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Obstructive Sleep Apnea and Its Treatment in Aging: Effects on Alzheimer's disease Biomarkers, Cognition, Brain Structure and Neurophysiology

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Abstract

Here we review the impact of obstructive sleep apnea (OSA) on biomarkers of Alzheimer's disease (AD) pathogenesis, neuroanatomy, cognition and neurophysiology, and present the research investigating the effects of continuous positive airway pressure (CPAP) therapy. OSA is associated with an increase in AD markers amyloid-β and tau measured in cerebrospinal fluid (CSF), by Positron Emission Tomography (PET) and in blood serum. There is some evidence suggesting CPAP therapy normalizes AD biomarkers in CSF but since mechanisms for amyloid-β and tau production/clearance in humans are not completely understood, these findings remain preliminary. Deficits in the cognitive domains of attention, vigilance, memory and executive functioning are observed in OSA patients with the magnitude of impairment appearing stronger in younger people from clinical settings than in older community samples. Cognition improves with varying degrees after CPAP use, with the greatest effect seen for attention in middle age adults with more severe OSA and sleepiness. Paradigms in which encoding and retrieval of information are separated by periods of sleep with or without OSA have been done only rarely, but perhaps offer a better chance to understand cognitive effects of OSA than isolated daytime testing. In cognitively normal individuals, changes in EEG microstructure during sleep, particularly slow oscillations and spindles, are associated with biomarkers of AD, and measures of cognition and memory. Similar changes in EEG activity are reported in AD and OSA, such as "EEG slowing" during wake and REM sleep, and a degradation of NREM EEG microstructure. There is evidence that CPAP therapy partially reverses these changes but large longitudinal studies demonstrating this are lacking. A diagnostic definition of OSA relying solely on the Apnea Hypopnea Index

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Conflict of Interest

The authors declare no competing financial interests.

(AHI) does not assist in understanding the high degree of inter-individual variation in daytime impairments related to OSA or response to CPAP therapy. We conclude by discussing conceptual challenges to a clinical trial of OSA treatment for AD prevention, including inclusion criteria for age, OSA severity, and associated symptoms, the need for a potentially long trial, defining relevant primary outcomes, and which treatments to target to optimize treatment adherence.

Introduction

Obstructive sleep apnea (OSA) is a type of sleep-disordered breathing (SDB) (ICSD-3 2014) characterized by recurrent complete or partial closure of the upper airway followed by blood oxygen desaturation and/or arousal from sleep. Untreated, these repetitive respiratory events can lead to fragmented, disrupted sleep and chronic nocturnal intermittent hypoxia, re-oxygenation, and hypercapnia or hypocapnia. OSA diagnosis is made using assessment of physiological signals from oronasal airflow, respiratory effort and pulse oximetry during sleep. Polysomnography (PSG), including EEG, is considered the gold standard for investigation of suspected SDB, however recordings with only airflow and/or pulse oximetry are commonly used for diagnosis (Woods et al. 2014). OSA severity is predominantly classified with reference to the apnea-hypopnea index (AHI), defined as the number of respiratory events (apneas and hypopneas) per hour of sleep. Critically, there are multiple definitions of “hypopnea,” leading to multiple AHI’s, and no one definition of AHI is used consistently in clinical research investigating OSA and its effect on health outcomes.

A review of eleven population-based epidemiological studies from around the world between 1993 and 2013 found an average prevalence rate of 22% in men and 17% in women for at least mild OSA, and 6% in men and 4% in women for the OSA syndrome (OSAS), also known as OSA with excessive daytime sleepiness (EDS) (Franklin and Lindberg 2015). One of the more recent large studies of community-recruited individuals, the HypnoLaus study, used the AASM 2012 hypopnea definition ≥30% drop of airflow lasting at least 10 s with either an arousal or ≥3% oxygen desaturation (AHI3A). In this study, when subjects were dichotomized by age (ages 40–60 years and ages 60–85 years), the proportion of subjects with AHI3A ≥ 15/hour was 26.8% in the younger group (39.6% in men, 13.9% in women) and 48.7% in the older group (64.7% in med, 35.2% in women), highlighting the extraordinary prevalence of OSA in older individuals (Heinzer et al. 2015). Treatment options for OSA include positive airway pressure devices, oral appliances, behavioral/lifestyle modification, surgery and/or a combination of approaches. Deciding on the most effective treatment for an individual diagnosed with sleep OSA depends on disease severity, presenting symptoms and contributing causes. Continuous positive airway pressure (CPAP) is the most commonly prescribed treatment and works by the delivery of positive pressure via a mask worn over the nose (and/or mouth), functioning to splint the upper airway open during sleep (Sullivan et al. 1981).

Over the last few years, the literature has expanded regarding the links between sleep disruption, markers of Alzheimer’s disease (AD) pathogenesis, and the development of cognitive impairment and/or dementia. A recent meta-analysis showed SDB was a risk factor of all-cause dementia, AD, and vascular dementia (Shi et al. 2018), however many

studies used self-reported measures of OSA, and few longitudinal studies were included. In older women, those diagnosed with OSA via PSG had increased risk of developing mild cognitive impairment (MCI) or dementia over a 5-year follow-up (Yaffe et al. 2011). In Asian populations, there are two large longitudinal community-based studies finding OSA/SDB is associated with increased risk of developing dementia and AD (Chang et al. 2013; Lee, Yang, et al. 2019). Analysis of the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort found the presence of OSA was associated with an earlier age of cognitive decline and suggests CPAP treatment may delay the progression of cognitive impairment (Osorio et al. 2015). Here we present a narrative review of the literature investigating how sleep and sleep-disordered breathing influences markers of increasing risk of neurodegeneration through measures of amyloid-β and tau, neuroanatomy, cognition and neurophysiology. Lastly, we review the evidence concerning modification of these various markers with CPAP treatment. The literature included was selected using SCOPUS, searching with terms "OSA" and "Alzheimer's disease", "neuroimaging", "cognition" and "EEG", and with "CPAP" subsequently added to each pair of search terms. In addition, meta-analysis and systematic reviews focusing sleep and Alzheimer's disease were reviewed along with their bibliographies for associated cited work.

OSA impacts markers associated with increasing AD risk

Amyloid/tau biomarkers

There is mounting evidence that OSA is associated with an increase in markers associated with AD, specifically amyloid-β and tau measured in cerebrospinal fluid (CSF), by Positron Emission Tomography (PET) and in blood serum. In several studies where OSA was diagnosed using PSG, reduced CSF amyloid-β levels compared to age-matched controls without OSA have been demonstrated (Ju et al. 2016; Liguori et al. 2017; Liguori et al. 2019). When groups were stratified by ApoE allele status, OSA severity positively correlated with amyloid-β_{42}, phosphorylated tau (P-tau) and total tau (T-tau) in ApoE3 carriers and negatively correlated with amyloid-β_{42} levels in those with ApoE2 (Osorio et al. 2014). Interpreting AD risk based solely on CSF amyloid-β in cognitively normal older individuals at cross section is not straightforward. While there is consensus that CSF amyloid-β is lower in individuals with bona fide AD dementia versus age matched controls, there is evidence for elevated CSF amyloid-β with a steeper subsequent decline in individuals with genetic risk for AD (Bateman et al. 2012; Fagan et al. 2014). Additionally, an analysis of interrelationships between CSF amyloid-β and tau across a wide variety of ages showed that there was an overall positive correlation between CSF amyloid-β and tau between the ages of 45 and 70, whereas there was an overall negative correlation between CSF amyloid-β and tau between the ages of 71 and 90 (de Leon et al. 2018).

PET amyloid tracer uptake levels are a robust predictor of amyloid burden as well as of future development of AD (Waragai et al. 2009). The first PET study to show greater amyloid deposition with increasing OSA severity was a small pilot study of 5 people with MCI (Spira et al. 2014). However, the association between amyloid and OSA was not observed among the 8 cognitively normal participants. A more recent analysis in 14 OSAS patients with normal cognition also found no association between SDB and amyloid uptake

(Handa et al. 2019). In contrast, a case control study of 19 participants with SDB found higher amyloid deposition in the right posterior cingulate gyrus and right temporal cortex compared to controls (Yun et al. 2017). Also, a cross sectional study of 117 cognitively normal Australian veterans (42 with OSA diagnosed by PSG) showed cortical uptake of 18F-florbetaben (ligand binding to amyloid aggregates) was higher in OSA group than in those without symptoms of OSA. In this study, a regression analysis revealed the relationship between amyloid deposition and OSA was independent of age and vascular risk factors, but not BMI or ApoE4 status, where the presence of ApoE4 amyloid burden was increased to a greater degree in those with OSA (Elias et al. 2018). Another cross-sectional analysis found 96 of 127 community dwelling, cognitively normal individuals with OSA showed greater amyloid burden via PET in the posterior cingulate cortex and precuneus areas which overlapped with increased grey matter volumes, perfusion and glucose metabolism (Andre et al. 2020).

Tau has been less studied overall with relation to OSA. Individuals with OSA have been shown to have elevated plasma concentrations of T-tau (Motamedi et al. 2018) and P-tau (Bu et al. 2015) in comparison to individuals without OSA. Although there is poor correlation between serum and CSF tau concentrations, serum tau may nonetheless be useful as a predictive marker for dementia (Pase et al. 2019). Relatedly, individuals with OSA were shown to have elevated concentrations of T-tau/Aβ42 in the CSF in comparison to either individuals without OSA or with PAP-treated OSA (Liguori et al. 2017), although no differences in individual T-tau or P-tau in the CSF were observed in another cross-sectional study (Ju et al. 2016). Tau PET imaging was employed in a cross-sectional analysis of 292 cognitively unimpaired adults who, when their bed-partners positively reported “witnessed apnea,” had more elevated tau-PET levels in the entorhinal cortex and inferior temporal cortex (Carvalho et al. 2020).

Longitudinal studies are therefore useful in clarifying some of the cross-sectional inconsistencies. Our group has reported two longitudinal studies using both CSF and PET imaging markers of Alzheimer’s disease in OSA. In Sharma et al. (2018), baseline severity of OSA was associated with a longitudinal decrease in CSF amyloid-β_{42} and longitudinal increase in cortical amyloid deposits by PET imaging. In Bubu et al. (2019), self-reported OSA in cognitively normal and MCI individuals was associated with increases in amyloid burden by both CSF and PET measures, and in CSF concentration of T-tau and P-tau over 2.5 years.

Changes in markers of disease with CPAP treatment

There is a paucity of literature demonstrating CPAP treatment effects on amyloid and tau biomarkers of AD. In the only study to examine a CPAP treatment effect that incorporated in-lab PSG, CSF sampling and neurocognitive testing, Liguori et al. (2017) compared 10 OSA positive patients treated with CPAP (for <1 year with good compliance), 25 untreated OSA patients, and 15 controls. Untreated OSA patients showed lower CSF amyloid-β_{42} concentrations, and higher T-tau/ amyloid-β_{42} ratio compared to both CPAP-treated individuals and controls. Furthermore, lower CSF amyloid-β_{42} levels correlated with lower average nocturnal oxygen saturation and cognition in OSA patients. In contrast, an

observational study by Elias et al. (2018) found self-reported CPAP use in 24/42 veterans with OSA had no significant impact on amyloid deposition or cognition. In another study using a within participant design, Ju et al. (2019) measured CSF biomarkers in 18 adherent CPAP users before and after 1–4 months of CPAP therapy and found that greater improvement of OSA as a result of CPAP therapy (reduction of AHI and arousals) positively correlated with greater changes in amyloid and tau levels in a direction of reduced AD pathology. There were no significant changes in CSF biomarkers at the group level, suggesting a potential need to focus on individuals with more moderate to severe OSA.

Summary

In cognitively normal older subjects, OSA appears to be associated with an increase CSF measures of AD pathology at cross section, with heterogeneity potentially stemming from differences in OSA severity inclusion/exclusion criteria. CPAP reduces these markers perhaps more profoundly with increasing OSA severity, but the evidence is scant. A better understanding of the mechanisms by which OSA influences CSF amyloid-β and tau concentrations could stem from evaluating the independent contributions of sleep fragmentation and hypoxia within individuals in paradigms using withdrawal of therapeutic CPAP. Large cross-sectional and longitudinal studies indicate OSA increases AD biomarker burden measured using PET imaging, but it is still not clear if treatment with CPAP can reverse these effects long-term. Table 1 summarizes the OSA and AD biomarker research referenced in this section.

