Impact of Obstructive Sleep Apnea on Neurocognitive Function and Impact of Continuous Positive Air Pressure

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KEYWORDS

- Obstructive sleep apnea • Neurocognitive function • Cognition
- Continuous positive airway pressure (CPAP)

KEY POINTS

- Obstructive sleep apnea is associated with impairment of multiple aspects of cognition, including attention, delayed visual and verbal memory, visuospatial skills, and some aspects of executive function.
- The mechanism of this impairment includes neuro-inflammation, oxidative stress, and sympathetic overactivity.
- Treatment with continuous positive air pressure (CPAP) is shown to improve executive function and verbal memory at 2 to 3 months.
- CPAP use of at least 6 hours per night may lead to further improvements in neurocognitive function.

INTRODUCTION

Obstructive sleep apnea (OSA) is a relatively common breathing disorder known to increase in prevalence with obesity and age.[1,2] The repetitive interruptions in breathing typically cause fragmented, poor quality sleep as well as oxygen desaturations. Other sleep disorders, including insomnia, restless legs syndrome, and parasomnias, such as sleepwalking, can be exacerbated by sleep-disordered breathing. OSA has been associated with excessive daytime sleepiness,[3] hypertension,[4] cardiovascular disease,[5] stroke,[6] depression,[7] impaired glucose tolerance,[8] endocrine dysfunction,[9] and increased risk of motor vehicle accidents (MVAs).[10] Hospitalization days and medical costs are increased per annum for persons with OSA.[11] In addition, multiple aspects of cognition can be affected; this is not only due to the sleepiness that often accompanies OSA but also because of direct pathologic effects on the brain. Although continuous positive air pressure (CPAP) has been shown to improve many of the conditions mentioned, opinions vary regarding improvement of neurocognitive impairments with CPAP. In this article, literature from the last 5 years on the neurocognitive impact of OSA, proposed mechanisms of these sequelae, and effect of CPAP, are reviewed.

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OBSTRUCTIVE SLEEP APNEA EFFECTS ON ATTENTION AND VIGILANCE

Attention is the ability to maintain focus on certain sensory stimuli while de-emphasizing other stimuli. Vigilance is the ability to sustain focus over an extended period of time. These neurocognitive domains are among the most consistently affected by OSA.[12–14] Although differences are seen when treating OSA as a dichotomous variable, a dose-response relationship between OSA severity and level of inattention has not been shown.[15] Batool-Anwar and coworkers[15] found significant worsening of attention as measured by the psychomotor vigilance test (PVT) associated with the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index. Results were adjusted for age but not IQ. Olaithe and colleagues[16] also failed to find a correlation between measures of attention and apnea hypopnea index (AHI), even when controlling for age and premorbid intelligence. The investigators hypothesized that hypercapnia is inversely proportional to cognition given evidence that hypercapnia severity correlates with overall neurocognitive impairment.[17] Given the clear association between vigilance and driving ability, with implications for public safety, efforts have been underway to predict risk for MVAs in persons with OSA. Wong and colleagues[18] investigated the effects of 40 hours of sleep deprivation on cognition and simulated driving performance in OSA patients as compared with healthy controls. Vigilance was measured with the PVT. They found no association between OSA and attention, driving performance, or subjective sleepiness. Vakulin and colleagues[19] used the Stroop test to measure focused and selective attention in OSA patients undergoing driving simulator testing after normal sleep with or without alcohol, or sleep restriction. There was no association between poor driving performance and Stroop test outcomes. Recently, Karimi and colleagues[20] used the Gothenburg Sleep Resistance Test (GOSLING) to assess sustained attention in OSA patients with and without a MVA. Both reaction time and the proportion of lapses were significantly higher in OSA patients with a MVA. This study failed to show a dose-response relationship between OSA severity and MVA risk. Gozal and colleagues[21] proposed genetic differences to explain susceptible versus resilient OSA patients.

