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Research Article

Positive airway pressure improves amnestic mild cognitive impairment in patients diagnosed with obstructive sleep apnoea hypopnoea syndrome. A review of the evidence

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Abstract:

There is growing clinical evidence showing the impact of sleep disturbance on the development of Alzheimer's disease (AD). It has been proposed that intermittent hypoxia and sleep fragmentation, which are hallmarks of obstructive sleep apnoea hypopnoea syndrome (OSAHS), are physiological changes that may contribute to cognitive impairment. Sleep fragmentation reduces slow-wave sleep duration affecting the efficiency of the brain clearance system, allowing metabolic proteins to accumulate. These proteins contribute to neurodegeneration, brain atrophy, and cognitive impairment. Improvements in fluid diffusion which leads to the reduction in the accumulation of metabolic proteins, have been observed after positive airway pressure (PAP) treatment. Treating OSAHS may be effective in reducing the risk of neuronal damage and improve cognitive function.

This review outlines the current knowledge associating OSAHS and AD and discusses the effect of PAP treatment on cognitive function, AD biomarkers, and the brain clearance system.

Key words: obstructive sleep apnoea; glymphatic system; Alzheimer's disease; positive airway pressure; cognition

Abbreviations

Aβ – amyloid beta

AD – Alzheimer's disease

AHI – apnoea/hypopnoea index

aMCI – amnestic mild cognitive impairment

CSF – cerebrospinal fluid

MCI – mild cognitive impairment

MRI – magnetic resonance imaging

OSAHS – obstructive sleep apnoea hypopnoea syndrome

PAP – positive airway pressure

1.Introduction

Obstructive sleep apnoea hypopnoea syndrome (OSAHS) is characterised by recurrent episodes of partial or complete pharyngeal collapse, causing a reduction or cessation of airflow [1]. This leads to key physiological changes during sleep including intermittent hypoxia, swings in intrathoracic pressure and sleep fragmentation, leading to alterations in the sleep architecture [2-5].

Alzheimer's disease (AD) is regarded as a world-wide epidemic that currently cannot be prevented, treated, nor slowed down [5,6]. Memory loss is the main feature of amnestic mild cognitive impairment (aMCI) which is the prodromal phase to AD [7]. It is imperative for early identification of those with an increased probability of developing aMCI to allow for early treatment of the AD risk factors [4,8].

There is discrepancy in the information associating the prevalence of OSAHS in the AD population. A potential reason for the differing results is largely dependent on the populations studied (community compared to nursing home) which may result in survivor bias [4].

In addition, the sleep and breathing measurements analysed vary and so the diagnosis of OSAHS may be under or over-estimated when gold-standard measures are not used (respiratory parameters e.g. oxygen desaturation index compared to apnoea hypopnoea index (AHI)) [4]. For example, a systematic review of 5 studies undertaken by Mubashir et al. [9] found OSAHS prevalence ranging between 11 and 71% in the mild cognitively impaired (MCI) population. The large prevalence range highlights the methodological differences across the 5 studies, with 1 study using qualitative methods and another relying on the self-reporting from participants to diagnose OSAHS. Interestingly, two of the studies using objective methods to diagnose OSAHS demonstrated an OSAHS prevalence of 70 and 71% in the MCI population. In contrast, the study relying of the self-reporting of OSAHS demonstrated a significantly lower prevalence at 11%. This suggests the OSAHS is highly prevalent in the MCI population.

The mechanisms mediating the pathological alterations in cognition observed in OSAHS patients are unclear. There are hypotheses suggesting that intermittent hypoxia and sleep fragmentation, key features of OSAHS, cause cognitive decline contributing to the development of aMCI and eventually AD [1-5]. Fundamentally, intermittent hypoxia and sleep fragmentation cause changes in the sleep architecture, oxidative stress, and intrathoracic pressure swings (Figure 1).