Cognition

Deficits in the cognitive domains of attention, vigilance, memory and executive functioning during daytime testing are observed in those suffering from OSA (Bucks, Olaithe, and Eastwood 2013; Leng et al. 2017). However, evidence from longitudinal studies show disparate finding with some linking OSA to cognitive decline (Yaffe et al. 2011; Spira et al. 2014; Osorio et al. 2015; Blackwell et al. 2015) whilst others produce weak or null findings in this regard (Boland et al. 2002; Martin et al. 2015; Lutsey et al. 2016). Overall, the magnitude of impairment emerges to a greater degree in younger and middle aged OSA patients from clinical settings than in older healthy community samples (Cross et al. 2017).

Cross-sectional studies investigating middle age and older adults with OSA have demonstrated cognitive impairments in executive function (Bawden, Oliveira, and Caramelli 2011; Mathieu et al. 2008; Quan et al. 2006; Hrubos-Strom et al. 2012; Blackwell et al. 2011; Nikodemova et al. 2013; Salorio et al. 2002; Spira et al. 2008; Yesavage et al. 1985; Sharma et al. 2010), attention (Bawden, Oliveira, and Caramelli 2011; Mathieu et al. 2008; Naegele et al. 1995; Quan et al. 2006; Yesavage et al. 1985), reaction time and psychomotor vigilance testing (PVT) (Sharma et al. 2010; Kim, Dinges, and Young 2007; Alchanatis et al. 2008) and memory (Bawden, Oliveira, and Caramelli 2011; Kloepfer et al. 2009; Naëgelé et al. 2006; Nikodemova et al. 2013; Salorio et al. 2002; Sharma et al. 2010; Ju et al. 2012; Yesavage et al. 1985; Berry et al. 1990). In contrast other groups have found no significant association between OSA and measures of executive function, attention or memory (Hayward et al. 1992; Phillips et al. 1992; Foley et al. 2003; Sforza et al. 2010).

Proposed explanatory mechanisms for findings relating OSA to cognitive impairment include daytime sleepiness from sleep fragmentation and/or neurovascular damage as a result of intermittent hypoxia, although the contributions of each are not well established (Cedernaes et al. 2017). Indeed, some of the aforementioned studies find the severity of disease corresponds to degree of cognitive impairment, though invariably it depends on not only on the measure investigated but the method of measurement of both OSA and cognition (Gagnon et al. 2019; Gosselin et al. 2019). Some earlier research suggests the degree of sleep fragmentation results in deficits of attention and memory (Naegele et al. 1995; Roehrs et al. 1989) whilst severity of hypoxemia influences motor function, vigilance and executive function (Bliwise 1993; Bedard et al. 1991). In a large study of 743 people undergoing a clinical PSG study who had an AHI ≥ 5 and completed a pre-sleep PVT assessment, Kainulainen et al. (2020) demonstrated novel measures of hypoxemia (median saturation of peripheral oxygen (SpO_2) dip and desaturation area) were significantly associated with increased risk of impaired evening PVT performance whilst all other measures of OSA severity and sleep fragmentation did not. However, there have been no recent or sufficiently large studies corroborating such delineations with memory or executive function.

A complicating factor in the assessment of cognitive outcomes in people with OSA is the issue of sleepiness which is purported to worsen cognitive performance (Gagnon et al. 2014; Steiropoulos, Galbiati, and Ferini-Strambi 2019). Mathieu et al. (2008) found sleepiness contributed to poorer cognitive performance only in younger (< 50 years) patients with OSA. A review of the literature (Zhou et al. 2016) concluded that EDS contributes to greater neurocognitive dysfunction in OSA but highlights the need to sufficiently examine neurocognitive impairments in OSA without sleepiness.

Overnight memory

Most studies investigating cognitive function in OSA assess general cognitive abilities during daytime neuropsychological test batteries or neurobehavioral vigilance rather than sleep related memory processing which involves encoding and recall separated by a period of sleep (Ahuja et al. 2018). In the small number of studies incorporating overnight memory assessments in OSA patients, there is demonstrated impairment in processing of declarative and procedural memory tasks compared to healthy controls (Kloepfer et al. 2009; Landry et al. 2014), but memory encoding and implicit motor memory formation appear intact (Cellini 2017). In a series of studies showing impaired overnight motor sequence task learning in moderately severe OSA, a negative relationship was observed between task performance and a polysomnographic (PSG) arousal index (Djonlagic et al. 2015, 2014), with the later study showing increasing age to be associated with less overnight improvements.

CPAP withdrawal is a way to observe the deleterious effect of OSA on overnight memory task. A study by our group found the benefits of overnight sleep for improvements on a spatial navigation task are attenuated when OSA is induced by selective CPAP withdrawal during REM sleep (Varga et al. 2014).

Changes in cognition with CPAP treatment

CPAP treatment results in variable changes to cognition (Kielb et al. 2012), with the greatest effect seen for attention (Kylstra et al. 2013; Pan et al. 2015) in younger and middle age adults with more severe SDB and sleepiness (Zhou et al. 2016).

In the largest randomized controlled trial (RCT) to date, 6 months of CPAP treatment was associated with transient improvements (at 2 months only) in attention and executive functioning, with greater effects on a sustained working memory task at 6 months in those with higher baseline daytime sleepiness (ESS > 10) (Kushida et al. 2012). A summary of the existing RCTs shows both short and long-term CPAP treatment improves some of the deficits associated with OSA in middle-aged adults (Canessa et al. 2011; Castronovo et al. 2014; Ferini-Strambi et al. 2003). Alternatively, Saunamaki et al. (2010) did not observe any improvements in executive or visuospatial functioning, even after long-term CPAP treatment in a group of 17 men. In older adults, similar observations are made with large multi-center trials (Martinez-Garcia et al. 2015; McMillan et al. 2014) showing minimal or null effects of CPAP on cognition. However, a lack of treatment related outcomes could be explained by low CPAP adherence levels at least in the study by McMillan et al. (2014). In smaller, single center trials, improvements in attention, psychomotor speed, memory and executive function are observed particularly in those with higher CPAP usage (Aloia et al. 2003; Dalmases et al. 2015).

In an observational study of moderate- severe OSA, Antic et al. (2011) found a treatment dose-response effect for CPAP in terms of Epworth Sleepiness Scale (ESS) scores. Moreover, whilst a greater number of patients showed a normalization of sleepiness and neurobehavioral function with longer nightly durations of CPAP, a substantial number did not. In a large cross-sectional study, patients with mild-moderate OSA, Jackson et al. (2018) did not observe a reversal of neurocognitive impairments after 3 months of CPAP therapy, even with adequate CPAP use. Bhat et al. (2018) assessed changes in subjective sleepiness (via ESS) and objective vigilance (via PVT) after at least 1 month of CPAP therapy and found that although significantly less sleepiness was reported irrespective of OSA severity, improvements in vigilance measured using PVT was only observed in those with severe OSA before treatment.

Studies investigating OSA treatment and overnight memory consolidation find longer-term use, but not a single night of CPAP therapy, augment offline sleep-mediated motor memory consolidation (Djonlagic et al. 2015; Landry et al. 2016).

By looking at age of onset of MCI in subjects with self-reported OSA and use of CPAP for treatment in the Alzheimer's Disease Neuroimaging Initiative, we observed that cognitively normal older individuals with self-reported untreated OSA had an average age of onset of MCI that was 11 years earlier than those subjects without OSA (72 year vs 83 years), while those individuals with self-reported CPAP treatment had an average age of MCI onset that was similar to those without OSA at all (82 years) (Osorio et al. 2015).

Treatment in MCI/AD with OSA

There is some evidence that CPAP treatment in those already suffering from cognitive impairments can improve symptoms or delay further cognitive decline. Chong et al. (2006: author) saw a reduction in sleepiness after 3 and 6 weeks of treatment in patients with mild to moderate AD after randomization to CPAP therapy but not after using a sham device. A pilot study investigating rate of cognitive decline in patients with moderate AD and severe OSA found CPAP-treated individuals had a significantly slower cognitive decline (Mini Mental State Exam (MMSE) score changes) compared to untreated individuals over three years (Troussiere et al. 2014). A recent quasi- experimental study investigating MCI and OSA found significant improvements in psychomotor/cognitive processing speed in CPAP adherent patients after 1 year compared to a non-adherent control group (Richards et al. 2019). They also observed improvements in memory, sleepiness and daily functioning suggesting CPAP may slow the progression of dementia.

Summary

Overall, more consistent findings of cognitive impairment are seen in young and middle-aged patients with OSA rather than in elderly community dwelling cohorts with findings likely driven by treatment-seeking individuals (Bubu et al. 2020). CPAP may be effective in improving cognition, particularly in the presence of sleepiness and given good treatment adherence. CPAP treatment also shows promise for delaying further cognitive decline in those with MCI and AD, but more cognitive assessments where encoding and recall are separated by a period of sleep are needed to understand OSA-related impaired cognition within individuals. Table 2 summarizes the OSA and cognition research referenced in this section.

Neuroanatomical changes in OSA

OSA is clinically characterized by intermittent hypoxia and chronic sleep fragmentation, and both are proposed to alter normal brain morphology. OSA-related hypoxemia has been thought to be associated with an increase in sympathetic vasoconstriction and a concurrent decrease in vascular protective mechanisms thereby leading to changes in structure and function of blood vessels (Zimmerman and Aloia 2006). In addition, effects of OSA-related sleep fragmentation on brain structure and function can be inferred from studies on chronic and acute sleep deprivation. It has been suggested that sleep loss, either independently or as part of a comorbid condition such as OSA or other neurological disorders, is associated with increased atrophy within the frontal, temporal and parietal regions (Sexton et al. 2014). While delineating the relative contribution of intermittent hypoxia and sleep fragmentation to the neuroanatomical changes seen in OSA is challenging, neuroimaging tools can nevertheless provide a global picture of abnormal brain structure in OSA patients.

A growing body of studies utilizing neuroimaging tools have identified neuroanatomical abnormalities that coexist with OSA. Using voxel based morphometry (VBM), several studies identified gray matter (GM) density reduction in frontal, parietal, temporal, and hippocampal regions in patients with OSA (Macey et al. 2002; Canessa et al. 2011; Morrell et al. 2003; Gale and Hopkins 2004; Yaouhi et al. 2009). In these studies, the hippocampus and fronto-parietal cortices are noted to be the most sensitive to GM loss in OSA (Canessa et

al. 2011). Care must be taken however, when interpreting observed changes in gray matter volume based on T1-weighted MR measurements. It has been observed that myelin or iron content rather than neurodegeneration (Lambert et al. 2013) may result in GM changes. As a result, it is likely that these GM changes are explained in part due to the tissue's physical properties rather than neuronal loss. Either acquisition methods that go beyond T1-weighted imaging or analyses methods that supplement the T1-weighted imaging modality would help to better assess gray matter changes in OSA.

In addition to GM, white matter (WM) abnormalities are also seen in patients with OSA. Cross et al. (2018) and colleagues observed that reduced cortical thickness in the bilateral temporal lobes, evaluated using surface-based techniques as opposed to voxel-based, was associated with oxygen desaturation in OSA patients. Diffusion Tensor Imaging (DTI) studies revealed WM lesions in OSA to be more pronounced in the cortices, limbic system, pons and cerebellum tracts (Macey et al. 2008). Fractional anisotropy (FA) measures are routinely measured in DTI studies. The FA values measure directionality of water movement in brain tissue and can be used to infer the integrity of brain tissue. Using this technique, a recent study revealed a loss of WM integrity and structural connectivity in a largely mild-moderate OSA population (Lee, Yun, et al. 2019). Of note, at least some studies have suggested OSA might be associated with gray matter hypertrophy, rather than atrophy (Rosenzweig et al. 2013; Baril et al. 2017; Andre et al. 2020), a phenomenon that could represent underlying inflammation/edema early in the development of OSA before atrophic changes take place.

In addition to MRI and DTI studies, other modalities of neuroimaging have also been used to study the neuroanatomical changes seen in OSA. Magnetic resonance spectroscopy (MRS) has been widely used to non-invasively study biochemical changes in brain. MRS studies in OSA suggest metabolite profiles in the hippocampus (Bartlett et al. 2004) and anterior cingulate gyrus (Duffy et al. 2016) are related to disease severity and neurocognitive impairment. Other observations include significantly decreased levels of N-acetylaspartate (NAA), a marker or neuronal injury, and increased levels of the excitatory neurotransmitter glutamate in limbic regions including the hippocampus, thalamus, putamen and midbrain (Macey et al. 2017).