OBSTRUCTIVE SLEEP APNEA EFFECTS ON VERBAL MEMORY

Verbal memory can be divided into immediate recall, verbal learning, verbal delayed recall, and verbal recognition. A meta-analysis compiled by Wallace and Bucks[22] included studies using tests designed to provide delineation of these memory domains such as the Buschke Selective Reminding Test and the California Verbal Learning Test. OSA was found to have a medium adverse effect on verbal immediate recall compared with norm and control referenced data. OSA had a medium effect on verbal learning compared with controls and no significant effect compared with norms. There was a more consistent medium effect on verbal delayed recall using these reference sets. Verbal recognition, however, was not affected when comparing OSA to norm subjects and significantly affected compared with patients without OSA. The variability for verbal data could not be explained by age, publication status, study design, sample source, or disease severity. In addition, screening by polysomnogram or questionnaire did not affect the significance of results. A recent study by Hoth and colleagues[23] examined the differential effects of hypoxemia on memory. Forty subjects with an average AHI of 37.8/h of sleep were divided into relatively mild and severe hypoxemia groups based on minimum oxygen saturation and time less than 90% blood oxygenation. The mild group spent no more than 6% of sleep time less than 90%, whereas this was at least 20% for the severe group. Surprisingly, the severe hypoxemia group performed better on tests of immediate and delayed verbal recall. Compared with normative data, the severe hypoxemia group was average, but the low hypoxemia group was borderline low. This counterintuitive result is supported by studies in humans and animals demonstrating protective effects of intermittent hypoxemia for the brain and cardiovascular system.[24] Another study suggested that intermittent hypoxemia in rat brains can decrease nitric oxide related toxicity.[25]

Ramos and coworkers[26] evaluated the effects of OSA in a Hispanic/Latino population. Neurocognitive tests included the Brief-Spanish English Verbal Learning Test. The mean AHI was 9.0 with a range of 0 to 142. One of the important findings was that women were more likely to have verbal memory and learning deficits associated with OSA compared with men. Although the prevalence of OSA is higher in men,[1] there has been some suggestion that women are more susceptible to the effects of OSA at lower AHI levels.[27]

Edwards and colleagues[28] examined the effect of moderate to severe OSA on several neurocognitive domains, including learning and memory (L/M). OSA severity was based on AHI and oxygen desaturation index (ODI). Verbal and visual test results were grouped. In addition, blood cortisol

levels were measured over a 24-hour period. ODI, but not AHI, severity was associated with 24-hour cortisol levels. AHI, ODI, and cortisol levels were all associated with L/M deficits. The investigators hypothesized that sympathetic overactivity manifest through the hypothalamic-pituitary-adrenal axis, as opposed to the apneas themselves, was responsible for neurocognitive impairment.

A review by Vaessen and colleagues[29] focused on subjective neurocognitive complaints comparing OSA patients to controls. They did not find a consistent memory complaint for OSA patients and attributed this in part to small sample sizes. It should also be noted that due to the gradual progression of OSA, these persons are not always aware of their deficits, which has significant implications for identification and treatment of OSA and undoubtedly contributes to the estimated large percentage of untreated individuals.[30]

OBSTRUCTIVE SLEEP APNEA EFFECTS ON VISUAL AND VISUOSPATIAL MEMORY

Analogous to verbal memory, visual memory consists of immediate recall, delayed recall, and recognition. There is a paucity of data examining the effect of OSA on this neurocognitive domain. The meta-analysis of Wallace and Bucks[22] showed visual immediate recall to be unimpaired for OSA patients compared with norms and controls. This unexpected finding was thought to be due to limitations in matching OSA to non-OSA data. They did not identify enough studies to qualify for meta-analysis of visual delayed recall or recognition.

Visuospatial memory involves recall of how image components relate to each other and is typically tested using a drawing task or recalling a specific image location. Effects of OSA vary depending on the comparison data.[22] Using control references, medium deficits were found in immediate and delayed visuospatial recall. No significant deficit was found compared with norms. The 2 studies identified testing visuospatial learning had conflicting results rendering the overall analysis insignificant. There were insufficient data to draw any conclusions regarding visuospatial recognition.

Lau and colleagues[31] recently reported effects of OSA on cognition including immediate and delayed visual memory in a Chinese cohort. Subjects with moderate to severe OSA (AHI >15) were compared with controls. They found a significant medium negative effect on delayed visual recall but no significant effect on visual learning. Further studies are needed to explore the effects of OSA on visual memory.

OBSTRUCTIVE SLEEP APNEA EFFECTS ON PSYCHOMOTOR FUNCTION AND PROCEDURAL MEMORY

Psychomotor function represents neurocognitive processing speed and is often measured by 2-hand coordination or reaction times. The meta-review by Bucks and colleagues[12] found an effect of OSA on psychomotor function in only 2 of 5 studies. No clear relationship with disease severity was identified. Only 2 of the 5 reviews considered age as a potential influence but found no relationship with cognition. None of the studies considered premorbid IQ as confounding factor. Kilpinen and colleagues[32] reviewed the effects of OSA on information processing, including psychomotor performance. Six of the studies reviewed used tests assessing pure psychomotor speed. Four of the 6 studies showed deficits associated with OSA. The review by Lal and colleagues[33] indicated fine-motor coordination to be diminished by OSA but motor speed was unimpaired.