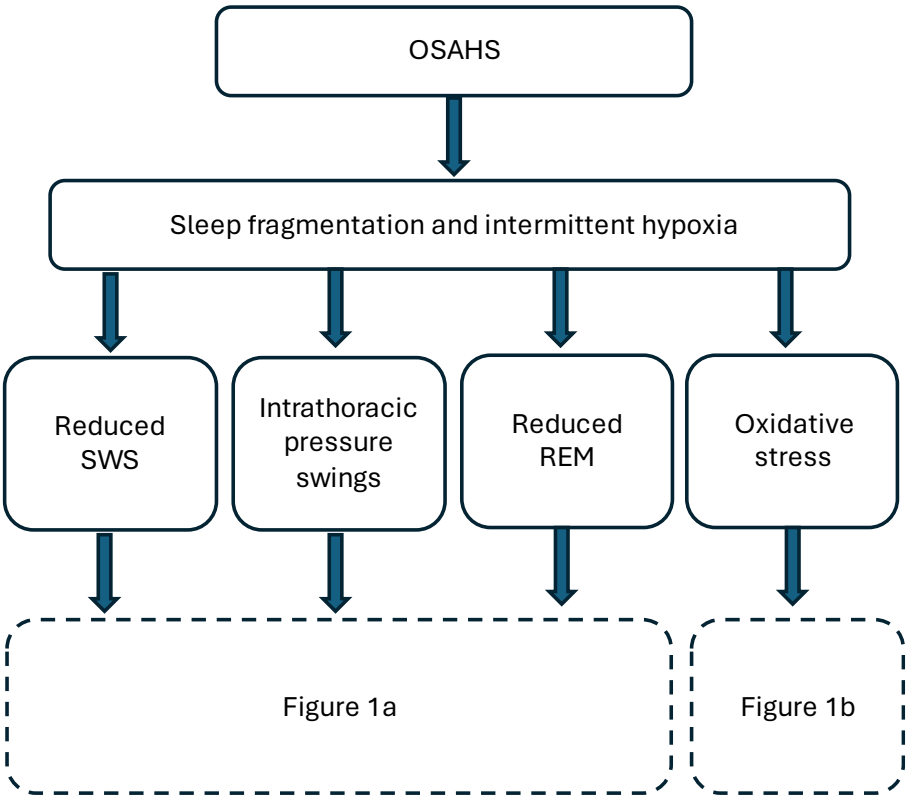

Figure 1: Proposed pathways linking OSAHS to cognitive impairment. Two key physiological features of OSAHS, sleep fragmentation and intermittent hypoxia, are proposed to cause cognitive dysfunction [30,49]. These features are proposed to promote oxidative stress, reduce slow wave sleep (SWS) duration, generate intrathoracic pressure swings, and reduce rapid eye movement sleep (REM) [11,18,49,60]. The proposed pathways by which each of these physiological changes leads to cognitive impairment will be discussed in Figure. 1a and 1b respectively.

A reduction in slow wave sleep (SWS) and changes in the intrathoracic pressure causes a reduction in the fluid diffusivity through the brain, which leads to impairments in the clearance pathway, known as the glymphatic system (Figure 1a). When the glymphatic clearance is reduced it promotes the accumulation of metabolic waste products in the brain. This can cause over excitability in the brain immune cells, such as microglia, causing inflammation, cell death, and neurodegeneration. Over time this can eventually cause neuronal death, changes in brain structure and function leading to cognitive decline (Figure 1a) [10-12]. This will be discussed further in the next section.