Changes in brain structure with CPAP treatment

In moderate to severe OSA, Rosenzweig et al. (2016) found improvements in sleepiness after 1 month of CPAP treatment that correlated with neuroplastic brain changes. These changes corresponded to improvement in attentional regulation and working memory capacity compared to a 'wait list' control condition (patients randomly allocated to group, stratified for OSA severity, age and level of education).

Treatment of OSA with CPAP is known to improve intermittent hypoxia and sleep fragmentation. As such it is plausible to hypothesize that CPAP treatment would also result in neuroanatomical changes that may reach levels seen in non-OSA subjects. Rosenzweig et al. (2015) found that one month of CPAP along with lifestyle modifications and psychoeducation induced hypertrophic changes in the bilateral thalamus. Canessa et al. (2011) showed that three month of CPAP treatment was associated with increases in GM

volume within the hippocampus and frontal structures. On the other hand, O'Donoghue et al. (2005) did not observe any changes in GM density or regional volumes after 6 months of CPAP treatment. Notably, they also did not observe any changes in GM density or volumes at baseline, i.e., before treatment when compared to healthy controls. Subsequent commentaries reveal that the source of the discrepancies between results of the study by O'Donoghue et al. (2005) and that of other groups might be due to the methodologic differences and small sample sizes (Zimmerman and Aloia 2006). However, average nightly CPAP use is equally likely to be the source of the discrepancies between the results of these studies.

In addition to GM volume changes seen with CPAP treatment, normalization of WM changes seen in OSA has also been reported. Castronovo et al. (2014) evaluated a group of seventeen treated OSA subjects at baseline and after treatment at 3- and 12-month follow-ups. They reported a normalization of WM fiber integrity using DTI based FA measures after 12 months, with the 3-month follow up showing only limited changes. This study and those by others highlight another important aspect that is often observed in OSA studies looking at treatment effects, i.e. 3 months of CPAP treatment may not be enough to reverse presumed adverse effects of OSA. Using dynamic susceptibility contrast imaging (a sub-type of DTI), Maresky et al. (2019) observed changes in whole brain FA, mean diffusivity and brain perfusion. The FA and mean diffusivity changes imply improvements in the brain's microstructural integrity. Moreover, CPAP treatment was observed to improve brain perfusion measured by quantifying cerebral blood flow and cerebral blood volume.

Summary

Advances in neuroimaging have enabled observation of significant neuroanatomical changes in OSA patients. Notably, these changes parallel those seen in healthy aging (Veasey 2012). Whether the progression of these neuroanatomical changes in healthy elderly is accelerated in presence of OSA or other comorbid neurological disorders remains to be tested. CPAP treatment is shown to induce neuroanatomical changes in treatment naïve OSA patients with indication of a presumed cumulative benefit from long-term CPAP use. However, several questions remain to be addressed given that there are various sources of variability that could influence the results namely methodology, severity and chronicity of disease, as well as nightly CPAP adherence. Table 3 summarizes the OSA and neuroanatomy research referenced in this section.

Sleep disruption and markers of AD

Sleep disruption can be described in many ways including poor-quality, short duration and/or fragmented sleep. Varied approaches to sleep measurement, such as subjective reporting via questionnaires (Sprecher et al. 2015) and objective assessment via Actigraphy, where sleep is inferred by an absence of movement, are shown to be associated with CSF markers of AD (Ju et al. 2013; Lim et al. 2013; Musiek et al. 2018).

EEG is a powerful tool to investigate intra-individual stability and inter-individual variation in sleep/wake biology and behavior (Buckelmuller et al. 2006) as it displays fingerprint-like trait characteristics (De Gennaro et al. 2008). Scalp EEG is a low cost, non-invasive measure

of brain activity with high temporal resolution widely used in diverse settings to determine sleep/wake state, diagnose disease and assess response to treatment (Jobert et al. 2012).

EEG measures as correlates of AD

Quantitative electroencephalographic (qEEG) measures during wakefulness in AD show a slowing of the dominant occipital rhythms compared to age-matched controls (Petit et al. 2004; Dauwels, Vialatte, and Cichocki 2010), and a combination of EEG markers have been shown to predict conversion from MCI to AD (Poil et al. 2013). Specifically, EEG theta activity during wakefulness has been observed to correlate positively with CSF T-tau, P-tau and cognitive decline (Stomrud et al. 2010). Some researchers suggest that EEG measures during sleep, particularly REM sleep, are more sensitive than wake measures in detecting EEG slowing indicative of progressing dementia (Petit et al. 1993; Brayet et al. 2016). One explanation offered is that the cholinergic neurons of the basal forebrain, known to degenerate early in AD, are more active during REM than during wake (Petit et al. 2017).

During PSG analysis, EEG components are visually inspected to determine sleep architecture measures in terms of sleep macrostructure, i.e. duration of non-REM stages N1, N2 and N3 (Slow Wave Sleep), rapid eye movement (REM) sleep and wake. Sleep EEG microstructure refers to the background rhythms and transient events that comprise the EEG signal. Slow waves (SWs), K-complexes (KCs) and sleep spindles are key EEG microstructure events used in visual sleep scoring to define and differentiate the three stages of NREM sleep. EEG microstructure oscillations can be automatically quantified using spectral and/or event-based analysis techniques and provide a more nuanced understanding of sleep neurophysiology (Younes 2017). SWs and slow wave activity (SWA) are in the frequency range of ~0.3 to 4 Hz and encapsulate both slow oscillations (SOs) of < 1 Hz and delta band activity between ~1–4 Hz (Achermann and Borbely 1997; Rasch and Born 2013). It may be important to functionally differentiate slow oscillations from delta activity as they have been shown to have differing impacts on both memory (in rodents) (Kim, Gulati, and Ganguly 2019) and cortical amyloid deposition (Mander et al. 2015). Slow wave sleep (SWS) and SWA during NREM sleep are putative markers of sleep homeostasis (Borbely 1982; Borbely et al. 1981) and are observed to attenuate with age (Carrier et al. 2001; Ohayon et al. 2004) but less so in women (Carrier et al. 2011).

High-density EEG and neuroimaging studies investigating the spatiotemporal dynamics of the slow oscillation find each wave originates at a definite (mostly prefrontal) site and travels in an anteroposterior direction across the scalp (Massimini et al. 2004; Nir et al. 2011), overlapping with neuroanatomical structures of the default mode network (DMN) (Dang-Vu et al. 2008; Murphy et al. 2009). Slow oscillations, and associated cortical neuronal activities, cycle between depolarization (active state of intense firing) and hyperpolarization (silent state), and are thought to group or coordinate other NREM oscillations such as delta waves and spindles (Steriade 2006; Molle et al. 2002; Staresina et al. 2015; Mak-McCully et al. 2017).

In cognitively normal individuals, EEG microstructure changes during sleep are associated with biomarkers of AD and measures of cognition and memory. NREM SWA has been shown to negatively correlate with CSF amyloid-β levels (Varga, Wohlleber, et al. 2016; Ju

et al. 2017), amyloid-β burden within medial prefrontal cortex (mPFC) (Mander et al. 2015) and prefrontal cortical atrophy (Mander et al. 2013; Varga, Ducca, et al. 2016). Recently Lucey et al. (2019) found SWA, particularly in the < 2 Hz spectral frequency range, to be negatively associated with AD pathology according to both PET imaging and CSF measures. Moverover, impairments in declarative (Mander et al. 2013; Mander et al. 2015) and spatial memory transformation (Varga, Ducca, et al. 2016) have been shown to negatively correlate with SWA in older adults.

Sleep spindles are defined as waxing-and-waning oscillations of sigma frequency (~11–16 Hz) activity lasting around 0.5–3 seconds (De Gennaro and Ferrara 2003) that have a proposed role in intelligence (Fogel and Smith 2011), learning (Gais et al. 2002; Kam, Pettibone, et al. 2019), memory (Schabus et al. 2004) and sleep stability (Dang-Vu et al. 2010). Along with SOs and K-complexes they are also involved in cortical activity related to arousal stimuli (Halasz et al. 2014) from both the external environment and within the central nervous system. Using intra-cranial EEG and single unit neuronal recordings during preoperative localization of epileptic foci in humans, Andrillon et al. (2011) recorded the presence of two distinct spindles: slow (9–12 Hz) and fast (12–15 Hz) spindles with different topographical distributions over the scalp. Fast spindles dominated centro-parietal regions, while slow spindles dominated frontal areas during SWS. Neuroimaging, pharmacological and memory studies also support the existence of two topographically and functionally distinct spindles (Ayoub et al. 2013; Schabus et al. 2007; Barakat et al. 2011; Molle et al. 2011). Furthermore, spindle frequency activity (SFA) is reduced in middle-aged and older adults, relative to younger adults (Dijk, Beersma, and van den Hoofdakker 1989; Landolt et al. 1996; De Gennaro and Ferrara 2003). This age-related reduction in SFA is related to impairments in the number of sleep spindles generated (density per unit time) and other morphological features such as amplitude and duration. Spindle density shows more marked reductions frontally with age (De Gennaro and Ferrara 2003) whilst spindle durations become shorter, most noticeably in parietal regions (Martin et al. 2013). Evidence of sexual dimorphism in spindle activity is widely reported with females showing higher sleep spindle densities compared to men (Gaillard and Blois 1981; Huupponen et al. 2002; Purcell et al. 2017).

There is evidence from scalp EEG that fast spindles are synchronized to the depolarizing SO up-state and slow spindles to the transition towards the down-state (Molle and Born 2011; Klinzing et al. 2016). A recent study demonstrates less slow oscillation-spindle coupling to be associated with greater temporal lobe tau burden but not with amyloid-β burden, which was independently associated with < 1 Hz SWA (Winer et al. 2019). This is interesting in the context of recent work from our group showing fast spindle density and duration are inversely related to T-tau levels. In this work, spindle activity from a central EEG derivation was negatively correlated with both CSF measures of amyloid-β and tau, and with cognition (Kam, Parekh, et al. 2019).

Inventive applications of quantitative EEG analysis methodologies are being used to interpret sleep EEG changes in the context of brain health. For example, Latreille et al. (2019) demonstrate age-related reductions of EEG delta power during REM and NREM are mediated by thinning of the medial frontal and anterior cingulate cortices. Sun et al. (2019)

demonstrate that sleep EEG has extractable features that can be identified by machine learning to reasonably predict brain age.

EEG features characteristic of non-REM sleep are seen to degrade with progressing MCI/AD beyond that of normal aging. Spontaneous K-complexes (De Gennaro et al. 2017) and fast sleep spindles show a gradually decreasing density in MCI and AD (Rauchs et al. 2008; Gorgoni et al. 2016). Furthermore, a study using auditory evoked K-complexes during sleep showed a decreased density and amplitude in AD, whilst greater dementia severity was associated with a lower probability of eliciting a K-complex (Crowley et al. 2005). A recent study demonstrated age-related cognitive impairment was related to a reduction in delta, theta and sigma power during NREM sleep in patients with subjective cognitive complaints or MCI (N=29) compared to controls (N=29). One-year follow-up of these patients showed changes in spindle characteristics (amplitude, duration, density or frequency) to be associated most strongly with cognitive decline (Taillard et al. 2019). In contrast, a larger analysis of older women found those who developed mild cognitive impairment or dementia (N=85) after 5 years had increased theta and sigma EEG power density during both REM and NREM sleep at baseline compared to those women who did not deteriorate (N=85) (Djonlagic et al. 2019). Possible reasons for the differing direction of findings relating to theta and sigma frequencies in these two studies include the differences between groups regarding medication usage and inclusion of males and females in the Taillard et al. (2019) study compared to the balanced group medication usage and older, exclusively women studied in the analysis by Djonlagic et al. (2019). It is worth noting that in the study by Taillard et al. (2019) approximately two thirds of participants met diagnostic criteria for OSA which may influence EEG measures as discussed in the next section.

Cyclic alternating pattern (CAP) analysis is a useful way to quantify EEG arousal and sleep instability phenomena. Briefly, the analysis identifies alternating sequences of cortical activation (phase A) followed by periods of deactivation (phase B). The phase A subtype A1-A3 events are described according to the proportion of event duration dominated by either high-voltage slow waves (EEG synchrony) or low-amplitude fast rhythms (EEG desynchrony) and include characteristic sleep EEG oscillations and transient events (Terzano et al. 1996; Parrino and Terzano 2017). CAP phases subtype A1 often contain SWs, K-complexes and spindles, and subtypes A2 and A3 are akin to AASM defined microarousal events (Parrino et al. 2012). Using CAP analysis, (Carnicelli et al. 2019) observed a decrease in A1 (SWs and K-complexes) and A2 events (starting with a SW and finishing in arousal) during NREM 2 sleep in those with MCI who converted to AD.