The study by Ramos and colleagues[26] examined the effects of mild to moderate OSA on processing speed using the digit symbol substitution test (DSST). A deficit was seen for older women but not men in the unadjusted model. Accounting for age, education, sex, and other comorbidities eliminated a significant relationship. Although a large cohort of 8000 was included, the relatively lower mean AHI of 9.0 per hour may explain the lack of effect. Bawden and colleagues[34] also used the DSST to study the effects of OSA on psychomotor performance. Roughly 75% of the OSA subjects had moderate to severe disease. Control subjects were matched for age and education. OSA subjects were slower than controls but had fewer errors.

There is evidence that motor skill learning is also affected by OSA. Landry and colleagues[35] compared subjects with moderate OSA (mean AHI: 25.0) to controls matched for age and education. Performance on the sequential finger tapping task showed similar rates of improvement for OSA and control subjects in the evening. There was however a trend toward worse performance by OSA subjects with fewer typed sequences. The following morning, control subjects showed a significantly greater rate of improvement (15.4%) over baseline compared with OSA sufferers (1.8%). This greater rate of improvement was thought to reflect impaired memory consolidation and learning due to worse sleep quality for the OSA group. In a similar study, Djonlagic and colleagues[36] compared performance on a motor sequence learning task (MST) for moderate OSA subjects (mean AHI: 17.1) with age and subjective

sleepiness-matched controls. There was no difference in rate of improvement with practice in the evening. Significantly greater improvement was noted the following morning for the control group. Subjects without OSA showed 14.7% improvement after a night of sleep compared with just 1.1% improvement for the OSA group. These results were not explained by diminished attention in the OSA subjects as PVT results were similar for both groups. This difference remained despite multiple learning trials in the morning. By matching sleep architecture for the 2 groups, the investigators were able to demonstrate a significant inverse correlation between arousal index and MST improvement. The same relationship was noted but less robust for AHI and MST scores. There was no such finding for oxygen saturation measures. Therefore, consolidation of procedure memory appears to be affected by sleep fragmentation but not oxygen desaturations.

OBSTRUCTIVE SLEEP APNEA EFFECTS ON EXECUTIVE FUNCTION

Olaithe and Bucks[37] examined the effects of OSA on various aspects of executive function, including shifting or mental flexibility, updating or changing working memory, inhibition, generativity or ability to access long term memory, and fluid reasoning, in a recent meta-analysis. Studies included patients with AHI greater than 5.0 compared with controls. Medium effect sizes were seen for shifting and generativity. Large effects were seen for updating and fluid reasoning. A very large effect was seen for inhibition. Because there were relatively few subjects with mild or moderate OSA, a dose-response over the full range of AHI severity could not be determined. Nonetheless, comparison of severe to very severe OSA did not reveal a graded effect on cognition. This review was not able to distinguish whether the deficits in executive function were directly due to OSA or to excessive daytime sleepiness from OSA.

Executive function can be divided into several subdomains. In addition to more traditional aspects of executive function including planning, cognitive shifting, and inhibition, Borges and colleagues[38] chose updating or the ability to change the content of working memory as well as dual task performance, and efficient access to long-term memory to analyze effects of OSA. Moderate to severe OSA subjects were compared with controls matched for age, IQ, and education. All subjects were free of diabetes, hypertension, or depression and had body mass indexes less than 26 kg/m^2. No significant differences were found for any aspects of executive function between the OSA and control groups. The investigators suggested that comorbidities, including obesity, hypertension, diabetes, and depression, alone or in combination with OSA, may play a greater role in executive dysfunction than OSA alone.

Several studies have looked at effects of OSA on certain aspects of executive function as part of a larger examination of neurocognitive domains in the setting of sleep-disordered breathing.[16,39–44] Four of the studies showed executive function deficits associated with OSA.[39,41,43,44] Two of the studies did not show any effect of OSA on executive function.[16,40] One study had mixed results.[42] Although all studies except one[42] used the trail making test B, results were not consistently itemized for each test. Therefore, it was difficult to make direct comparisons as to the relative significance of individual findings.

