order sleep and cognitive constructs may have been more perceptible to participants than lower-order constructs. Subjective sleep quality is a higher-order construct that requires reflection on the global sleep experience the previous night. The PROMIS sleep disturbance, PROMIS cognitive function, and ISI require reflection on sleep and cognitive function within the past week to two weeks. Higher-order constructs of sleep quality, sleep disturbance, and insomnia may have been the result of cumulative small, non-significant changes in sleep efficiency, nighttime awakenings and WASO. Subjective cognitive function may have shown significant overall improvement from collective, non-significant change in individual cognitive domains. Moreover, subjective cognitive function may have also benefitted from improved global sleep, anger, and small, non-significant change in anxiety—factors associated with cognitive function (Beaudreau & O'Hara, 2008; Lindert et al., 2021; Miyata et al., 2013). Therefore, while non-significant change occurred within individual sleep characteristics and cognitive domains, the cumulative change in lower-order constructs may have led to significant change in higher-order sleep and cognitive constructs.

Limitations and Future Directions

The current study had several limitations. First, while the initial goal of the study was to obtain AHI data at baseline and post-assessment to examine change in OSA severity from post-HNS, AHI data was not available for all participants at post-assessment. Prior research has demonstrated the efficacy of the intervention in reducing OSA severity (Certal et al., 2015; Costantino et al., 2020), but it may be informative to determine whether significant reductions in OSA severity can be detected as early as 3 months after HNS. It may also be beneficial to

evaluate the relationship between changes in OSA severity and mental health and cognitive outcomes. Second, objective sleep onset latency data was unavailable due to corruption of actigraphy data. While the estimation of sleep-wake states is limited with actigraphy (Halson, 2019), sleep onset latency may provide additional information regarding the resolution of specific problems and the extent to which residual sleep initiation problems remain.

The study did not obtain information from participants regarding comorbid chronic health conditions, prescribed and non-prescribed medications, or substance use. Health factors such as such chronic pain (Fiedler et al., 2018), medication side effects and interactions (Do & Schnittker, 2020), and substance use (Angarita et al., 2016) may impact participants' functioning on study outcomes. These factors should be included and controlled in future research evaluating hypoglossal nerve stimulation to isolate the therapeutic effects of the intervention. Towards this goal, it is also recommended that a control group be included to strengthen internal validity of the study. Changes in behavioral health and lifestyle habits such as diet, exercise, and improved sleep hygiene have also led to significant improvement in OSA symptoms (Carneiro-Barrera et al., 2019). Power was also generally very low and ranged from .05 to .99. This limited the ability of the study to detect small to medium effect sizes. There were notable differences in observed power among self-report measures and subjective and objective measures. Power disparities may be partially due to greater measurement error associated with objective and sleep diary instruments compared to self-report. For example, some research suggests that the RBANS may not contain sufficient sensitivity to detect subtle cognitive impairment or change in functioning among older adults (Duff et al., 2010). Unaccounted measurement variance may have produced additional noise in the study and obscured significant effects.

Recruitment for surgical procedures and evaluation of health outcomes require significant time investment and resources; however, larger samples will be needed to increase confidence regarding the clinical benefits of hypoglossal nerve stimulation. Study recruitment encountered challenges primarily related to eligibility for hypoglossal nerve stimulation, limited mobility, living far distances from the hospital and study site, concern for risk of COVID-19 infection, and declining to pursue hypoglossal nerve stimulation. In light of RCI analyses also showing minimal improvement on study outcomes at the individual level, it is hypothesized that extending the post-assessment and follow-up period to 6 months or longer will significantly enhance the ability of the study to capture significant change. With a few exceptions, most of the sleep, mental health, and cognitive outcomes showed small, non-significant changes from baseline to post-assessment at 3 months. The provision of additional time to address adverse events and titration would likely maximize the effects of the HNS device.

Demographically, the study sample was also not racially/ethnically diverse. Future studies should include participants from diverse backgrounds to determine the range of effectiveness of hypoglossal nerve stimulation, especially in light of evidence indicating OSA symptoms and sleepiness may vary by race (Dudley & Patel, 2016). Furthermore, research should continue its focus on middle-aged and older adults due to the elevated risk of OSA in this population. Moreover, individuals with more severe presentations of sleep, mental health, and cognitive function should be recruited in order to determine the range of efficacy for hypoglossal nerve stimulation.