EEG in OSA, correlates of AD markers?

Changes in EEG activity are reported in OSA during both wake and sleep states, and are reviewed comprehensively in D'Rozario et al. (2017). In a similar way to findings reported in those with cognitive decline, EEG slowing during wakefulness is observed in OSA compared to controls (Morisson et al. 1998; Morisson et al. 2001; Mathieu et al. 2007; Greneche, Krieger, et al. 2008; Xiromeritis et al. 2011). Furthermore, increased EEG slowing is related to worse daytime symptoms, such as sleepiness (Lee et al. 2012), abnormal event related potentials (ERPs) during attention (Baril et al. 2013), and impaired

PVT and driving simulator performance (D'Rozario et al. 2013; Wang et al. 2015). Whilst some investigations have found EEG slowing during wakefulness is associated with worsening OSA severity (increased arousal index, AHI or hypoxia) (Mathieu et al. 2007; Greneche, Saremi, et al. 2008), others have not observed the magnitude of EEG slowing to correspond to OSA severity using current diagnostic measures (Sforza et al. 2002).

Early investigations using qEEG analysis in OSA also found increased EEG slowing during REM sleep compared to controls (Morisson et al. 1998; Morisson et al. 2001) but these included a small number of individuals and only short segments of EEG. However, these original findings have since been replicated in a large study examining ambulatory qEEG measures in 664 men (> 40 years), demonstrating a positive association between OSA severity and both the EEG slowing ratio and EEG power in all frequency bands during REM (Appleton et al. 2019). Importantly, an earlier study by the same authors found greater EEG slowing (delta power) in REM sleep to predict worse simulated driving performance in 76 people with a range of OSA severity (Vakulin et al. 2016). In a small study of 8 males with moderate-severe OSA undergoing an extended wakefulness protocol, greater EEG slowing during REM sleep at baseline was associated with slower PVT reaction times, more PVT lapses, and more AusEd crashes after 24hrs awake. Across the same time period, decreased spindle density in NREM sleep was also associated with slower PVT reaction times (Mullins et al. 2020).

Most research quantifying EEG microstructure during NREM sleep in those with OSA shows reduced SWA compared to controls (Guilleminault et al. 2001; Saunamaki et al. 2009; Jones et al. 2014; Ju et al. 2016), or a slower dissipation of SWA across the sleep period (Ondze et al. 2003; Himanen, Joutsen, and Virkkala 2004). Given more SWS/SWA is associated with better next-day performance both in healthy younger (Jurado, Luna-Villegas, and Buela-Casal 1989) and older subjects (Anderson and Horne 2003) it is not surprising SWS duration and delta power during NREM sleep also predicts poorer driving simulator performance in OSA (Vakulin et al. 2016). Of note, only one small study has examined the relationship between SWA and CSF amyloid-β in OSA (Ju et al. 2016). In this study, NREM SWA was negatively correlated with CSF amyloid-β levels in controls but not in those with OSA.

Studies using CAP analysis in people with sleep-disordered breathing find CAP subtype A2 and A3 rates and durations are higher compared to controls in: OSA (Terzano et al. 1996), upper airway resistance syndrome (Guilleminault et al. 2007), and in OSA with excessive daytime sleepiness (EDS) compared to those without sleepiness (Korkmaz et al. 2018). The extent to which any changes in respiratory-related EEG microstructure events could influence measures of spectral power during NREM is not often acknowledged in investigations reporting EEG changes in those with AD pathology. This is pertinent given the partial spectral frequency overlap between slow wave oscillations and K-complexes (De Gennaro et al. 2017), and particularly salient considering that the specifics of how sleep EEG microstructure is altered in individuals with OSA is not well characterized. In respiratory failure patients with sleep-disordered breathing, a positive association between the partial pressure of carbon dioxide (PCO_2) and percentage of SWS was observed, indicating abnormal blood gas exchange at night appears to influence the appearance of slow

waves (Wang et al. 2011). Furthermore, there is evidence that OSA impairs the both the normal homeostatic reduction in SWA and K-complex amplitude across the sleep cycle (Parapatics et al. 2015), and whilst K-complexes are frequently elicited by respiratory events during sleep (Nguyen et al. 2016; Parekh et al. 2019), respiratory elicited K-complexes are morphologically different in OSA compared to spontaneous K-complexes (Sun et al. 2019). Some work by Chervin, Burns, and Ruzicka (2005) demonstrate that respiratory cycle related EEG changes, particularly sigma power variations, are predictive of sleepiness in those with SDB and likely reflect increased sigma (arousal activity) during inspiration.

Although findings are inconsistent, a systematic review of spindle oscillations in sleep disorders (Weiner and Dang-Vu 2016) shows that overall OSA patients have less spindle activity (using spectral, visual and automatic event analysis methods) and slower spindle frequencies (Schonwald et al. 2012) than those without OSA. Additionally, different spindle dynamics throughout the nocturnal sleep period are observed in OSA compared to controls (Ondze et al. 2003; Huupponen et al. 2008; Carvalho et al. 2014). Interestingly, work quantifying spindles in overweight adolescents with OSAS found increased spindle activity (number and density) compared controls matched for age and BMI (Madaeva et al. 2017), and highlights the potential influence of an adaptive cortical response to OSA in young adults. A study of EEG spectral power differences between young (~24 years) and older patients (~59 years) with OSAS, not taking medications, found both slow (<13 Hz) and fast (>13 Hz) sigma activity during NREM were higher in the older group and a ratio of slow/fast sigma activity was positively correlated with OSA severity measures in younger participants only (Lee et al. 2016).

Despite the well documented association between spindle activity and cognitive functioning (De Gennaro and Ferrara 2003; Schabus et al. 2004; Schabus et al. 2006), few have investigated the relationship between sleep spindle activity and cognition in OSA. A moderate positive correlation (not statistically significant) between spindles and overnight task improvement has been observed in OSA participants but not controls (Landry et al. 2014). Additionally, an enhancement of spindles after learning in OSA patients was not observed by Barner et al. (2016) as is seen in healthy young adults (Gais et al. 2002). However, the older age of the participants may explain the lack of effect (average age 52 years in Barner et al. (2016) compared to 24 years in Gais et al. (2002)). To date, no studies have been published investigating the effect of OSA on slow oscillation-spindle coupling.

Effects of CPAP treatment on EEG

Adequate CPAP treatment restores sleep macrostructure measures towards that of individuals without OSA, most notably SWS and REM durations increase and sleep latencies to these stages decrease (Parrino et al. 2000; McArdle and Douglas 2001; Brillante et al. 2012). Beyond these changes in sleep macrostructure and a reduction in respiratory-related arousals (Fietze et al. 1997), a modest amount of literature examines changes to EEG microstructure during wake and sleep EEG recordings after CPAP treatment.

Early studies examined small numbers (N~10), of mostly male patients (~80%) and conducted comprehensive EEG analysis on features such as CAP (Parrino et al. 2000; Thomas 2002; Parrino et al. 2005) and spectral power calculations (Morisson et al. 2001;

Heinzer et al. 2001), comparing controls and OSA patients before, during and after various lengths of CPAP treatment. Parrino et al. (2000) noted a significant reduction in measures of arousal and CAP during the first night of CPAP below the levels of control participants, of which a reduced CAP rate showed significant correlation with improvements in sleepiness. Later the same group observed progressive normalization of CAP across a month of CPAP with the number of A1 subtype events remaining below the levels of control patients at the end of 30 days consecutive treatment (Parrino et al. 2005). In this study they also found Multiple Sleep Latency Test (MSLT) scores negatively correlated with arousals and CAP rate which was not the case in their earlier study. Initial studies using spectral power analysis before and after CPAP treatment observed a correction of EEG slowing in wake and REM but not complete resolution of sleepiness (Morisson et al. 2001). Furthermore, in a similar group of patients the same research group observed increased SWA during the first part of the night after 9 months of CPAP compared to during the untreated baseline sleep (Heinzer et al. 2001). A number of later studies also show several months CPAP treatment partially reverses waking EEG abnormalities (EEG slowing) and improves some daytime functioning (Greneche et al. 2011; Xiromeritis et al. 2011; Lee et al. 2012; Wang et al. 2014), see (D'Rozario et al. 2017) for detailed review.

Work investigating the effect of CPAP treatment on sleep spindle characteristics shows increased spindle density during a CPAP titration compared to a diagnostic night PSG (Chokroverty et al. 2015; Yetkin and Aydogan 2018). A study of spindle characteristics finds CPAP treatment partially normalizes spindle features of the group towards those seen in healthy controls (Saunamaki et al. 2017).

There is evidence that K-complexes also change as a result of CPAP treatment. Parapatics et al. (2015) found KC densities and homeostatic amplitude dissipation are returned to levels of normal controls after 3–6 months of CPAP treatment. Work from our group indicates CPAP treatment results in a decrease in KC density and an increase in SWA and slow wave activity surrounding K-complexes (ΔSWAK) (Parekh et al. 2019). Furthermore, in this analysis ΔSWAK was a significant predictor of vigilance (PVT lapses), where less slow wave activity elicited by a KC was associated with greater performance impairments. This relationship between sleep EEG and daytime performance was observed not only cross-sectionally in both chronic and acute OSA conditions, but also longitudinally with CPAP treatment.

Summary

There are well documented EEG changes with age and dementia during both wake and sleep states that differ in males and females. Preliminary findings indicate that in OSA sleep is disrupted such that EEG microstructure is altered in similar ways to those during aging and dementia, but large-scale studies are mostly lacking (Figure 1). Additionally, high levels of inter-individual variability in neurophysiological responses to SDB and CPAP treatment indicate complex relationships between the severity and chronicity of sleep fragmentation and intermittent hypoxia that are difficult to disentangle. Table 4 summarizes the OSA and EEG research referenced in this section.

Factors beyond Amyloid and Tau

OSA and ApoE—The ApoE gene has 3 common alleles, and carrying one or more copies of ApoE4 is the greatest known genetic risk factor for late onset Alzheimer disease (Corder et al. 1993). In the brain, ApoE protein is produced by astrocytes to transport cholesterol to neurons, a process essential to neuronal membrane function as well as neuronal integrity (such as neurite extension among others)(Mahley and Rall Jr 2000). While some early studies suggested having a single ApoE4 allele increases the odds of having moderate-severe OSA (Gottlieb et al. 2004; Kadotani et al. 2001), several subsequent studies have suggested no relationship between ApoE genotype and OSA (Saarelainen et al. 1998; Thakre, Mamtani, and Kulkarni 2009; Xu et al. 2015; Lu et al. 2016). Work by our group found ApoE genotype can influence the relationship between OSA severity and CSF amyloid-β_{42} or tau, with positive associations between OSA severity and both CSF amyloid-β_{42} or tau seen in ApoE3 carriers, but either no association (tau) or negative association (amyloid-β_{42}) observed in ApoE4 carriers (Osorio et al. 2014). However, the number of ApoE4 carriers was very small in comparison to ApoE3 carriers, so additional work is needed to ascertain the influence of ApoE genotype on this relationship. The effects of ApoE genotype on amyloid burden in general appear to extend to individuals with OSA, as higher cortical amyloid load by PET imaging in participants with OSA carrying the ApoE e4 allele was observed in a cross-sectional study (Elias et al. 2018). Negative effects of OSA and ApoE4 carrier status may be synergistic as cognitively normal middle-aged adult ApoE4 carriers had impaired spatial working memory versus non-carriers, only in subjects with comorbid OSA, but not in normally-breathing controls (Cosentino et al. 2008). These studies highlight the complex interaction of OSA severity and ApoE and suggest that untreated apnea can affect biomarkers and subtle cognitive deficits which precede clinical manifestation of AD by a decade.