OBSTRUCTIVE SLEEP APNEA EFFECTS ON OVERALL IQ

Several reviews have reported on the effects of OSA on global cognitive function.[14,33,45] The meta-review by Bucks and colleagues[12] found deficits in 2 of 4 reviews. It was suggested that hypoxemia may have more of an impact on overall IQ than sleep fragmentation. More recently, Canessa and colleagues[41] used the Mini-Mental State Evaluation (MMSE) to assess global cognition in controls and subjects with severe OSA. They found no significant difference in MMSE scores. The MrOS study[40] also examined cognition in a large cohort (n = 2636) of community-dwelling older men with mild versus moderate OSA followed an average of 3.4 years. The Modified MMSE (3MS), a more sensitive instrument than the MMSE, was used to measure overall cognition. They found that men with 1% or more of sleep time with oxygen saturation less than 90% had a greater decline on the 3MS compared with men with less than 1% of their sleep time less than 90%. No significant association between AHI and 3MS was found. A previous cross-sectional study of the same cohort did not reveal any association between sleep-related hypoxemia and the 3MS. It was hypothesized that oxidative stress, impaired glucose tolerance, and inflammation represented the pathologic response to sleep-related hypoxemia resulting in neurocognitive decline.

The effect of OSA on cognition has also been evaluated in older women. A prospective study by Yaffe and colleagues[46] evaluated 298 women (average age 82.3 years) without dementia and found that those with at least moderate OSA (defined as an AHI $\geq$ 15 per hour of sleep) at

mean follow-up of 4.7 years were more likely to have mild cognitive impairment or dementia compared with women with AHI less than 15 per hour of sleep, even after adjusting for potential confounders (odds ratio 1.85; 95% confidence interval, 1.11–3.08). ODI and increased sleep time in apnea or hypopnea were also associated with cognitive decline; however, measures of sleep fragmentation were not.

NEUROCOGNITIVE EFFECTS OF OBSTRUCTIVE SLEEP APNEA FOR CHILDREN

The prevalence of OSA has been estimated at 13% to 66% in obese children[47–50] and 1.2% to 5.7% in nonobese children.[51] Neurocognitive development is a particularly critical aspect of maturation during childhood. These findings may have implications for overall IQ in later years. A recent review[52] noted any severity of OSA and even snoring increases the risk for problems with attention, executive function, behavior, and scholastic performance in children.

Bourke and colleagues[53] looked at children aged 7 to 12 classified as controls, snorers, mild OSA, and moderate/severe OSA. Overall cognition and executive function were measured. In addition, reading, spelling, and arithmetical skills were assessed. They found significantly lower full-scale and verbal IQ scores for all other groups compared with controls. Although nonverbal and performance IQ scores were lower than controls, these findings did not reach statistical significance. Executive function was not significantly different for snorers or OSA subjects as compared with controls. Similarly, reading, spelling, and arithmetical skills did not differ between snorers, OSA subjects, and controls. These results support the importance of treating snoring as well as mild and severe sleep-disordered breathing in children.

Another study by Jackman and colleagues[54] evaluated behavior as well as cognition in preschool children (age 3–5) also divided into controls, snorers, mild, and moderate/severe OSA. Behavior in the home was assessed by standardized parental rating. Snorers and mild OSA subjects were found to have poorer behavior compared with controls. For some behaviors, these 2 groups were even worse than the moderate/severe OSA group. No differences were seen for measures of global intelligence, attention, language, visuospatial ability, fine-motor skills, memory, or executive function. The investigators speculated that behavioral dysfunction was due to a higher degree of sleep fragmentation not captured by current measurement techniques in this pediatric population. They furthermore reasoned that a greater drive to protect the brain from hypoxia at the expense of sleep consolidation produced these findings.

Landau and coworkers[55] studied children with of mean age 45 months ($\pm$9 months) with OSA (mean AHI 13.2 $\pm$ 10.7) compared with age-matched controls. They assessed cognition, behavior, and quality of life. Impairment of executive function (planning and fluency), attention, and receptive vocabulary were noted for OSA subjects compared with controls using the Kaufman assessment battery for children but not for the Behavior Rating Inventory of Executive Function-Preschool version (BRIEF-P). This correlates with the Jackman study that also used the BRIEF-P to assess executive function. Landau, like Jackman, also found more behavior problems in the OSA group. In addition, Landau documented worse quality of life in OSA children compared with controls. This study underscores the impact of OSA in early childhood and the importance of identifying and treating OSA in this population.

