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Sleep Apnea and the Brain: Neurocognitive and Emotional Considerations

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Abstract

Sleep apnea research has become increasingly relevant to the field of psychology. Although the physiological sequelae have been researched extensively, and treatment options are now available for those diagnosed, much is left to be done. Specifically, to date, the cognitive and psychological consequences of sleep apnea have received less attention. As such, this paper serves to review the current state of the literature and presents relevant neuropsychological and emotional domains. Given that sleep apnea may cause psychological dysfunction over-and-above those expected from hypersomnia alone, the role of physiological damage in relation to these impairments will also be explored. Furthermore, a brief synopsis of established and proposed treatment options is undertaken in relation to psychological symptom expression and cognitive performance improvement. Finally, this paper highlights areas for future inquiry and offers guidance regarding the inclusion of psychological domains in subsequent research.

Sleep Apnea and the Brain: Neurocognitive and Emotional Considerations

Sleep apnea is a sleep-related breathing disorder characterized by upper airway obstruction during sleep, decreased oxygen saturation in the blood, and hypercapnia [1]. Common symptoms include daytime sleepiness, hypertension, and possible cognitive impairment [2,3]. Obstructive sleep apnea (OSA), the most common subtype, is characterized by loud snoring, as well as, repeated slowing or suspension of breathing during sleep due to upper airway obstruction leading to anoxia. Central sleep apnea (CSA), a less common subtype, is characterized by absence of respiratory exertion during cessations of breathing due to neural feedback malfunctions between the brain and the muscles controlling ventilation. While OSA and CSA are the main subtypes of sleep apnea, individuals can also experience a mixed/combination type of both characteristics called complex sleep apnea syndrome [4]. Given the disparity in prevalence rates of these conditions, the remainder of this paper will focus on the OSA subtype of sleep apnea, as it is much more common and better represented within the research literature.

The diagnosis of OSA is often initiated when a family member or bed partner complains of snoring and labored breathing during sleep, or the affected individual seeks treatment for symptoms of sleep deprivation (e.g. daytime sleepiness, morning headaches, sore or dry throat, trouble concentrating). A definitive diagnosis is established by utilizing a sleep diagnosis tool, called a polysomnography, to rule out other sleep disturbances and determine an individual's apnea-hypopnea index (AHI). The AHI is based on the number of apnea/hypopnea episodes that occur during a one-hour period of sleep and is used to indicate severity of the disorder. An AHI above 5 but less than 15 is considered to be in the mild and impacts 3-28% of individuals, while an AHI above 15 is considered moderate and impacts 1-14% of individuals [1]. Cases of 30 or more episodes per hour are considered severe and are almost always associated with intensified sequelae (e.g. stroke, GERD, coronary heart disease, heart failure [5-7].

Etiological considerations for OSA include genetic risk factors, obesity, and upper airway anatomy. Research suggests that the apolipoprotein E4 phenotype, which also has implications as a marker for high cholesterol, is common in patients with sleep apnea [8]. Additionally, patients with OSA had higher body mass indexes and higher frequency of hypertension, diabetes mellitus, and coronary artery disease compared to a group with non-apnea sleep disorders [9]. Prevalence rates of OSA also increase with age [1,10,11].

According to the *Sleep in America* 2005 Poll conducted by the National Sleep Foundation, OSA may be one of the most common sleep disorders in America. Of the national poll, 26% of the respondents met criteria for being at high risk of OSA [11]. The poll also revealed that high-risk individuals reported lower quality of life. Given such a large percentage of the population is affected by OSA, it is imperative that increased research efforts be made to investigate etiology, symptomatology and treatment. Furthermore, it is essential that research further investigate the impact that OSA has on individual cognitive and psychological functioning. Studying the negative consequences that OSA has on cognitive and psychological functioning is a budding area in the scientific literature with vast potential for clinical utility.