OSA and Immune factors—Research in AD and sleep fields has identified an important crosstalk between the brain and immune system. Microglia are the primary immune cells of the brain with a diverse set of functions in neurodevelopment, infection response, and neuronal synaptic homeostasis. These resident immune cells can also be activated by astrocytes, another glial cell type in the brain. Exactly how OSA affects this crosstalk is largely unknown due to the available methods to measure the immune system. While microglia secrete cytokines as a response to clear pathogens in the brain, much of the findings from the OSA field come from systemic immune sources measured in the blood. For example, in moderate to severe OSA, blood derived IL6 and tau were greater than controls without OSA (Motamedi et al. 2018). Other circulating factors like CRP, IL-1Ra, IL-8 and TNF-α show elevation in patients with OSA and an acute cardiovascular event (Testelmans et al. 2013). Nevertheless, missing from the field is widespread adoption of biomarkers of microglial activation from the brain in vivo. One candidate is YKL-40, an astroglial secreted protein that activates microglia and is shown to track with early cognitive decline in MCI when measured from the CSF (Craig-Schapiro et al. 2010). In sleep apnea, serum-derived YKL-40 offers a less invasive biomarker but at the cost of still being of systemic immune origin. For example, elevated levels of serum YKL-40 were found in patients with OSA and coronary artery disease (Sui and Gao 2013), OSA and diabetes (Sun, Liu, and Li 2015), as well as OSA and hypertension measured cross-sectionally (Jafari and

Mohsenin 2016). When measured from the CSF, cognitively normal elderly with subjectively defined poor sleep show detectably higher YKL-40 levels (Sprecher et al. 2017). In order to dissect the role of SWS disruption on multiple CSF derived proteins including YKL-40 Ju et al. (2017) conducted a single night SWS disruption paradigm and CSF YKL-40 did not correlate with the change in delta power compared to sham. These results indicate microglial activation likely requires chronic sleep fragmentation with intermittent hypoxia seen with OSA (Ju et al. 2017). Soluble CSF TREM2 is a microglial protein product of a genetic risk factor for AD (Jonsson et al. 2013; Guerreiro et al. 2013) and is found to be higher in AD compared to cognitively normal elderly (Heslegrave et al. 2016; Ewers et al. 2019). Development of PET tracers to monitor microglial activation in vivo and in specific brain areas is actively being investigated in AD and warrants future consideration in OSA (Edison, Donat, and Sastre 2018). In an animal model of sleep restriction without intermittent hypoxia, morphological evidence for both microglial and astrocytic phagocytosis of synapses suggests one way that the brain responds to prolonged wakefulness in order to maintain synaptic homeostasis (Bellesi et al. 2017). However, dissecting the pathological crosstalk between microglia and astrocytes in OSA will require specific biomarkers that can be assayed both simultaneously and longitudinally in vivo.

OSA and Blood-Brain barrier/Glymphatic system—The blood-brain-barrier (BBB) functionally separates the brain from circulating blood. Hypotheses have been put forth regarding how OSA may disrupt BBB permeability (Lim and Pack 2014) but only recently have imaging methods been developed to measure BBB permeability in vivo in humans (Raja, Rosenberg, and Caprihan 2018). Pseudo-continuous arterial spin labeling MRI indicates patients with OSA have reduced water diffusion across the BBB compared to non-OSA controls (Palomares et al. 2015). Once the BBB breaks down, circulating cells could be allowed to infiltrate into the brain. Using perfusion imaging, reduced global cerebral blood flow and increased leucocyte apoptosis, primarily of granulocytes, was found in the OSA group compared to controls (Chen et al. 2017). When combined with the finding of regional cerebral blood hypoperfusion, particularly in elderly severe OSA patients (Baril et al. 2015), it appears that OSA contributes to region-specific BBB breakdown. However, this same study found that other brain regions such as the hippocampus, amygdala and caudate had paradoxically hyperperfusion which correlated positively with AHI, suggesting region-specific hyperactivity as a result of frequent apneas and hypopneas (Baril et al. 2015).

Work in animals identified a glymphatic system that clears amyloid-β and other brain metabolites from the interstitial space into the CSF (Xie et al. 2013). However, the field is contentious due to lack of evidence for interstitial fluid (ISF) clearance of solutes (Abbott et al. 2018). Methods to directly measure the exchange of solutes from the ISF to the CSF in vivo in humans are lacking, but one method uses ultrafast magnetic resonance encephalography to identify cardiac, respiratory, and very low frequency pulse-mediated flow in the brain (Kiviniemi et al. 2016). The temporal relationship between sleep stages and CSF flow has remained an enigma of the sleeping human brain. Using simultaneous EEG and ultrafast MRI, delta waves were found to precede BOLD and CSF rhythms during slow wave sleep (Fultz et al. 2019). The authors propose CSF inflow from the 4th ventricle is a new pathway by which CSF and ISF mix during SWS (Fultz et al. 2019). Ideally, these

advanced imaging methods will be applied in future studies to understand how OSA potentially impacts glymphatic clearance. The disruption of slow wave sleep from OSA and large intrathoracic pressures changes between apneas and recovery breaths could be acting at odds to impact cyclic CSF pulsations and potentially regulate glymphatic clearance.

OSA and Neuronal factors—Orexin (aka hypocretin) is a neuropeptide involved in wake maintenance, arousal and feeding, and is produced primarily in the lateral hypothalamus. In a mouse model of amyloid overproduction, orexin delivered into the brain increased ISF amyloid-β while a dual orexin receptor antagonist decreased ISF amyloid-β and decreased wake duration across 24 hours (Kang et al. 2009). In humans without OSA, an experimental 5 nights of sleep restriction led to increased CSF orexin without increases to amyloid-β, tau, or neuron-derived proteins (neurofilament light, neuron-specific enolase, and fatty acid–binding protein) (Olsson et al. 2018). In an older cohort of cognitively normal elderly, CSF orexin positively correlated with CSF AD biomarkers amyloid-β, P-tau, and T-tau which was not driven by AHI (Osorio et al. 2016). Orexin measures in patients with obstructive sleep apnea, however, are inconsistent with one study showing no change in CSF orexin between subject with and without OSA (Kanbayashi et al. 2003) and another showing elevated CSF orexin levels in untreated OSA subjects in comparison to both treated OSA subjects and normally-breathing subjects (Liguori et al. 2019). Additionally, plasma orexin levels in OSA appear tied to sleepiness with higher levels in sleepy subjects with OSA (ESS ≥ 13 vs ESS ≤ 9) (Sanchez-de-la-Torre et al. 2011). Other promising neuronally derived biomarkers are CSF VILIP-1 and neurogranin which are both shown to be lower in a moderately-severe OSA group compared to mild OSA (Ju et al. 2016). These heterogenous findings of neuronally derived biomarkers warrants a larger study of the effect of OSA on markers of neuronal integrity.

Summary—The immune system in particular has gained increasing attention as playing an important role in the pathogenesis and progression of AD. OSA likely has direct impact on cytokines and immune cells, as well as access of immune cells to the brain via influences on the blood brain barrier, but an understanding of to what extent these effects impact risk for and progression of AD is in its nascency. Table 5 summarizes the OSA biomarker research referenced in this section.

Challenges and Future Directions

Difficulties with definitive trials investigating the effect of CPAP treatment on biomarkers of AD and dementia – Future directions

One fundamental challenge to the intersecting research fields of AD and sleep-disordered breathing appears to be one of measurement, in relation to both defining sleep apnea severity and adequate treatment response.

According to *The AASM manual for the scoring of sleep and associated events: Rules, Terminology and Technical Specifications* (Iber et al., 2007), there are four types of respiratory events contributing to an AHI score: obstructive, central, and mixed apnea events (complete cessation of airflow), and the hypopnea event (reduction in airflow). The hypopnea lacks a single definition and is categorized according to event sequelae (EEG

micro-arousal and/or oxygen desaturation events classically, but for example events associated with change in heart rate have been used in research studies). This heterogeneity results in several fundamental barriers to understanding the negative consequences of OSA, as does the reliance purely on frequency of events. For example, is someone with an AHI of 10/hour where each event lasts 120 seconds and is associated with significant oxygen desaturation into the 70's better or worse than someone with an AHI of 30/hour where each event lasts 10 seconds and is associated purely with arousal and no change in oxygen? It is impossible to disentangle sleep fragmentation (due to arousals) and hypoxemia (due to oxygen desaturation) within a single AHI measure. Furthermore, if large epidemiological or clinical trials are conducted using one definition, it is difficult to integrate research using an alternative definition into existing knowledge. Perhaps to understand the contribution of fragmentation and hypoxia to negative outcomes in OSA, the field may need to move beyond the AHI for OSA diagnosis.

This could possibly be achieved with more detailed characterization of sleep physiology in OSA during both diagnosis and treatment using novel analysis of existing measures of sleep physiology in PSG. Novel quantification of the rich oscillatory activity collected from multiple organ systems during PSG creates possibilities for explaining individual variation in vulnerability to the negative consequences of sleep disorders. This possibility, however, is hampered by the strong push to complete sleep testing at home, where home sleep tests increasingly focus on collecting just enough signals to provide an AHI. There is a high degree of inter-individual variability inherent to human physiology which likely contributes to our limited understanding about how OSA exerts its negative health effects within an individual (Davies and Harrington 2016) or the inability to predict who will benefit from CPAP treatment. Despite being the most effective and frequently recommended treatment for OSA, CPAP acceptance and compliance rates are variable and can be particularly poor in individuals who are not sleepy or other otherwise symptomatic from their OSA (McArdle et al. 1999; Weaver and Grunstein 2008). Furthermore, the benchmark used in clinical and research settings for adequate CPAP usage is greater than 4 hours for at least 70% of nights but this recommendation was selected virtually at random (Weaver et al. 2007; Sawyer et al. 2011) and ignores any individual's habitual sleep duration, the fraction of untreated sleep, and the severity of apnea during untreated sleep. In partial users of CPAP, the untreated portion of sleep is most typically the latter half, which is rich in REM, a stage of sleep in which OSA is often at its worst due to REM muscle atonia. Research highlighting the detrimental outcomes of REM related OSA could inform the research agenda concerning AD and sleep (Varga and Mokhlesi 2019). In a secondary analysis of the Sleep Heart Health Study, Pase et al. (2017) observed a reduced REM sleep duration and an increased latency to REM were associated with incident AD dementia. Furthermore, REM sleep is reported to be reduced in MCI (Maestri et al. 2015; Liguori et al. 2016). In an interesting study focusing on REM related OSA, Baril et al. (2020) found more SDB during REM sleep was associated with reduced daytime regional cerebral blood flow in frontal areas.

While there can be inter-individual variability in OSA, there may also be features common to subsets of individuals that allow for common grouping (i.e. OSA driven by high upper airway collapsibility vs low arousal threshold) (Seely and Macklem 2004; Buckelmuller et al. 2006), and encouragingly there is much focused research investigating endophenotypes

(Eckert et al. 2013) and personalized medicine approaches (Pack 2016; Zinchuk et al. 2018) in OSA. One area historically neglected in OSA research is sexual dimorphism. Emerging evidence of significant differences between males and females with respect to OSA phenotypes (Won et al. 2020) and the impact of CPAP therapy on health outcomes (Gagnadoux et al. 2017) necessitate the consideration of sex in study design rather than in post-hoc analysis. Understanding individual rather than group changes in response to treatment with respect to sleepiness, vigilance and cognition will likely yield a better indication on treatment modality or required usage to achieve improvements in daytime functioning for the individual.

Another difficulty with using the AHI as a method of diagnosis and disease severity is the insensitivity to chronicity of disease. Implicit in understanding the effect of OSA on health is the propensity for adaptive processes in response to stressors to the system, also understood as resilience. The high level of heritability of sleep EEG (Ambrosius et al. 2008), the intra-individual stability (Lewandowski, Rosipal, and Dorffner 2013; Poon et al. 2019), plus the known influence of genes on EEG patterns and sleep/wake regulation (Shi et al. 2017), could be leveraged to understanding sleep disorder heterogeneity and risk. The concept of a resilience brain in the face of perturbations to sleep during SDB offers a framework with which to use sleep EEG microstructure identify biomarkers of neurodegeneration (Melpignano et al. 2019) or strategies to achieve healthy sleep for the individual (Parrino and Vaudano 2018). In a similar vein, non-linear methods of signal analysis (Ma et al. 2018) to assess biological complexity (Goldberger 2006) and fractal properties (Franca et al. 2018) are interesting approaches to characterize sleep disruption and physiological changes with age (Goldberger et al. 2002) and AD (Li et al. 2018). For example, Zhang et al. (2009) showed severity of OSA could be assessed using a fractal dimension sequence analysis of sleep EEG which stabilized with CPAP treatment (Zhang et al. 2015). Perhaps such methods could be applied to sleep EEG quantitatively distinguish ‘healthy’ homeostatic slow waves from ‘detrimental’ pathologic slow waves or EEG slowing (Petit et al. 2017). Despite the potential for novel measures of sleep to better characterize individual vulnerability to negative consequences of sleep disruption, it also adds to the multitude of sleep features currently tested when investigating the link between sleep, OSA and AD. To this end, the literature may have considerable publication bias with many measures tested, only significant associations reported and without adequate correction for multiple comparisons.