Summary

In summary, hypoglossal nerve stimulation improves the subjective global sleep experience of individuals with OSA. Participants reported significant improvement in subjective

sleep quality, self-reported sleep disturbance and insomnia severity, and subjective cognitive function after 3 months. However, the non-significant findings of the study also yielded important information regarding the therapeutic duration of the hypoglossal nerve stimulation. Although 3 months may be sufficient to capture global subjective improvement, it is insufficient for the detection of change in objective function and specific components of functioning. Prolonged and extensive monitoring is necessary to obtain a comprehensive view of the clinical utility of hypoglossal nerve stimulation. Further study will assist in identifying the strengths and limitations of the intervention and appropriate post-operative care for individuals with comorbid conditions or residual sleep, mental health, and/or cognitive symptoms.

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Tables

Table 1

Sample Demographic Information (N = 11)	
Age, *M* (*SD*)	64.73 (7.38)
Body Mass Index, *M* (*SD*)	28.30 (2.89)
Apnea-Hypopnea Index, *M* (*SD*)	29.96 (11.41)
Gender (%)	
Male	63.6
Female	36.4
Race (%)	
White/Caucasian	90.9
Multiracial	9.1
Marital Status (%)	
Married	72.7
Divorced	18.2
Widowed	9.1
Education (%)	
GED	18.2
High school diploma	18.2
Associates Degree	18.2
Bachelor's Degree	36.4
Master's degree	9.1
Employment Status (%)	
Full-time	27.3
Retired	45.5
Prefer not to respond	27.3
Household Income (%)	
$25,001-$50,000	18.2
$50,001-$100,000	18.2
$100,001-$150,000	18.2
$150,001-$200,000	18.2
$200,001+	9.1
Prefer not to respond	18.2
Mini-mental status exam total score, *M* (*SD*)	28.27 (2.10)

Table 2

Paired-samples t-test statistics for outcome variables

	***Pre-HNS* *M* (*SD*)**	***Post-HNS* *M* (*SD*)**	**(*t*-value)**	**(*p*-value)**	***Observed power***
Subjective sleep efficiency	79.06 (9.28)	80.16 (10.37)	-.39	.71	.06
Subjective total sleep time (minutes)	413.51 (65.78)	418.32 (76.62)	-.28	.78	.06
Subjective sleep onset (minutes)	30.22 (23.47)	35.71 (36.03)	-.45	.66	.07
Subjective nighttime awakenings	2.88 (2.25)	2.81 (2.03)	.09	.93	.05
Subjective wake after sleep onset	30.59 (21.00)	18.73 (11.28)	1.85	.10	.38
Subjective sleep quality	2.97 (.60)	3.76 (.59)	-3.03	.014	.77
Objective sleep efficiency	89.90 (5.93)	90.70 (4.77)	-.40	.70	.06
Objective total sleep time	376.33 (71.41)	391.59 (88.48)	-.46	.66	.07
Objective nighttime awakenings	15.74 (11.09)	13.92 (7.23)	.75	.48	.10
Objective wake after sleep onset	37.64 (22.73)	34.03 (16.91)	.56	.59	.08
RBANS Total score	95.10 (16.68)	95.60 (12.62)	-.15	.88	.05
RBANS Immediate Memory	100.10 (21.15)	96.40 (15.33)	.70	.51	.10
RBANS Visuospatial/constructional	92.10 (18.52)	93.10 (18.93)	-.15	.88	.05
RBANS Language	98.60 (10.08)	102.00 (7.97)	-1.02	.33	.15
RBANS Attention	94.20 (19.10)	100.00 (14.14)	-1.59	.15	.29
RBANS Delayed memory	96.90 (16.82)	93.80 (16.78)	.76	.47	.11
Trails A completion time (seconds)*	47.04 (12.59)	57.89 (40.37)	-.71	.50	.10
Trails B completion time (seconds)*	92.31 (31.85)	106.22 (40.56)	-1.67	.13	.31
PROMIS Cognitive function	16.50 (6.24)	25.10 (4.68)	-4.68	.001	.99
PROMIS Anxiety*	13.60 (5.91)	11.80 (5.77)	1.44	.18	.25
PROMIS Depression*	13.50 (6.24)	13.40 (7.11)	.11	.91	.05
PROMIS Anger*	12.50 (4.79)	9.40 (3.75)	2.96	.016	.75
PROMIS Sleep Disturbance*	26.50 (5.95)	19.20 (5.92)	3.05	.014	.78
Epworth Sleepiness Scale*	7.50 (5.52)	5.80 (5.25)	1.24	.25	.20
Insomnia Severity Index*	15.60 (5.76)	8.60 (5.30)	3.16	.012	.80

Note: * = Lower scores indicate better functioning.