Brain Structural and Functional Damage

As mentioned previously, OSA is characterized by periods of anoxia during which the brain is restricted of oxygen. Current literature exhibits mixed results on whether periods of anoxia negatively impact the brain structurally and functionally [12]. Research conducted by O'Donoghue et al. found no evidence that a group of individuals with severe OSA differed significantly in gray matter volume or focal structural changes compared to normal individuals using a voxel-based morphometry (VBM) technique

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[13]. The authors argued that research results implicating structural changes could be attributable to comorbid conditions in the populations studied. However other research supports the hypothesis that anoxia negatively impacts structural and functional brain domains [14]. According to Beebe and Gozal, sleep disruption and blood deoxygenation via OSA can attenuate the restorative process during sleep and cause central nervous system cellular injury [15]. Beebe and Gozal further proposed an integrative model to account for prefrontal cortex dysfunction due to a combined sleep disruption and intermittent hypoxia/hypercarbia [15]. This model ultimately implicates prefrontal dysfunction with a number of problematic side effects including behavioral disinhibition, emotional lability, poor working memory, disorganization, poor judgment, and inattention.

Furthermore, research conducted at the Sungkyunkwan University School of Medicine in Seoul, South Korea suggested OSA is linked to specific encephalopathy in the brain [16,17]. In comparison to same-age male healthy controls, severe OSA males showed gray matter concentration reduction in limbic areas, cingulate gyri, prefrontal areas, caudate nuclei and the cerebellum [16]. These results were reported to be consistent with the cognitive and behavioral disturbances observed in OSA patients. Interestingly, the overall gray matter volume did not differ significantly between the groups, which the authors noted was consistent with the findings reported by O'Donoghue et al. and Joo et al. further researched the connection between OSA and brain pathophysiology and found overall and localized cortical thinning in severe OSA individuals [13,17].

Widespread structural changes and output have also been reported in OSA individuals using an electroencephalography [18]. Children with severe OSA showed decreases of the mean neuronal metabolite ratio N-acetyl aspartate/choline in the left hippocampus and right frontal cortex [19]. Other research showed OSA patients give abnormal fMRI results in multiple brain areas and neural structures involved in effect, motor control, and respiratory function [20]. Changes in the brain using VBM were observed, showing less grey matter concentration specifically in the left hippocampus of OSA patients [21]. Macey et al. also found gray matter reduction in temporal regions and proposed that the loss might be a consequence of OSA or a preexisting issue initiated or potentiated by OSA [14]. Finally, rats that experienced intermittent hypoxia showed increased neuronal death rates, a finding that increased with age [22]. As is evident, the current scientific literature is rich but mixed on what structural and functional damage occurs as a result of OSA and through what process damage occurs.

Neurocognitive and Mood Implications

Another budding avenue of research has indicated that various neurocognitive and mood disorders are linked to OSA. Research investigating the neurocognitive and mood changes exhibited in hypoxia prominent OSA has shown that several domains are affected. These domains include neuropsychological functioning, executive functioning, attention, memory, intelligence, dementia, and depression.

Research investigating the effects of OSA on neuropsychological functioning exhibits mixed results. Foley et al. found that OSA had no negative impact on neuropsychological functioning. Specifically, Foley et al. examined 718 men aged 79 to 97 and found that although OSA increased sleepiness, it did not affect cognitive performance [23]. However, Foley and colleagues noted that, given the participant's good health, more extensive testing may have been necessary to reveal deficits. Other studies have found that OSA negatively impacts neuropsychological functioning in multiple domains. For instance, Naismith and colleagues (2004) found poorer sleep quality related to slower processing speed, subjective sleepiness related to executive functioning deficits, and hypoxemia related to decreases in visual abilities, processing speed, and mental flexibility. Additionally, Beebe and colleagues (2003) noted that widespread hypoxia in the brain may affect a variety of cognitive functions with potentially significant reductions in executive functioning.

Executive dysfunction is correlated more with severity of measured hypoxemia than with other symptoms of sleep apnea such as excessive daytime sleepiness; however, both can influence cognitive functioning to some extent [24,25]. A disruption in executive functioning can lead to a variety of issues spanning the cognitive processes. Findings reported by Beebe and Gozal implicate the prefrontal cortex as a link between the sleep disturbances experienced in sleep apnea and the cognitive deficits observed [15]. Specifically, they propose that the hypoxemia and repeated waking can damage the restoration process that occurs during sleep. It also appears that these findings may translate to children. Halbower et al. suggested that children (ages 6-16) with severe OSA had significant deficits in executive functioning as compared to a control group [19]. Hoth, Zimmerman, Meschede, Arnedt, & Aloia, however, found no difference in executive functioning between a group with high hypoxemia and a group with low hypoxemia [26]. These mixed results suggest that the hypoxemia-cognition relationship may not be so linear, and future research is necessary to better understanding these findings.