Based on the available evidence, many would argue that a clinical trial of OSA treatment for AD prevention is warranted. But there are several fundamental issues in conceptualizing such a trial, many of which are intrinsic to any intervention designed to slow or prevent AD. The AD field recognizes that there is a long preclinical phase, lasting years to possibly decades, during which changes to the brain occur, including dysfunction of synapses and the accumulation of amyloid and tau *before* any hint of cognitive change is apparent. Therefore, an idealized clinical trial for AD prevention would target recruitment of participants who are relatively young and such preclinical brain changes are just beginning to occur. But this presents the obvious question of how long such a trial would need to last to determine an impact on AD development. The answer is likely to be many years – 10 to 20 would not be out of the question – which negatively impacts the feasibility (and fundability) of such a proposal. Instead of the development of frank dementia as the primary outcome,

intermediate surrogate outcomes could be assessed (e.g. brain amyloid and/or tau load by PET imaging), but the field still lacks consensus on whether such outcomes ultimately would or would not impact the development of dementia. While recruitment age, duration of follow-up, and defining primary outcome are problems in designing any AD treatment trial, there are additional issues specific to OSA. In an idealized trial, one would likely want to recruit individuals who stand the most to gain from treatment – individuals with severe OSA and daytime sleepiness, particularly in light of the observation that all cause sleepiness was shown to be associated with longitudinal accumulation of brain amyloid in older subjects (Carvalho et al. 2018). However, randomizing individuals with severe OSA and daytime sleepiness to a control arm lacking treatment is probably not ethically justifiable, particularly if it would need to occur over many years. Therefore, one could focus on individuals from the community with incidentally identified severe OSA who lack daytime symptoms. However, in such individuals, adherence to CPAP in the treatment arm is likely to be quite low, as was observed in a recent clinical trial of CPAP for cardiovascular endpoints (McEvoy et al. 2016), a study in which mean CPAP use was just 3.3 hours per night over a mean follow-up duration of 3.7 years. The adherence issue could be minimized by liberalizing the treatment arm to “any intervention that lowers the AHI” below some threshold value, a concept championed by our colleague Dr. David Rapoport, which could include use of mandibular advancement devices, nasal EPAP, positional therapy, or other interventions. While appealing, the feasibility of using multiple interventions in a trial and tracking adherence as can easily be done with CPAP, are factors that remain to be worked out.

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Abbreviations

AD	Alzheimer’s disease
ADNI	Alzheimer’s Disease Neuroimaging Initiative
AHI	Apnea hypopnea index
AHI3A	Apnea hypopnea index - hypopnea criteria of ≥3% oxygen desaturation or arousal
AHI4%	Apnea hypopnea index - hypopnea criteria of ≥4% oxygen desaturation only
ApoE	Apolipoprotein E
CSF	Cerebrospinal fluid
CPAP	Continuous positive airway pressure
EDS	Excessive daytime sleepiness

ESS	Epworth sleepiness scale
ERPs	Event related potentials
ISF	Interstitial Fluid
KC	K-comple
mPFC	Medial prefrontal cortex
MCI	Mild cognitive impairment
MMSE	Mini mental state exam
MSLT	Multiple Sleep Latency Test
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
PCO_2	Partial pressure of carbon dioxide
P-tau	Phosphorylated tau
PPG	Photoplethysmography
PiB	[11C] Pittsburgh compound B
PSG	Polysomnography
PET	Positron Emission Tomography
PVT	Psychomotor vigilance test
qEEG	Quantitative electroencephalographic
SDB	Sleep-disordered breathing
SWA	Slow wave activity
SpO_2	Saturation of peripheral oxygen
T-tau	Total tau

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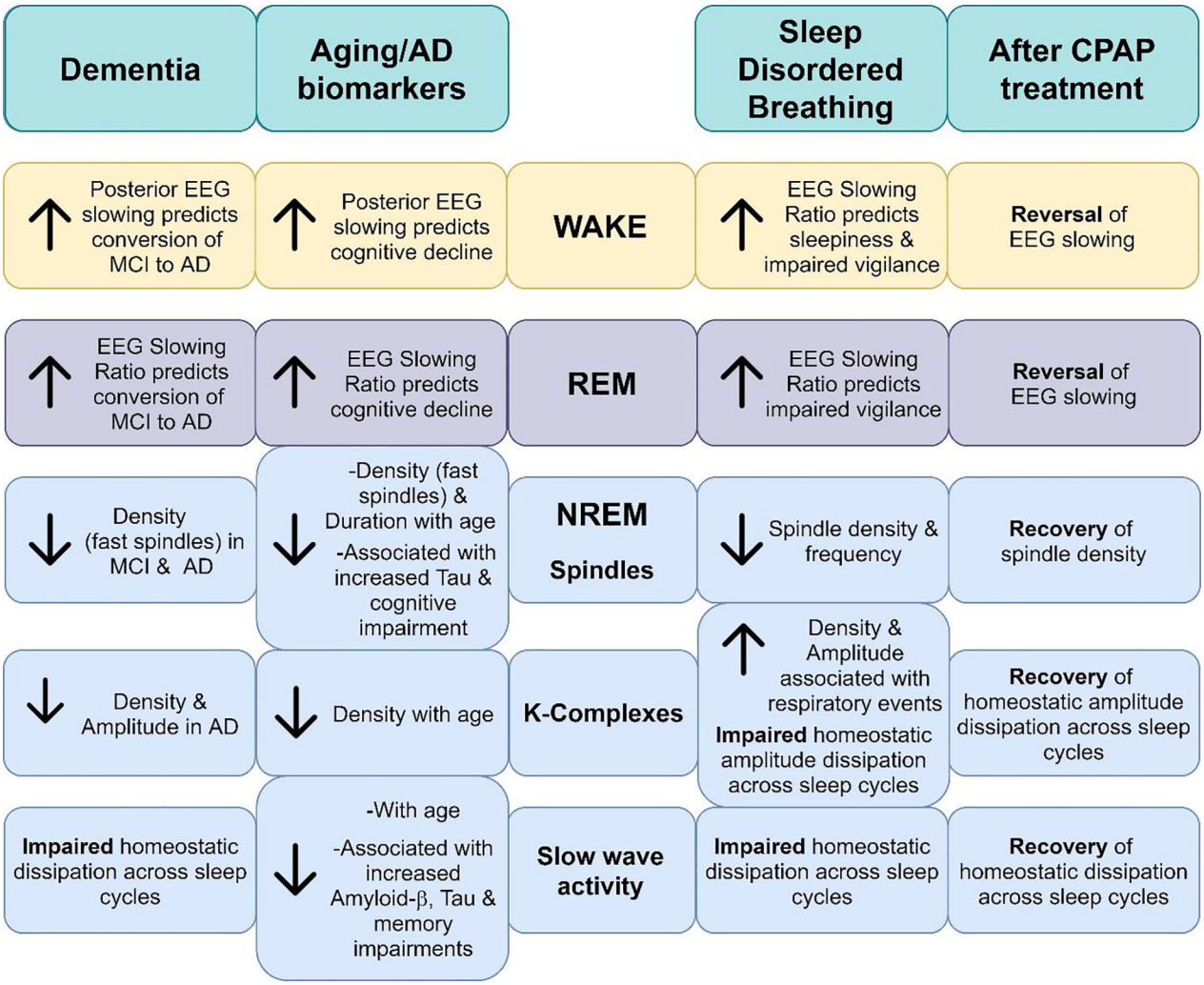

Figure 1:

Illustration summarizing EEG features seen in dementia, aging, with AD biomarkers, sleep-disordered breathing and CPAP treatment.

Table 1:

Research reviewed involving OSA and AD biomarkers

Authors	Study design and recruitment	Population	Age (years)	Sex (% female)	AD Biomarkers
Spira et al. 2014	Cross-sectional, community volunteers	5 MCI, 8 controls	MCI 75±11, controls 69±6	MCI 20%, controls 62.5%	Aβ deposition (PET-PiB)
Bu et al. 2015	Cross-sectional, sleep center	45 OSAS, 49 controls	OSAS 44±10, controls 43±10,	OSAS 27%, controls 31%	Serum $A\beta_{40}/A\beta_{42}$
Ju et al. 2016	Cross-sectional, community volunteers	10 OSA, 31 controls	OSA 56±4, control 53±6	OSA 30%, controls 48%	CSF $A\beta_{40}$, $A\beta_{42}$, tau, P-tau181
Liguori et al. 2017	Cross-sectional, sleep center	25 OSA, 10 OSA-CPAP, 15 controls	OSA 68±8, OSA-CPAP 67±7, controls 66±9	OSA 32%, OSA-CPAP 30%, controls 40%	CSF $A\beta_{42}$, P-tau, T-tau
Yun et al. 2017	Cross-sectional, community volunteers	19 OSA, 19 controls	OSA 57±4, controls 57±4	OSA 53%, controls 53%	Aβ deposition (PET-PiB)
Elias et al. 2018	Cross-sectional, war veterans	42 OSA, 77 non-OSA	OSA 68±5, non-OSA 68±4	No females	Aβ deposition (PET 18F-florbetaben, 18F-AV1451)
Motamedi et al. 2018	Cross-sectional, military personnel	28 mod-severe OSA, 22 mild OSA, 24 controls	Mod-severe OSA 36±8, mild OSA 34±8, controls 31±8	Mod-severe OSA 0%, mild OSA 4% controls 8%	Serum $A\beta_{40}$, $A\beta_{42}$, Tau
Sharma et al. 2018	Longitudinal, community volunteers	35 mod-severe OSA, 76 mild OSA, 97 controls	Mod-severe OSA 71±8, mild OSA 69±7, controls 68±7	Mod-severe OSA 51%, mild OSA 58%, controls 69%	CSF $A\beta_{42}$, P-tau181, T-tau, Aβ deposition (PET-PiB)
Liguori et al. 2019	Cross-sectional, community volunteers	20 OSA, 20 AD, 15 controls	OSA 59±4, AD 66±4, controls 64±8	OSA 30%, AD 65%, controls 47%	CSF $A\beta_{40}$, Aβ42, P-tau, T-tau,
Handa et al. 2019	Cross-sectional, tertiary hospital	14 OSA	65±10	29%	Aβ deposition (PET-PiB)
Bubu et al. 2019	Longitudinal, community volunteers	798 (103 OSA+) MCI, 325 (22 OSA+) AD, 516 (29 OSA+) cognitively normal	MCI 74(68,79) AD 76(71,80) cognitively normal 74(71,78)	MCI 40% (25% OSA+), AD 37% (27% OSA+), cognitively normal 49% (27% OSA+)	CSF $A\beta_{42}$, P-tau181, T-tau, Florbetapir PET uptake
Ju et al. 2019	Interventional, community volunteers	18 (14) OSA-CPAP	57±8	23%	CSF $A\beta_{40}$, $A\beta_{42}$, T-tau
Carvalho et al. 2020	Cross-sectional, population based	292 cognitively unimpaired (43 with “witnessed apneas”)	WA+ 73 (range 69–80), WA− 75 (range 69–82)	WA+ 23% WA− 75 38%	AV-1451 Tau-PET, Aβ deposition (PET-PiB)
André et al. 2020	Cross-sectional, community volunteers	96 SDB+, 31 SDB−	SDB+ 69±4, SDB− 69±4	SDB+ 58%, SDB− 77%	Florbetapir PET uptake

Aβ; amyloid-β; AD: Alzheimer’s disease; CPAP: continuous positive airway pressure; CSF: cerebrospinal fluid; OSA: obstructive sleep apnea; OSAS: obstructive sleep apnea syndrome; PET: positron emission tomography; WA: witnessed apnea. Median (SEM), Median [IQR]. Ages and percentages values are rounded from the source manuscript. **Studies involving CPAP are highlighted in green**.

Table 2:

Research reviewed involved OSA and cognition.