Table 3

Reliable change indices for subjective and objective sleep characteristics.

	Subjective						Objective			
	SE	**TST**	**SOL**	**WASO**	**NA**	**SQ**	**SE**	**TST**	**WASO**	**NA**
P1	-.17	-.95	-.65	-.89	-.06	-.70				
P2	2.10	1.61	2.16	1.62	-1.72	.52	2.39	-.50	.68	2.55
P3	1.26	2.00	1.46	.60	-1.19	1.22				
P4	-.37	-.84	.00	.14	.00	1.05	-.59	.38	-.28	-1.31
P5	1.87	2.45	.30	2.10	-.33	1.05	.44	1.01	.07	.13
P6	.57	.09	-.43	.41	2.57	.18	.14	-.53	.10	.15
P7	-.94	-1.18	-2.14	.06	.18	2.96	.53	-.69	.28	.82
P8	.38	.56	-.03	.38	.12	.18	.47	-.18	.26	1.43
P9	-.10	-.70	.03	1.21	-.06	1.74	-2.21	-.60	-.39	-.69
P10	-2.82	-1.73	-2.78	-.36	.81	1.39	.29	2.60	-.17	-.45

Note: SE = Sleep efficiency, TST = Total sleep time, SOL = Sleep onset latency, WASO = Wake after sleep onset, NA = Nighttime awakenings, SQ = Sleep quality

Table 4

Reliable change indices for sleep questionnaires.

	Daytime sleepiness	Sleep Disturbance	Insomnia symptoms
P1	1.82	-.85	-.47
P2	1.82	.85	.47
P3	.30	2.26	2.21
P4	-.91	2.54	2.37
P5	.30	.14	1.89
P6	-.91	.56	.32
P7	-.61	1.13	.32
P8	.00	.14	-.16
P9	.30	1.83	1.89
P10	3.03	1.69	2.21

Table 5

Reliable change indices for RBANS and Trail making test scores.

	RBANS Total score	RBANS Immediate memory	RBANS Visuospatial	RBANS Language	RBANS Attention	RBANS Delayed memory	Trails A	Trails B	PROMIS Cognitive function
P1	-.43	.00	-.73	.57	.94	-1.60	.03	-1.08	.00
P2	2.60	2.07	-.37	2.19	3.36	1.80	.43	-1.31	1.16
P3	-.43	-.78	-.37	-.38	-.31	.30	-5.88	2.78	1.94
P4	.33	.00	1.22	-.19	.31	-.90	.27	-3.39	2.91
P5	1.54	-.95	2.08	.67	.00	.00	-.58	.07	.78
P6	-.33	-.17	-.37	-1.24	.94	.30	-.18	-1.09	2.33
P7	-1.73	-1.45	-1.48	-.38	-1.26	1.00	.81	-1.63	.97
P8	-.11	-.28	-.85	1.43	.31	.00	-.04	-.75	.78
P9	-.54	-.61	-.55	.76	1.36	-2.30	.76	-2.10	2.13
P10	.54	.11	2.08	-.19	.42	-1.70			3.68

Table 6

Reliable change indices for mental health questionnaires.