In addition to overall executive dysfunction, OSA patients also show abnormalities in attention and vigilance. Research has supported this hypothesis both with executive tasks that are relatively short and in studies with children suffering from sleep disordered breathing (SDB) [15]. Generally, SDB ranges in severity and includes snoring and obstructive sleep apnea, both of which have been shown to negatively impact children's attention, concentration, and hyperactivity [27]. What makes SDBs particularly problematic for children is that tonsil and adenoid growth outpace that of their airway, thus leading to obstruction. As a result, sleep disordered breathing is a common pediatric condition, such that 30% of children snore, and 3-4% have OSA [27]. The majority of the research examining the cognitive impact that sleep disordered breathing has on children's functioning is derive from studies assessing behavior prior to and following adenotonsillectomy surgery [28-30]. For example, Ali and colleagues (1996) compared behavioral and psychological functioning following adenotonsillectomy surgery and found that post-surgery participants in the snoring group showed reduced hyperactivity and children with SDB demonstrated diminished levels of aggression, inattention and hyperactivity [28]. Interestingly, but perhaps not surprisingly, the control group's post-surgery performance was not significantly different compared to prior surgery [28].

Additional evidence for the cognitive toll that poor breathing quality may have amongst children can be drawn from Avior and colleagues' (2004) study where participants with OSA were asked to complete the Test of Variables of Attention (TOVA), a measure used in the diagnosis of ADHD, prior to and following adenotonsillectomy. Results indicated that eight out of the study's 19 participants met TOVA's criteria for an ADHD diagnosis prior to surgery, and did not following surgery. Similar results were found by Dillon and colleagues (2007) wherein 50% of participants initially meeting criteria for ADHD no longer did so following adenotonsillectomy as measured by the Disruptive Behavior Disorder Rating Scale (DBDRS), the ADHD Rating Scale, and the Children's Psychiatric Rating Scale (CPRS). Given that sleep disordered breathing, including OSA, has the potential to elicit an inappropriate psychiatric diagnosis such as ADHD it is important to note that symptom remission is possible following surgery.

Research regarding the effects of OSA on intelligence remains inconclusive. According to Beebe et al., OSA does not typically affect core intellectual and verbal abilities [31]. However, research has shown that individuals at higher risk for OSA had significantly lower cognitive scores [32]. It has been proposed that OSA may negatively impact the developing brain and thus could cause long-term scholastic underachievement in children [33] albower et al. supported this hypothesis finding that children with severe OSA had significant deficits in IQ [19] however, Kielb, Ancoli-Israel, Rebok, & Spira did not find this same effect on intelligence, and proposed pre-morbid intelligence may serve as a protective factor against decline, in line

with Alchanatis et al. cognitive reserve theory [34,35]. Both research groups found that cognitive deficits observed between OSA and non-OSA individuals of average intelligence were attenuated in the high-intelligence group. These results warrant special attention be paid to children suffering from OSA. If untreated, childhood OSA could severely and perhaps irreversibly alter cognitive potential. If failure to diagnose OSA in children occurs, they may simply be labeled as having low drive or a learning disorder. However research suggests that proper treatment with a Continuous Positive Airway Pressure (CPAP) may reverse these effects and elicit some improvements in attention and vigilance [34].

The research on memory and sleep apnea is also inconsistent [31]. Some research suggests that memory problems are not simply a function of sleepiness, and that hypoxemia independently predicts both declarative memory and working memory [24]. However, Hoth et al. found that a high hypoxemia group performed significantly better on immediate recall than a low hypoxemia group, suggesting the memory deficits may be more related to long-term memory than short-term or working memory [26]. An MRI study by Torelli et al. showed decreased hippocampal volume and caudate nuclei volume, as well as general reduction in cortical grey matter in individuals with OSA [36]. These findings are consistent with a structural damage cause for memory impairment, as these are areas implicated in memory. These results also concluded that brains of individuals with OSA are more susceptible to the effects of aging, introducing the possibility that normal, expected memory loss due to aging may be potentiated by OSA. Torelli et al. also found evidence that OSA patients have reduced volume of a variety of brain areas, most notably the hippocampus [36]. In this study, age was correlated with these results, suggesting that OSA may mediate and accelerate the process of brain deterioration due to aging. These results warrant advocacy for early treatment to attenuate these deleterious effects.