Other reports in children age 7 to 15 with OSA have shown deficits in working memory,[56,57] psychomotor efficiency,[57] executive function,[58] and IQ.[59] Variability of results can in part be seen due to varying tests to assess particular neurocognitive domains.

IMAGING: MAGNETIC RESONANCE SPECTROSCOPY, DIFFUSION TENSOR IMAGING, FUNCTIONAL MRI STUDIES

In the last few years, imaging modalities, including MRI, magnetic resonance spectroscopy (MRS), functional MRI (fMRI), and diffusion tensor imaging (DTI), have provided insights into structural, functional, and metabolic correlates of the neurocognitive effects of OSA. Recent reviews[60–62] have highlighted volume loss in the anterior cingulate, hippocampus, frontal, parietal, and temporal lobes associated with OSA severity. The study by Canessa and colleagues[41] used voxel-based morphometry (VBM) analysis of MRI-T1 images to assess gray-matter (GM) volumes and cognition in subjects with severe OSA compared with age- and education-matched controls. Reduced GM volume in left hippocampus, left posterior parietal cortex, and right superior frontal gyrus correlated with significant impairment in short- and long-term verbal memory, constructional ability, attention, and especially executive function.

Castronovo and coworkers[43] examined white matter (WM) tracts with DTI along with assessments of similar neurocognitive domains in severe OSA subjects compared with age- and education-matched controls. As opposed to correlating with

gross numbers of neurons such as with VBM techniques, the fractional anisotropy evaluation of DTI attempts to determine the integrity of groups of neurons working together as functional units. Neurocognitive deficits involving attention, executive function, and memory were associated with diffuse reduction of WM tract integrity involving the bilateral parietal and frontal lobes. These changes are thought to contribute to slowed information processing.

O'Donoghue and colleagues[44] applied MRS to elucidate effects of severe OSA on neuronal viability. Vigilance, memory, and executive function were quantified as well and compared with age-matched controls. Although changes suggestive of decreased frontal lobe neuronal viability were seen, there were no correlations with neurocognitive function. Cerebral metabolite concentrations did, however, correlate with OSA severity.

Zhang and colleagues[63] used a visual mismatch task to show changes in fMRI activation for severe OSA subjects compared with age- and education-matched controls. They found reduced frontal activation in the anterior cingulate cortices (ACC), middle frontal gyri, and inferior frontal gyri, but increased activity in the right anterior prefrontal gyri (aPFG). Reaction times were significantly slower for OSA subjects. These results along with lower frontal activation were associated with duration of time below oxygen saturation less than 80% and arousal index. Other measures of sleep-disordered breathing, such as the apnea, hypopnea, and desaturation indices, showed no such relationship. These data indicate that oxygen desaturation and sleep fragmentation play a role in executive dysfunction for tasks such as this. Effects on reaction time implicate circuits responsible for the transfer of information as opposed to a primary failure of neuronal units per se. Furthermore, the increased right aPFG activity suggests a compensatory response needed for OSA subjects to complete the mismatch task.

MECHANISMS OF OBSTRUCTIVE SLEEP APNEA EFFECTS ON COGNITION

The intermittent hypoxia (IH) and sleep fragmentation seen in OSA provide a link between sleep-disordered breathing and impairment over a range of neurocognitive domains as asserted by Gozal.[64] To further elucidate the mechanisms of neuronal damage due to IH, Sapin and colleagues[65] exposed mice to 1 day (acute) versus 6 or 24 weeks (chronic) of IH. They found that chronic but not acute IH was associated with significant microglial changes in the dorsal hippocampus. Acute but not chronic IH increased cytokines associated with neuro-inflammation. These findings complement the data showing impaired memory and learning in human OSA subjects. Smith and colleagues[66] showed increases in inflammatory gene expression of cortical microglia for rats exposed to IH.

Sales and colleagues[67] measured cognition and biomarkers of oxidative stress in subjects with severe OSA and age-matched controls. Vitamin E, superoxide dismutase (SOD), and vitamin B11 were lower, while homocysteine was higher in OSA subjects. These subjects also performed worse on measures of attention, executive function, working, verbal, and delayed visual memory. An association was found between executive function measures and vitamin E levels as well as SOD. Nair and colleagues[68] identified NADPH oxidase as the driving force of oxidative stress induced spatial learning impairments in mice exposed to IH.