	Depression	Anxiety	Anger
P1	1.60	.34	.36
P2	-2.14	-1.72	1.45
P3	1.07	1.37	2.90
P4	.00	2.75	2.54
P5	.00	.69	2.54
P6	-2.14	-.69	-.36
P7	-.53	.00	.36
P8	.00	2.41	.72
P9	2.67	1.03	-.36
P10	.00	.00	1.09

Appendices

Appendix A: Demographics Survey

Demographic Survey

Age: _____

Height: _____ft _____inches

Weight _____lbs

Gender:
□ Male
□ Female
□ Transgender male
□ Transgender female
□ Non-binary
□ Prefer not to respond

Race
□ Latinx/Hispanic
□ Black or African American
□ Asian or Asian American
□ White
□ American Indian or Alaska Native
□ Native Hawaiian or Other Pacific Islander
□ Multiracial
□ Prefer not to respond

Marital Status
□ Single
□ Married
□ Separated
□ Divorced
□ Widowed
□ Prefer not to respond

Highest Level of Education
□ Less than high school
□ High school degree
□ GED or equivalent degree
□ Bachelor's degree (BA/BS/AB)
□ Master's degrees (MA/MS/MBA)
□ Doctoral degree (PhD/MD/DSW)
□ Prefer not to respond

Employment Status
□ Unemployed
□ Student
□ Part-time employment
□ Full-time employment
□ Retired
□ Prefer not to respond

Household Income
□ Under $25,000
□ $25,001 - $50,000
□ $50,001 - $100,000
□ $100,001 - $150,000
□ $150,001 - $200,000
□ $200,001+
□ Prefer not to respond

Appendix B: Consensus Sleep Diary

Sample Consensus Sleep Diary-Core ID/Name:________________________________

Today's date	4/5/11							
1. What time did you get into bed?	10:15 p.m							
2. What time did you try to go to sleep?	11:30 p.m							
3. How long did it take you to fall asleep?	55 min.							
4. How many times did you wake up, not counting your final awakening?	3 times							
5. In total, how long did these awakenings last?	1 hour 10 min.							
6. What time was your final awakening?	6:35 a.m.							
7. What time did you get out of bed for the day?	7:20 a.m							
8. How would you rate the quality of your sleep?	☐ Very poor ☑ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good
9. Comments (if applicable)	I have a cold							

Appendix C: PROMIS Depression Short Form

PROMIS Emotional Distress—Depression—Short Form

Instructions: On the DSM-5 Level 1 cross-cutting questionnaire that you just completed, you indicated that *during the past 2 weeks* you (the individual receiving care) have been bothered by "no interest or pleasure in doing things" and/or "feeling down, depressed, or hopeless" at a mild or greater level of severity. The questions below ask about these feelings in more detail and especially how often you (the individual receiving care) have been bothered by a list of symptoms **during the past 7 days.**
Please respond to each item by marking (✓ or x) one box per row.

							Clinician Use
In the past SEVEN (7) DAYS....							**Item Score**
		Never	**Rarely**	**Sometimes**	**Often**	**Always**	
1.	I felt worthless.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
2.	I felt that I had nothing to look forward to.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
3.	I felt helpless.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
4.	I felt sad.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
5.	I felt like a failure.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
6.	I felt depressed.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
7.	I felt unhappy.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
8.	I felt hopeless.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
					Total/Partial Raw Score:		
					Prorated Total Raw Score:		
						T-Score:	

Appendix D: PROMIS Anxiety Short Form

*PROMIS Emotional Distress—Anxiety—Short Form

Instructions to patient: On the DSM-5 Level 1 cross-cutting questionnaire that you just completed, you indicated that *during the past 2 weeks* you (individual receiving care) have been bothered by "feeling nervous, anxious, frightened, worried, or on edge", "feeling panic or being frightened", and/or "avoiding situations that make you anxious" at a mild or greater level of severity. The questions below ask about these feelings in more detail and especially how often you (individual receiving care) have been bothered by a list of symptoms **during the past 7 days.** **Please respond to each item by marking (✓ or x) one box per row.**

							Clinician Use
In the past SEVEN (7) DAYS....							**Item Score**
		Never	**Rarely**	**Sometimes**	**Often**	**Always**	
1.	I felt fearful.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
2.	I felt anxious.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
3.	I felt worried.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
4.	I found it hard to focus on anything other than my anxiety.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
5.	I felt nervous.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
6.	I felt uneasy.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
7.	I felt tense.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
						Total/Partial Raw Score:	
						Prorated Total Raw Score:	
						T-Score:	

Appendix E: PROMIS Anger Short Form

LEVEL 2—Anger—Adult*

*PROMIS Emotional Distress—Anger—Short Form

Name: _____ **Age:** ____ **Sex:** ❑ **Male** ❑ **Female** **Date:**_____

If the measure is being completed by an informant, what is your relationship with the individual receiving care? _____