Authors	Study design and recruitment	Population	Age (years)	Sex (% female)	Cognitive domain or task
Yesavage et al. 1985	Cross sectional, sleep clinic	41 OSA	70±7	No females	Attention, executive function, memory
Berry et al. 1990	Cross sectional, sleep clinic	8 OSAS, 12 controls	OSAS 69±5, controls 68±2	No females	Memory
Bedard et al. 1991	Cross sectional, sleep clinic	20 mod-severe OSAS	52±9	Not reported	Reaction time, vigilance
Hayward et al. 1992	Cross sectional, retirement village	96 non-demented elderly	78±4	22%	Attention, executive function, memory
Phillips et al. 1992	Cross sectional, community volunteer	92 healthy adults	64±9	52%	Attention, executive function, memory
Naëgelé et al. 1995	Cross sectional, clinic & community volunteers	17 OSA, 17 controls	OSA 49±3, controls 49±3	No females	Attention, memory
Boland et al. 2002	Cross sectional, population based	1700 SHHS cohort	62 (range 52–75)	54%	Attention, executive function, memory
Salorio et al. 2002	Cross sectional, clinic & community volunteers	28 OSA, 24 controls	OSA 44±8, controls 44±9	OSA 29%, controls 42%	Memory, executive function
Foley et al. 2003	Cross sectional, community volunteer	718 OSA	Range 79–97	No females	Attention, executive function, memory
Ferini-Strambi et al. 2003	RCT, sleep clinic	23 OSA (CPAP+ 15 days), 23 controls	OSA 57±6, controls 56±5	OSA 9%, controls 17%	Processing speed, executive function
Aloia et al. 2003	RCT, sleep clinic	12 OSA (6 CPAP+)	65±6	Not reported	Attention, executive function, memory
Quan et al. 2006	Cross sectional, population based	67 OSA, 74 controls	OSA 59±9, controls 57±9	OSA 33%, controls 47%	Attention, vigilance, executive function, memory
Naëgelé et al. 2006	Cross sectional, clinic & community volunteers	95 OSA, 95 controls	OSA 46±11, controls 46±8	OSA 21%, controls 27%	Memory
Chong et al. 2006	RCT, clinic	AD with OSA: 19 (CPAP+ 3 weeks), 20 (Sham CPAP)	78±7	CPAP 76%, Sham 75%	Sleepiness
Kim et al. 2007	Cross sectional, population based	611 Wisconsin cohort	53±8	43%	Vigilance
Mathieu et al. 2008	Cross sectional, sleep clinic	14 young & 14 older OSAS, 12 young & 18 older controls	Young 38±2 & older 62±2 OSAS, young 39±2 & older 63±2 controls	Young 7% & older 7% OSAS, young 17% & older 11% controls	Attention, executive function, memory
Spira et al. 2008	Cross sectional, community volunteer	57 OSA, 391 controls	OSA 84±4, controls 83±3	100%	Executive function

Authors	Study design and recruitment	Population	Age (years)	Sex (% female)	Cognitive domain or task
Alchanatis et al. 2008	Cross sectional, sleep clinic	58 OSAS, 41 controls	OSA 49 (range 32–65), controls 49 (range 33–63)	Not reported	Attention/ alertness
Kloepfer et al. 2009	Cross sectional, clinic & community volunteers	15 OSA, 20 controls	OSA 46±6, controls 47±6	OSA 33%, controls 40%	Memory
Sharma et al. 2010	Cross sectional, clinic & community volunteers	50 severe OSA, 25 controls	OSA 43±8, controls 46±6	OSA 16%, controls 16%	Alertness, memory executive function
Sforza et al. 2010	Cross sectional, community volunteer	445 OSA, 382 controls	68±2	OSA 49%, controls 69%	Attention, executive function, memory
Saunamäki et al. 2010	RCT, sleep clinic	20 OSA, 17 controls	OSA 50 (range 37–65), controls 44 (range 30–63)	No females	Memory, verbal fluency
Bawden et al 2011	Cross sectional, clinic & community volunteers	17 OSA, 20 controls	OSA 41±13, controls 28±9	Not reported	Attention, memory executive function
Blackwell et al. 2011	Cross sectional, population based	2909 older men	76±6	No females	Executive function
Antic et al. 2011	Cross sectional, sleep clinic	174 mod-severe OSA	50±12	25%	Sleepiness
Hrubos-Strom et al. 2012	Cross sectional, community volunteer	290 mod-severe OSA	48±11	44%	Memory, executive function
Ju et al. 2012	Cross sectional, sleep clinic	42 OSA, 21 controls	OSA 68±4, controls 69±6	OSA 38%, controls 48%	Executive function
Kushida et al. 2012	RCT, sleep clinic	556 OSA (CPAP+ 6 months), 542 OSA (Sham CPAP)	CPAP 52±12, Sham 51±12	CPAP 35%, Sham 34%	Attention, vigilance, memory
Nikodemova et al. 2013	Cross sectional, community volunteer	755 Wisconsin cohort	54 (range 30–81)	38%	Memory, executive function
Landry et al. 2014	Cross sectional, sleep clinic	12 OSA, 12 controls	OSA 53±2, controls 53±2	OSA 25%, controls 25%	Overnight motor memory, sleepiness
Djonlagic et al. 2014	Cross sectional, sleep clinic	20 OSA, 20 controls	OSA 41±1, controls 35±3	Not reported	Overnight motor memory, vigilance
Varga et al. 2014	Interventional, sleep clinic	18 severe OSA (CPAP compliant 2+ months)	54	22%	Overnight spatial memory, vigilance
McMillan et al. 2014	RCT, sleep clinic	278 OSA (140 CPAP+ 3,12 months)	OSA-CPAP 71±5, OSA 71±5	OSA-CPAP 14%, OSA 21%	Sleepiness, global cognition
Troussière et al. 2014	Cross sectional, memory clinic	AD with severe OSA 14(CPAP+ >3 months), 9 (no CPAP)	CPAP+ 73 (range 68–80) CPAP− 78 (range 75–79)	CPAP+ 73 (range 68–80) CPAP− 78 (range 75–79)	Global cognition
Blackwell et al. 2015	Longitudinal, community volunteers	1132 OSA, 1504 controls	OSA76±5, controls 76±5	No females	Global cognition
Martin et al. 2015	Longitudinal, population based	599 OSA	67±1	56%	Global cognition
Djonlagic et al. 2015	Cross sectional, sleep clinic	29 OSA (14 CPAP+ 1 night), 15 controls	OSA 43±13, CPAP 44±11, controls 37±11	Not reported	Overnight motor memory, vigilance

Authors	Study design and recruitment	Population	Age (years)	Sex (% female)	Cognitive domain or task
Martínez-García et al. 2015	RCT, sleep clinic	115 (CPAP+ 3 months), 109 (no CPAP)	OSA-CPAP 75±4, OSA 76±4	OSA-CPAP 36%, OSA 27%	Sleepiness, executive function
Dalmases et al. 2015	RCT, sleep clinic	Severe OSA 17 CPAP+ 3 months, 16 no CPAP	OSA-CPAP 71±5, OSA 72±6	OSA-CPAP 35%, OSA 25%	Memory, executive function
Lutsey et al. 2016	Longitudinal, population based	445 OSA, 521 controls	OSA 62±5, controls 61±5	OSA 39%, controls 67%	Global cognition
Landry et al 2016	Cross sectional, sleep clinics	24 OSA, 13 CPAP+ 1night, 17 CPAP+ >6 weeks, 14 controls	OSA 47±2, CPAP 1night 48±2, CPAP compliant 49±2, Controls 47±3	OSA 17%, CPAP 1night 38%, CPAP compliant 24%, Controls 57%	Overnight motor memory, sleepiness, vigilance
Jackson et al. 2018	Cross sectional, clinic & community volunteers	110 OSA (88 CPAP+ 3 months), 31 controls	OSA 47±1, CPAP 46±1, controls 48±2	OSA 20%, CPAP 18%, controls 26%	Sleepiness, vigilance, executive function
Bhat et al. 2018	Cross sectional, sleep clinic	92 mild-mod & 90 severe OSA (CPAP+ >1 month)	Mild-mod OSA 50±12, severe 53±13	27%	Sleepiness, fatigue, vigilance
Gagnon et al. 2019	Observational, community volunteers	57 OSA, 54 mild/non OSA	OSA 63±6, non OSA 65±7	OSA 55%, non OSA 62%	Subjective and objective cognition
Richards et al. 2019	RCT, clinic & community volunteers	54 MCI with OSA (29 CPAP+ 6,12 months)	OSA-CPAP 67±7, OSA 73±9	OSA-CPAP 31%, OSA 60%	Global cognition, vigilance, memory
Kainulainen et al. 2020	Observational, sleep clinic	734 OSA	57 (IQR 46–67)	41%	Vigilance

AD: Alzheimer's disease; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnea; OSAS: obstructive sleep apnea syndrome; RCT: randomized controlled trial; SHHS: sleep heart health study. Median (SEM), Median [IQR]. Ages and percentages values are rounded from the source manuscript. **Studies involving CPAP are highlighted in green**.

Table 3:

Research reviewed involving OSA and neuroanatomy.

Authors	Study design and recruitment	Population	Age (years)	Sex (% female)	Neuroimaging approach
Macey et al. 2002	Cross-sectional, sleep clinic	21 OSA, 21 controls	OSA 49±11, controls 47±11	No females	T1w-VBM
Morrell et al. 2003	Cross-sectional, sleep clinic	7 OSA, 7 controls	50 (range 28–65)	No females	T1w-VBM
Bartlett et al. 2004	Cross-sectional, sleep clinic	8 OSA, 5 controls	OSA 47[16], controls 52[16]	No females	MRS
Gale & Hopkins 2004	Cross-sectional, tertiary hospital	14 OSA, 20 carbon monoxide (CO) poisoning	OSA 52±11, CO controls 38±7	OSA 14%, CO controls 45%	T1w-VBM
O'Donoghue et al. 2005	Interventional, sleep clinic	27 severe OSA (23 CPAP+ 6 months), 24 controls	OSA 46±10, controls 43±9	No females	T1w-VBM
Macey et al. 2008	Cross-sectional, sleep clinic	41 OSA, 69 controls	OSA 46±9, controls 48±9	OSA 21%, controls 57%	DTI
Yaouhi et al. 2009	Cross-sectional, sleep clinic	16 OSA, 14 controls	OSA 55±6, controls 53±7	OSA 6%, controls 7%	T1w-VBM, ^{18}FDG-PET
Canessa et al. 2011	Interventional, sleep clinic	17 severe OSA (16 CPAP+ 3 months), 15 controls	Severe OSA 44±8, controls 42±7	No females	T1w-VBM
Rosenzweig et al. 2013	Cross-sectional, sleep clinic	32 OSA, 32 controls	OSA 49±13, controls 50±12	OSA=controls	T1w-VBM
Castronovo et al. 2014	Interventional, sleep clinic	13 OSA (CPAP+ 3 & 12 months), 15 controls	OSA 43±8, controls 42±7	No females	DTI
Rosenzweig et al. 2016	Cross-sectional, sleep clinic	55 mod-severe OSA (28 CPAP+ 1 month), 35 controls	OSA 48±11, controls 42(2.1)	OSA 7%, Controls 20%	T1w-VBM
Duffy et al. 2016	Cross-sectional, aging clinic	24 at-risk dementia	68±6	71%	MRS
Baril et al. 2017	Cross-sectional, sleep clinic	18 severe, 11 moderate, 30 mild OSA, 12 controls	Severe 66±6, moderate 66±5, mild OSA 66±6, controls 62±5	Severe 17%, moderate 9%, mild OSA 33%, controls 18%	Volumes (voxel & surface based)
Macey et al. 2017	Cross-sectional, sleep clinic	14 OSA, 26 controls	OSA 47±10, controls 50±9	OSA 36% Controls 46%	MRS
Cross et al. 2018	Cross-sectional, aging clinic	83 at-risk dementia	67±8	64%	Volumes (voxel & surface based)
Lee et al. 2019	Cross-sectional, community volunteers	135 OSA, 165 controls	OSA 59±6, controls 58±6	OSA 71% Controls 72%	DTI
Maresky et al 2019	Interventional, sleep clinic	7 OSA	51±13	14%	DTI
André et al. 2020	Cross-sectional, community volunteers	96 SDB+, 31 SDB−	SDB+ 69±4, SDB− 69±4	SDB+ 58%, SDB− 775	T1w-VBM

CO- carbon monoxide; CPAP: continuous positive airway pressure; CSF- cerebrospinal fluid; DTI- diffusion tensor imaging; FA - fractional anisotropy; OSA: obstructive sleep apnea; T1w-VBM - voxel-based morphometry; ^{18}FDG-PET – Fluorodeoxyglucose Positron emission tomography. Mean ± standard dev. Median (SEM), Median [IQR]. Ages and percentages values are rounded from the source manuscript. **Studies involving CPAP are highlighted in green**.

Table 4:

Research reviewed involving OSA and quantitative EEG measures.