Sleep fragmentation has also been implicated in neurocognitive dysfunction mediated by neuroinflammation. Ramesh and colleagues[69] used a mouse model to examine the effects of disrupted sleep without reduced total sleep on cognition in mice. They found an association between poor spatial learning, memory, sleepiness, and increased cortical expression of tumor necrosis factor-α (TNF-α). They further demonstrated the absence of sleepiness or neurocognitive dysfunction in TNF-α double receptor knockout mice. Last, mice treated with a TNF-α neutralizing antibody did not develop sleepiness or neurocognitive dysfunction despite sleep fragmentation.

Sympathetic overdrive is another potential mechanism by which OSA affects cognition. Goya and colleagues[70] measured muscle sympathetic nerve activity (MSNA) in subjects with severe OSA and persons with mild OSA matched for age and education. Baseline MSNA was higher in severe OSA subjects. Further MSNA increases and worse executive function were seen in severe versus mild OSA subjects. The study by Fatouleh and colleagues[71] showed increased activation in the bilateral dorsolateral PFC, medial PFC, dorsal precuneus, ACC, retrosplenial cortex, and caudate nucleus associated with increased MSNA in OSA subjects. These cerebral areas are known to be involved in modulation of sympathetic outflow.

IMPACT OF CONTINUOUS POSITIVE AIR PRESSURE

CPAP is the most commonly prescribed treatment of OSA. This therapy has been shown to eliminate respiratory disturbances and improve daytime

alertness.[72] Its effect on domains of neurocognitive function has been less consistently demonstrated.

The previously described meta-analysis by Olaithe and Bucks described reductions in OSA-related impairment across 5 subcomponents of executive function (ie, shifting, updating, inhibiting, generating, and fluid reasoning) with CPAP therapy.[37] Although age and disease severity did not moderate these outcomes, this review was unable to exclude the effects of premorbid intelligence because not all included studies provided this information.

In a multicenter study of 174 subjects with moderate to severe OSA, measures of subjective and objective sleepiness and neurocognitive function were assessed before and after 3 months of CPAP therapy.[73] In regard to daytime sleepiness, CPAP treatment resulted in a marked and dose-dependent reduction in subjective daytime sleepiness (ESS) but did not affect Maintenance of Wakefulness Test–derived mean sleep latencies. Nearly 20% of subjects who used CPAP for more than 7 hours per night had abnormal sleepiness scores despite seemingly adequate use. There were significant improvements in verbal memory and executive function but not vigilance among these subjects at 3 months.

Research protocols attempting to determine the impact of CPAP therapy on neurocognitive outcomes have been hampered by a variety of methodological factors. In an effort to address many of these limitations, a large multicenter study (APPLES) randomly assigned 1105 subjects diagnosed with OSA to either active CPAP or sham CPAP.[74] CPAP use for the active arm averaged 4.2 hours per night. At 2- and 6-month follow-up, subjective and objective sleepiness were significantly reduced in actively treated participants and most prominently among those with severe OSA (AHI >30). The primary measure of executive and frontal-lobe function (E/F) was improved at 2 months in the active CPAP group compared with sham CPAP, but no differences were noted among groups in regard to measures of L/M or attention and psychomotor function (A/P) at 2 or 6 months. Further stratification by markers of sleep apnea severity (AHI or oxygen desaturation) resulted in transient differences among study arms in the primary E/F and one secondary E/F variable.[74] The study may have been somewhat limited by the absence of a healthy control group and the overall intelligence of the participants, who may have had relatively high neurocognitive reserve. However, adjustment for IQ did not alter the findings. Despite the lack of robust neurocognitive improvements with CPAP therapy, it is possible that the neurocognitive benefits related to CPAP may require more than 6 hours of use per night[43] or perhaps may occur among a genetically unique subset of subjects.

Lin and colleagues[75] recently investigated the effect of good versus suboptimal CPAP compliance on neurocognitive measures (CANTAB). Subjects that used CPAP for more than 70% of nights over 3 months had improvements in decision making and response control domains compared with less adherent subjects.

The effects of CPAP therapy on neurocognitive function specifically among older adults have been studied and have demonstrated inconsistent benefit. Gutierrez Iglesias and colleagues[76] found CPAP treatment was beneficial for selective and divided attention, working memory, verbal and short-term memory, and visual long-term memory.