In a typical week, approximately how much time do you spend with the individual receiving care? _____ hours/week

Instructions: On the DSM-5 Level 1 cross-cutting questionnaire that you just completed, you indicated that *during the past 2 weeks* you (the individual receiving care) have been bothered by "feeling irritated, grouchy, or angry" at a mild or greater level of severity. The questions below ask about these feelings in more detail and especially how often you (the individual receiving care) have been bothered by a list of symptoms **during the past 7 days. Please respond to each item by marking (✓ or x) one box per row.**

							Clinician Use
In the past SEVEN (7) DAYS....							**Item Score**
		Never	**Rarely**	**Sometimes**	**Often**	**Always**	
1.	I was irritated more than people knew.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
2.	I felt angry.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
3.	I felt like I was ready to explode.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
4.	I was grouchy.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
5.	I felt annoyed.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
						Total/Partial Raw Score:	
						Prorated Total Raw Score:	
						T-Score:	

Appendix F: PROMIS Sleep Disturbance Short Form

*PROMIS—Sleep Disturbance—Short Form

Instructions to patient: On the DSM-5 Level 1 cross-cutting questionnaire that you just completed, you indicated that *during the past 2 weeks* you (the individual receiving care) have been bothered by "problems with sleep that affected your sleep quality over all" at a mild or greater level of severity. The questions below ask about these feelings in more detail and especially how often you (the individual receiving care) have been bothered by a list of symptoms **during the past 7 days. Please respond to each item by marking (✓ or x) one box per row.**

						Clinician Use
In the past SEVEN (7) DAYS....						
	Not at all	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**	
1. My sleep was restless.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
2. I was satisfied with my sleep.	❑ 5	❑ 4	❑ 3	❑ 2	❑ 1	
3. My sleep was refreshing.	❑ 5	❑ 4	❑ 3	❑ 2	❑ 1	
4. I had difficulty falling asleep.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
In the past SEVEN (7) DAYS....						
	Never	**Rarely**	**Sometimes**	**Often**	**Always**	
5. I had trouble staying asleep.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
6. I had trouble sleeping.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	
7. I got enough sleep.	❑ 5	❑ 4	❑ 3	❑ 2	❑ 1	
In the past SEVEN (7) DAYS....						
	Very Poor	**Poor**	**Fair**	**Good**	**Very good**	
8. My sleep quality was...	❑ 5	❑ 4	❑ 3	❑ 2	❑ 1	
Total/Partial Raw Score:						
Prorated Total Raw Score:						
T-Score:						

Appendix G: Insomnia Severity Index

Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Appendix H: Epworth Sleepiness Scale

The Epworth Sleepiness Scale

The Epworth Sleepiness Scale is widely used in the field of sleep medicine as a subjective measure of a patient's sleepiness. The test is a list of eight situations in which you rate your tendency to become sleepy on a scale of 0, no chance of dozing, to 3, high chance of dozing. When you finish the test, add up the values of your responses. Your total score is based on a scale of 0 to 24. The scale estimates whether you are experiencing excessive sleepiness that possibly requires medical attention.

How Sleepy Are You?
How likely are you to doze off or fall asleep in the following situations? You should rate your chances of dozing off, not just feeling tired. Even if you have not done some of these things recently try to determine how they would have affected you. For each situation, decide whether or not you would have:

- No chance of dozing =0
- Slight chance of dozing =1
- Moderate chance of dozing =2
- High chance of dozing =3

Write down the number corresponding to your choice in the right hand column. Total your score below.

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

Total Score = _____

Appendix J: PROMIS Cognitive Function Short Form

PROMIS® Item Bank v2.0 – Cognitive Function- Short Form 6a

Cognitive Function- Short Form 6a

Please respond to each question or statement by marking one box per row.

	In the past 7 days...	**Never**	**Rarely (Once)**	**Sometimes (Two or three times)**	**Often (About once a day)**	**Very often (Several times a day)**
PC2r	My thinking has been slow.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC35r	It has seemed like my brain was not working as well as usual.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC36r	I have had to work harder than usual to keep track of what I was doing	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC42r	I have had trouble shifting back and forth between different activities that require thinking	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC8r	I have had trouble concentrating	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC25r	I have had to work really hard to pay attention or I would make a mistake	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1