As dementia and OSA increase in prevalence with advancing age, researchers have implemented several investigations to explore the relationship between these two conditions [10,37,38]. Current literature supports the relationship between sleep-related issues, including OSA, and dementia. Specifically, reports demonstrate that individuals with comorbid OSA and dementia experience more sleep apnea episodes than age-matched controls and severity of dementia is linked to severity of OSA symptomology also found a significant decrease in cognition functioning related to sleep disturbance in an older population [10,37,38]. Although these studies do not present causal evidence enabling investigators to understand how dementia and OSA interact in those with both conditions, research in this area continues to grow. In fact, a study conducted by Yaffe and colleagues used a longitudinal model to track cognitive impairment in a group diagnosed with sleep-disordered breathing without dementia [39]. In comparison to controls, those with sleep-disordered breathing or experiencing elevated oxygen desaturation via apnea showed mild cognitive impairment and increased risk of developing dementia. Moving forward, more studies investigating longitudinal cases are needed before confidentiality establishing the casual relationship between dementia and OSA.

In line with this goal, Bliwise has proposed two models by which OSA and Alzheimer's disease (AD) could be related [40]. The first model proposes that AD leads to sleep apnea as the destructive components of AD impact areas of the brain, such as the medullary centers, that monitor breathing. The second model is similar to other hypoxic outcomes in that sleep apnea causes AD as hypoxic events disrupt higher cortical functions. In addition to these models, a growing body of research supports a link between OSA and dementia, specifically AD, is a possible shared genetic predisposition on the apolipoprotein E gene (APOE). The presence of the allele epsilon 4 (E4) has been identified in clinical groups with AD and sleep apnea [38,40]. The APOE gene is associated with production of the protein amyloid-β (Aβ), which possibly has a role in sleep regulation [41,42]. Lucey and Bateman investigated the function of Aβ in apnea as the Aβ protein is associated with high concentrations in wakefulness and lower concentrations during sleep in normal populations [41]. The researchers found that Aβ alternations from AD pathogenesis impact sleep regulation, which is possible from the presence of Aβ plagues caused by these maladaptive proteins. In addition, chronic hypoxia is also thought to proliferate the presence of Aβ proteins by causing a cascade of B-secretase activity that increases Aβ proteins [43]. However, the link between APOE and sleep apnea is not definitive as many other variables, including cerebrovascular events, could be attributed to dementia and sleep apnea co-morbidity [40]. Therefore, more research is needed to isolate various biological processes that underlie the presence of dementia and OSA.

The impact of how sleep apnea impacts an individual's mood remains unclear due to the current state of scientific literature in this area. One of the most common mood states researched in the realm of OSA is depression. Using the 2005-2008 National Health and Nutrition Examination Survey, a sleep apnea diagnosis was associated with a 2.4-times likelihood of major depression [44]. Interestingly, Wheaton et al. found snorting/stopping breathing alone was associated with a 3-times likelihood of major depression [44]. Peppard et al. suggested a causal link between depression and OSA; however, they did not establish the directionality of this relationship [45]. OSA patients exhibit high rates of depression, though these depressive symptoms are, in some aspects, independent of this sleep disorder [46]. Mackinger and Svaldi postulated that a predisposition to depression combined with sleep apnea "seems to reactivate latent negative schemas" (p. 21) [47]. Some studies argue that independence of depression and OSA is made clear by the fact that depressive symptoms fail to improve following adequate CPAP treatment. Other studies argue that depressive symptoms exhibit clinically relevant improvement following CPAP treatment [48,49].