In the PROOF study, Crawford-Achour and colleagues[77] assessed the benefit of CPAP therapy on neurocognitive outcomes in those 65 years of age and older with severe OSA at baseline and at 10-year follow-up. Those subjects that received CPAP were very compliant with a mean usage of more than 6 hours per night. Compared with untreated controls, CPAP users demonstrated maintenance of memory and improvements in mental abilities. The limitations of this study are noteworthy as treated subjects were few (26% of sample), had worse OSA severity (higher AHI and ODI), were more symptomatic (higher ESS) at baseline, and were selected to receive therapy at the discretion of their primary care physician. Another study of CPAP therapy in older adults with OSA found improvements in daytime sleepiness at 3 months, particularly in those with increased CPAP use and higher scores on pretreatment ESS. These benefits were shown at 12 months but were not seen for other neurocognitive measures (MMSE, Trail Making Test-B, DSST, and simple and 4-choice reaction time), which remained unchanged at 12 months.[78]

CPAP therapy may provide cognitive benefits in patients with neurodegenerative disorders. In a recent study by Troussière and colleagues,[79] those subjects with mild-to-moderate Alzheimer disease and severe OSA who used CPAP had significantly less cognitive decline at 3-year follow-up compared with an otherwise matched non-CPAP group.

There is increasing evidence that CPAP therapy can reverse sleep apnea–related brain morphologic changes. The Canessa study, described previously, reported reversal of GM volume decrements after 3 months of CPAP treatment in specific hippocampal and frontal regions that correlated with improvements in memory, attention, and executive function.[41] Other investigators using brain MRS[44] found 6 months of CPAP

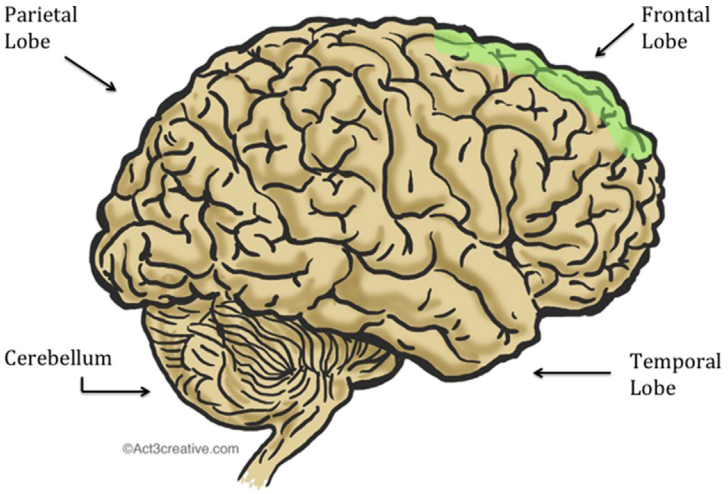

Fig. 1. Green area represents OSA effect on executive function that is localized to the frontal lobe. (Ron Hill/Act 3 LLC, www.act3creative.com. *Data from* Castronovo V, Scifo P, Castellano A, et al. White matter integrity in obstructive sleep apnea before and after treatment. Sleep 2014;37(9):1465–75.)

therapy did not improve metabolite ratios in the frontal lobe but did eliminate significant differences for the hippocampus compared with controls. Although measures of vigilance and executive function showed some improvement with this length of CPAP treatment, cerebral metabolite concentrations did not correlate with neurocognitive test results.

The effects of 3 and 12 months of CPAP therapy on WM fiber integrity, as measured by DTI, and neurocognitive performance were assessed in 17 positive air pressure–naïve OSA subjects and 15 healthy controls.[43] Despite only limited changes noted in WM integrity among treated subjects at 3 months, there was near complete normalization in affected regions in CPAP-compliant subjects at 1 year. These changes paralleled neurocognitive test improvements in memory, attention, and executive function.

CONTINUOUS POSITIVE AIR PRESSURE WITHDRAWAL

Others have evaluated the consequences of acute and short-term CPAP withdrawal on neurocognitive outcomes. In a study by Filtness and colleagues,[80] 11 subjects who were deemed long-term (mean 7.8 years) CPAP compliant users underwent 2 daytime driving simulations, one following regular nighttime CPAP use and the other after sleeping one night without therapy. There were significantly more driving incidents, decreased latency to first incident, marked increase in α and θ electroencephalogram activity and increased subjective sleepiness the day following CPAP withdrawal. Two nights of CPAP withdrawal among participants with either mild to moderate or severe OSA were associated with reappearance of both subjective and objective