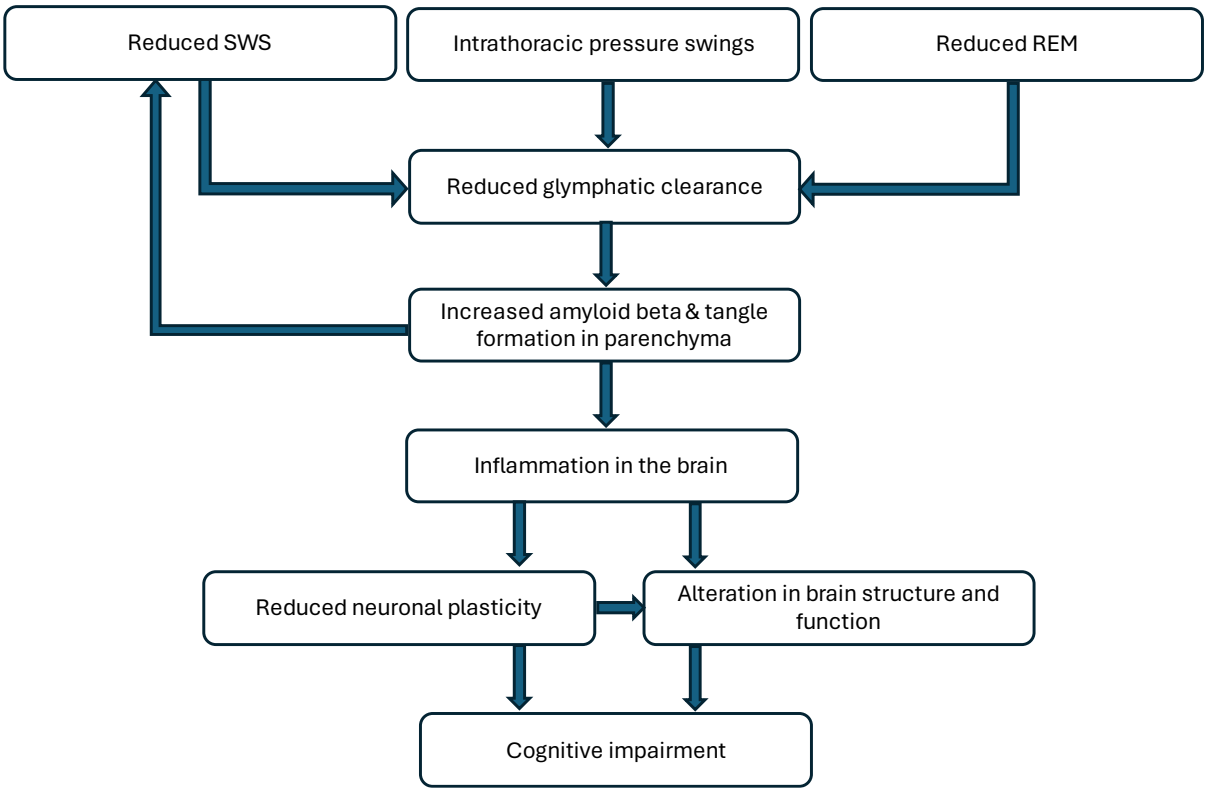

Figure 1a. Reduction in slow wave and rapid eye movement sleep, and intrathoracic pressure swings, has been proposed to reduce the activity of the glymphatic system by reducing the fluid diffusivity across the brain [11,18,36,37,38,60]. Reduction in brain clearance promote an increase in accumulated metabolites in the brain (such as amyloid beta and tau proteins) [6,56]. An increase in these proteins in the brain have been proposed to form a bidirectional relationship with sleep and therefore contributing to further slow wave sleep disruption due to inflammation interfering with sleep generating pathways [5,64]. This causes a repetitive cycle of events and hence further reductions in the glymphatic system activity [64]. Protein accumulation activates astrocytes and microglia as they clear these metabolites from the interstitial space. These cells became overactivated as the load of metabolites increase which leads to inflammation. Inflammatory processes are harmful to neurones affecting synaptic plasticity. In the long-term this inflammatory process leads to neuronal death causing structural changes in the brain [37,58]. Deficits in synaptic plasticity and neuronal death leads to cognitive impairment [11,29,31,35].