While results on treatment studies are mixed, Cross et al. showed that the same brain regions are implicated in depression and OSA: hippocampus, anterior cingulate, amygdala, and frontal cortex [46]. Due to these shared structural and functional deficits along with the high prevalence of depression in OSA patients, it is possible that the brain alterations in OSA may relate to depressive symptoms. One study conducted by Cross et al. comparing patients with OSA and depression to OSA-only patients found that OSA patients with depressive symptoms had more extensive and diverse neural injuries [46]. These results indicate that depression may exacerbate injury caused by OSA along with introducing damage in other areas typically associated with depression. Research has also proposed a connection between memory and depression, suggesting lower specificity of autobiographical memory is associated with depressive symptoms, particularly the cognitive aspects (i.e. negative thoughts) more than the somatic aspects [47]. The clinical implications of current research linking depression and OSA to a combined detrimental impact suggest that it is important to screen and treat patients for both depression and OSA.

In regards to other psychological disorders, future research is needed to further explore the damaging effects of OSA on cognition and emotion. There is currently limited research on the psychological toll of OSA as most research to date has focused on the physical ramifications of the disorder. In fact comprehensive research surrounding anxiety and OSA has yet to be conducted. Preliminary results suggest that anxiety severity seems to depend more on daytime sleepiness rather than on degree of nighttime hypoxemia [25]. In fact, Macey et al. did not find a strong relationship between AHI and anxiety, supporting the earlier research by Naismith et al. [25,50]. However, more recent literature has suggested otherwise, finding evidence that anxiety may be more common in severe OSA than depression [51]. Anger is another domain lacking research amongst individuals with OSA. Bardwell, Berry, Ancoli-Israel, and Dimsdale reported that, unlike anxiety, anger appears to be more related to hypoxemia [52]. While it is uncertain as to why this is the case, frontal lobe damage has been frequently implicated in OSA patients, and damage to the prefrontal cortex can drastically change temperament (e.g. Phineas Gage). However, further research on

comorbid conditions is needed to make confident conclusions in these and other domains.

Conclusion

It has been well established that OSA has a significant biological and physiological impact on physical health. Yet, as apparent through this review, to date research supporting the significant and severe effects of OSA mental health and cognitive functioning continues to contain many gaps. Moving forward, given the mixed findings of the impact of OSA on neuropsychological and psychological functioning, it is important the future research work to standardized methodology clearly states condition severity and controls for confounding variables such as affective states [11]. It is also imperative to expand the body of OSA research in order to better understand the causes of neuropsychological impairment and how psychological dysfunction should be addressed in people with OSA. Currently the most prominent treatment for OSA is CPAP. Little is known about whether or not CPAP alone is effective in treating not only hypoxia, but also the psychological and cognitive side effects of OSA. Conducting research on the effectiveness of CPAP in addressing symptoms outside of hypoxia and sleep disruption is crucial to identify if additional interventions, such as therapy or medication, are necessary to fully restore mental health to a baseline level.

Psychotherapy has been thoroughly researched in its effectiveness in treating various disorders, including helping individuals cope with various medical conditions, however, OSA has yet to be targeted specifically and thus should be included as a future area of study, especially given the recent research documenting the psychological impact OSA takes on individuals living with the disorder. Prior research has concluded that when sleep is restored or normalized in individuals with psychiatric conditions, symptoms of the disorders either improved or remitted. As such, OSA-affected individuals may see a great reduction in psychological distress and improvement in mood, mental health and other psychological areas. Thus is the recommendation of the authors that future research explore the effects of sleep normalization or improvement on OSA.

Research into sleep apnea is also imperative due to the number of comorbid conditions and ill effects of misdiagnosis. Undiagnosed and untreated sleep apnea can be mistaken for ADHD in children or exacerbate Alzheimer's and other dementias in older adults thus prolonging or preventing necessary treatment and resulting in deleterious effects. Understanding how OSA is diagnosed, making certain it is diagnosed properly, and better understanding of available treatments is essential in the progression of how professionals view the challenges and consequences of sleep apnea.

The prefrontal model of Beebe and Gozal provides a theoretical connection between brain dysfunction due to OSA-specific symptomatology and the psychological dysfunction observed in the literature [13]. Whether the theory holds true depends on future research projects investigating the always-evolving field of brain-behavior relationships. Including psychological outcome measures in future research will serve neuroimaging studies of OSA by examining consistency between any physiological and psychological/behavioral changes.

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