Authors	Study design and recruitment	Population	Age (years)	Sex (% female)	EEG Measure
Terzano et al. 1996	Cross-sectional, clinic & community volunteers	12 OSAS, 12 controls	OSAS 50±8, controls 49±6	OSAS 33%, controls 33%	CAP
Fietze et al. 1997	Interventional, sleep clinic	38 OSAS (CPAP+ 3 nights)	OSAS 49±21	No females	Arousals (visually identified)
Morisson et al. 1998	Cross-sectional, sleep clinic	21 OSAS, 10 controls	OSAS 44±7, controls 44±6	OSAS 10%, controls 10%	Spectral activity (sleep)
Parrino et al. 2000	Interventional, sleep clinic	10 OSAS (CPAP+ 1 night), 10 controls	OSAS 47±5, controls 48±6	OSAS 20%, controls 20%	CAP
Morisson et al. 2001	Interventional, sleep clinic	14 mod-severe OSAS (CPAP+ 6 months), 10 controls	OSAS 45±6, controls 44±6	OSAS 7%, controls 10%	Spectral activity (sleep)
Guilleminault et al. 2001	Cross-sectional, sleep clinic	12 OSHS, 12 OSAS, 12 UARS, 12 controls	OSHS 44±7, OSAS 42±7, UARS 42±7, controls 42±7	No females	Spectral activity (sleep)
Heinzer et al. 2001	Interventional, sleep clinic	12 severe OSA (CPAP+ 9 months), 10 controls	OSA 43±2, controls 44±2	No females	Spectral activity (SWA)
Sforza et al. 2002	Cross-sectional, sleep clinic	48 OSA	OSA 49±2	41%	Spectral activity (wake)
Thomas 2002	Cross-sectional, sleep clinic	12 OSA (CPAP+ 1 night)	OSA 44 (range: 22–64)	Not reported	CAP
Ondze et al. 2003	Cross-sectional, sleep clinic	18 mild SDB, 18 controls	SDB 36±11, controls 33±12	SDB 50%, controls 64%	Spectral activity (SWA, spindle)
Himanen et al. 2004	Cross-sectional, clinical	8 OSAS, 8 controls	OSAS 43(range 31–59), controls 45 (range 34–54)	OSAS 50%, controls 50%	SWs (visually identified)
Chervin et al. 2005	Cross-sectional, sleep clinic	27 SDB, 11 controls	SDB 45±14, controls 33±10	SDB 33%, controls 82%	Spectral activity (sleep)
Parrino et al. 2005	Interventional, sleep clinic	10 OSAS (CPAP+ night 1,2,3 & 30), 10 controls	OSAS 48±4, controls age-matched	No females	CAP
Mathieu et al. 2007	Cross-sectional, clinic & community volunteers	12 young & 13 older OSAS, 13 young & 14 older controls	Young 38±2 & older OSAS 62±2, Young 36±2 & older controls 60±2	Young 20% & older OSAS 0%, Young 8% & older controls 0%	EEG slowing
Guilleminault et al. 2007	Cross-sectional, clinic & community	30 UARS, 30 controls	Not reported	UARS 50%, controls 50%	CAP
Greneche et al. 2008a	Cross-sectional, clinical	12 OSA, 8 controls	OSA 51±3, controls 49±3	Not reported (No females inferred)	Spectral activity (wake)
Greneche et al. 2008b	Cross-sectional, clinical	12 mod-severe OSAHS	OSAHS 51±3	No females	Spectral activity (wake)
Saunamaki et al. 2009	Interventional, sleep clinic	15 OSAS (CPAP+ 6–12 months), 15 controls	OSAS 50 (range 37–59), controls 44 (range 30–63)	No females	Spectral activity (SWA)
Xiromeritis et al. 2011	Interventional, sleep clinic	131 OSA (29 CPAP+ 6 months), 30 controls	OSA 49±10, control 47±12	OSA 7%, control 7%	Spectral activity (wake)
Greneche et al. 2011	Interventional, sleep clinic	12 OSAHS (10 CPAP+ 3 & 6 months)	OSAHS 51±3	Not reported (No females inferred)	Spectral activity (wake)

Authors	Study design and recruitment	Population	Age (years)	Sex (% female)	EEG Measure
Lee et al 2012	Interventional, clinic	13 OSAS (CPAP+ 3 months)	OSAS range: 37–59	No females	Spectral activity (wake)
Schonwald et al. 2012	Cross-sectional, sleep clinic	11 mild & 10 mod OSA, 7 non-OSA	Mild 51±7 & mod 52±9 OSA, controls 46±6	Mild 55% & mod 20% OSA, controls 43%	Spindle characteristics
Baril et al. 2013	Cross-sectional, clinic	12 OSA, 12 controls	OSA 48±14, controls 44±10	OSA 25%, controls 8%	Spectral activity (wake), ERP
D'Rozario et al. 2013	Cross-sectional, clinic	8 OSA, 9 non-OSA	OSA 45±8, non-OSA 29±4	OSA 0%, non-OSA 11%	DFA
Jones et al. 2014	Cross-sectional, community volunteers	9 OSA, 9 controls	OSA 53±10, controls 52±9	OSA 33%, controls 33%	Spectral activity (sleep)
Carvalho et al. 2014	Cross-sectional, sleep clinic	11 mild & 10 mod OSA, 7 non-OSA	Mild 51±7 & mod 52±9 OSA, controls 46±6	Mild 55% & mod 20% OSA, controls 43%	Spindle characteristics
Parapatics et al. 2015	Cross-sectional, clinic & community volunteers	22 OSA (CPAP+ 3–6 months), 22 controls	OSA 59, controls 59	OSA 9%, controls 9%	K-complexes
Chokroverty et al. 2015	Interventional, sleep clinic	9 severe OSA (CPAP+ split night)	Range: 28–80	11%	Spindle density
Vakulin et al. 2016	Cross-sectional, sleep clinic	76 OSA	43 (range 23–65)	16%	Spectral activity
Nguyen et al. 2016	Cross-sectional, sleep clinic	10 severe & 10 mod OSA, 10 controls	Severe 48±12 & mod OSA 46±14, controls 39±12	Severe 30% & mod OSA 30%, controls 30%	K-complexes, spectral activity
Lee et al. 2016	Cross-sectional, sleep clinic	40 young OSAS & 36 older OSAS	Young OSAS 24±5, Older OSAS 59±5	Young OSAS 13%, Older OSAS 22%	Spectral activity
Barner et al. 2016	Cross-sectional, clinic	21 OSA	53±2	11%	Spindle density
Madaeva et al. 2017	Cross-sectional, sleep clinic	18 overweight OSAS, 12 overweight controls, 15 normal weight controls	Overweight OSAS 17, Overweight controls 16, Normal weight controls 16	No females	Spindle characteristics
Saunamaki et al. 2017	Interventional, clinic & community volunteers	20 OSA (CPAP+ 6 months), 20 controls	OSA 50 (range 37–65), controls 49 (range 34–60)	No females	Spindle characteristics
Korkmaz et al. 2018	Cross-sectional, sleep clinic	10 OSA with ES, 28 OSA without ES	OSA with ES 56±4, OSA without ES 54±5	No females	CAP
Yetkin & Aydogan 2018	Interventional, sleep clinic	73 consecutive patients	50±12	16%	Spindle density
Appleton et al. 2019	Cross-sectional, community volunteers	84 severe, 97 mod, 195 mild, 358 non-OSA	Severe 64±12, mod 63±10, mild 62±11, non-OSA 59±11	No females	Spectral activity
Parekh et al. 2019	Interventional, sleep clinic	28 OSA (CPAP+), 19 controls	OSA 47±11, controls 34±2	OSA 25%, controls 37%	K-complexes, spectral activity
Mullins et al. 2020	Cross-sectional, sleep clinic	8 mod-severe OSA	OSA 45±8	No females	Spectral activity, spindle density

CAP: cyclic alternating pattern; CPAP: continuous positive airway pressure; DFA: detrended fluctuation analysis; ERP: event related potential; ES: excessive sleepiness; OSA: obstructive sleep apnea; OSAS: obstructive sleep apnea syndrome; OSHS: obstructive sleep hypopnea syndrome; SDB: sleep-disordered breathing; SW: slow wave; SWA: slow wave activity; UARS: upper airway resistance. Median (SEM), Median [IQR]. Ages and percentages values are rounded from the source manuscript. **Studies involving CPAP are highlighted in green**.

Table 5:

Research reviewed involving OSA and biomarkers beyond amyloid and tau.

Authors	Study design and recruitment	Population	Age (years)	Sex (% female)	Biomarkers
Saarelainen et al. 1998	Cross-sectional, sleep clinic and population based	291 OSA, 728 controls	OSA 53 (range 26–75), controls 54 (range 39–70)	OSA 9%, Controls 22%	ApoE genotype
Kadotani et al. 2001	Cross-sectional, population based	791 middle-aged adults	49±8	40%	ApoE genotype
Kanbayashi et al. 2003	Cross-sectional, clinic	16 narcolepsy with OSA, 12 controls	55±15	No females	CSF hypocretin 1 (Orexin A)
Gottlieb et al. 2004	Cross-sectional, population based	1,775 SHHS cohort	71±10	55%	ApoE genotype
Cosentino et al. 2008	Cross-sectional, sleep clinic & community volunteers	123 OSA, 121 controls	OSA 59±9, controls 58±10	OSA 33%, controls 36%	ApoE genotype
Sanchez-de-la-Torre et al. 2011	Cross-sectional, sleep clinic	132 OSA with EDS, 132 OSA w/out EDS	OSA EDS+ 50±11, OSA EDS − 51±10	OSA EDS+ 17%, OSA EDS− 14%	Neuropeptides, metabolic hormones
Testelmans et al. 2013	Cross-sectional, sleep clinic	15 obese OSA, 15 non-obese OSA, 15 OSA +CV, 12 CV, 15 controls	OSA obese 52±10, non-obese OSA 52±8, OSA+CV 53±9, CV 53±9, controls 48±6	OSA obese 77%, non-obese OSA 20%, OSA+CV 7%, CV 17%, controls 47%	Cytokines
Sui & Gao 2013	Cross-sectional, Army hospital	134 OSAS with CAD, 112 OSAS without CAD	CAD+ 57±8, CAD − 56±9	CAD+ 28%, CAD − 26%	Serum YKL-40
Palomares et al. 2015	Cross-sectional, sleep clinic	9 OSA, 9 controls	OSA 47±11, controls 39±7	OSA 56%, controls 44%	BBB function
Baril et al. 2015	Cross-sectional, sleep clinic	50 OSA, 20 controls	OSA 64±6, controls 64±7	OSA 14%, controls 40%	Cerebral perfusion
Sun et al. 2015	Cross-sectional, population based	448 older women	83±3	100%	ApoE genotype
Jafari & Mohsenin 2016	Cross-sectional, sleep clinic	36 OSA+HT, 27 OSA-HT, 13 Non-OSA+HT, 19 Non-OSA-HT	OSA+HT 56±1, OSA-HT 48±2, Non-OSA+HT 46±2, Non-OSA-HT 48±2,	OSA+HT 19%, OSA-HT 26%, Non-OSA+HT 38%, Non-OSA-HT 68%	Serum YKL-40
Ju et al. 2016	Cross-sectional, community volunteers	10 OSA, 31 controls	OSA 56±4, control 53±6	OSA 30%, controls 48%	CSF VILIP-1, neurogranin
Osorio et al. 2016	Cross-sectional, community volunteers	63 cognitively normal individuals	70±9	57%	CSF Orexin-A, ApoE genotype
Chen et al. 2017	Cross-sectional, sleep clinic	20 mod-severe OSA, 16 controls	OSA 40±8, controls 38±9	No females	Cerebral perfusion, leucocyte apoptosis
Liguori et al. 2017	Cross-sectional, sleep center	25 OSA, 10 OSA-CPAP, 15 controls	OSA 68±8, OSA-CPAP 67±7, controls 66±9	OSA 32%, OSA-CPAP 30%, controls 40%	CSF Lactate
Liguori et al. 2019	Cross-sectional, clinic	20 OSA, 20 AD, 15 controls	OSA 59±4, AD 66±4, controls 64±8	OSA 30%, AD 65%, controls 47%	Orexin-A

ApoE: Apolipoprotein E; BBB: blood brain barrier; CV: cardiovascular event; EDS excessive daytime sleepiness; HT: hypertension; OSA: obstructive sleep apnea; SHHS: sleep heart health study; YKL-40: 40 kDa heparin- and chitin-binding glycoprotein. Median (SEM), Median [IQR]. Ages and percentages values are rounded from the source manuscript. **Studies involving CPAP are highlighted in green**.