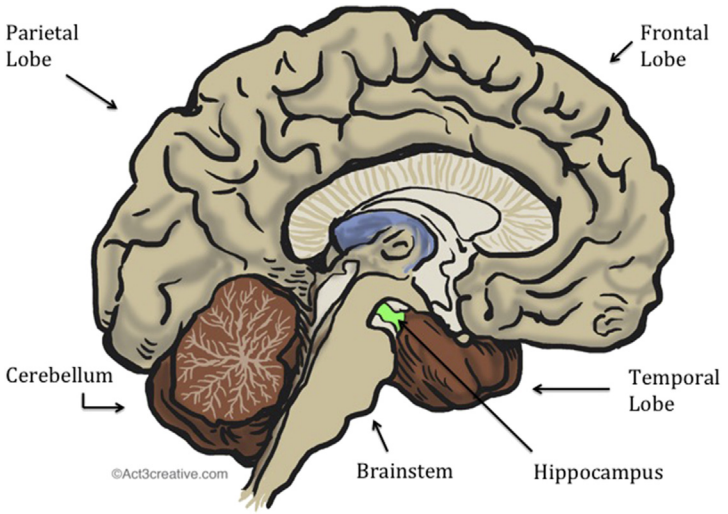

Fig. 2. Green area represents OSA effect on memory that is localized to the hippocampus. (Ron Hill/Act 3 LLC, www.act3creative.com. *Data from* Castronovo V, Scifo P, Castellano A, et al. White matter integrity in obstructive sleep apnea before and after treatment. Sleep 2014;37(9):1465–75.)

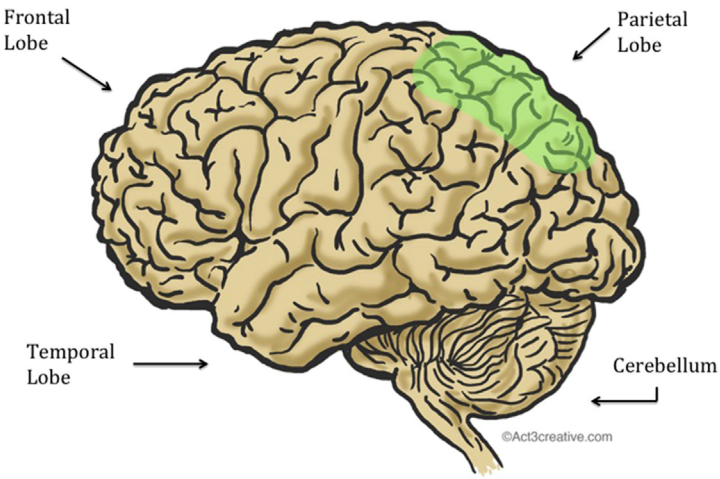

Fig. 3. Green area represents OSA effect on abstract reasoning that is localized to the parietal lobe. (Ron Hill/Act 3 LLC, www.act3creative.com. *Data from* Castronovo V, Scifo P, Castellano A, et al. White matter integrity in obstructive sleep apnea before and after treatment. Sleep 2014;37(9):1465–75.)

sleepiness and altered vigilance testing to pretreatment levels.[81] However, psychomotor performance measures of divided attention and vigilance were not significantly altered by 2 weeks of CPAP discontinuation in a study conducted by Kohler and colleagues.[82]

SUMMARY

Studies have shown that OSA can impair attention, verbal memory, executive function, and learning. Affected cognitive domains that localize to discrete regions of the brain, with documented structural changes, are shown in **Figs. 1–3**. There is a paucity of data examining OSA effects on delayed visual memory, visual perception, and visuospatial memory. Imaging modalities including MRI with VBM, DTI, MRS, and fMRI provide insight into the impact of OSA on brain structure and function. Magnetic resonance elastography is a relatively new technique to measure brain tissue integrity that could further expand this knowledge.[83] Mechanisms of cerebral remodeling include neuro-inflammation, oxidative stress, and sympathetic overactivation. CPAP use of at least 4 hours per night improves executive function at 2 months. CPAP use of 6 hours or more may provide additional neurocognitive improvement for vulnerable populations with decreased neurocognitive reserve in the setting of aging and comorbidities, such as cardiovascular disease, diabetes, mild cognitive impairment, and Alzheimer dementia. Genetic profiles may also help predict neurocognitive effects of CPAP. Further studies are needed to elucidate mechanisms of neurocognitive impairment and identify factors most likely to enhance the beneficial effects of CPAP on cognition for OSA patients.

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