Positive airway pressure (PAP), the gold standard treatment for OSAHS [13], stents the upper airway allowing for unrestricted airflow [14]. This treatment method maintains oxygen levels during sleep and improves quality of sleep. There is substantial evidence showing the efficacy of this treatment to recover the physiological changes including hypoxaemia and sleep fragmentation in OSAHS patients [15-17]. Due to the relationship between OSAHS and AD, PAP treatment has been proposed to improve cognitive impairment through the promotion of sleep consolidation and maintaining stable nocturnal oxygen levels [18]. Although the mechanism by which PAP treatment improves cognition in OSAHS patients [17,19] is not yet known, there are experimental findings supporting a delayed onset of MCI after PAP treatment [8,17,19,20,21]. This observation is not limited to aMCI and hence Alzheimer's disease and may include cognitive impairment associated with other diseases such as Parkinson's disease [7,17]. Nonetheless, OSAHS has been often regarded as a potential risk factor for developing AD [17,22,23].

The aim of this review is to present current evidence to establish whether the efficacy of PAP treatment ameliorates cognitive impairment in patients with OSAHS. We will also establish whether fluid diffusivity efficiency in the brain is improved with PAP treatment, and whether PAP treatment impacts cognitive function and levels of AD biomarkers in the cerebrospinal fluid (CSF) and blood.

2. Method

A literature search was performed using three databases from January 2003 until March 2024 and using the search term combinations in Table 1. References obtained were also hand searched for further articles that may have been missed.

3. Results

Database	Search term
PubMed	("Mild cognitive impairment" OR "cognitive decline" OR "cognitive dysfunction" OR "mild cognitive deficit" OR "Alzheimer disease" OR AD OR amyloid OR "MCI" OR "amnestic mild cognitive impairment" OR "degenerative disease" OR "amyloid precursor protein" OR preAlzheimer OR pre-Alzheimer OR "prodromal Alzheimer" OR "preclinical Alzheimer" OR "pre-clinical Alzheimer" OR "mild neurocognitive disorder" OR Alzheimer [Title/Abstract]) AND (OSA OR "obstructive sleep apnoea" OR "sleep disordered breathing" OR "sleep disorder" [Title/Abstract]) AND (CPAP OR "continuous positive airway pressure" OR "positive pressure" OR MRI OR "magnetic resonance imaging" [Title/Abstract])
CINAHL	("Mild cognitive impairment" OR "cognitive decline" OR "cognitive dysfunction" OR "mild cognitive deficit" OR "Alzheimer disease" OR AD OR amyloid OR "MCI" OR "amnestic mild cognitive impairment" OR "degenerative disease" OR "amyloid precursor protein" OR preAlzheimer OR pre-Alzheimer OR "prodromal Alzheimer" OR "preclinical Alzheimer" OR "pre-clinical Alzheimer" OR "mild neurocognitive disorder" OR Alzheimer [Abstract]) AND (OSA OR "obstructive sleep apnoea" OR "sleep disordered breathing" OR "sleep disorder" [Abstract]) AND (CPAP OR "continuous positive airway pressure" OR "positive pressure" OR MRI OR "magnetic resonance imaging" [Abstract])
Web of Science	("Mild cognitive impairment" OR "cognitive decline" OR "cognitive dysfunction" OR "mild cognitive deficit" OR "Alzheimer disease" OR AD OR amyloid OR "MCI" OR "amnestic mild cognitive impairment" OR "degenerative disease" OR "amyloid precursor protein" OR preAlzheimer OR pre-Alzheimer OR "prodromal Alzheimer" OR "preclinical Alzheimer" OR "pre-clinical Alzheimer" OR "mild neurocognitive disorder" OR Alzheimer [Abstract]) AND (OSA OR "obstructive sleep apnoea" OR "sleep disordered breathing" OR "sleep disorder" [Abstract]) AND (CPAP OR "continuous positive airway pressure" OR "positive pressure" OR MRI OR "magnetic resonance imaging" [Abstract])

AD, Alzheimer's disease; MCI, mild cognitive impairment; OSA, obstructive sleep apnoea; CPAP, continuous positive airway pressure; MRI, magnetic resonance imaging.

Table 1: Search terms used for specific databases.

A total of 45 studies were found. Of the 45, 15 studies discussed the hypothesised glymphatic system in relation to sleep [11,12,23-35], 5 studies assessed the impact of PAP on brain fluid diffusivity in patients with OSAHS [36-40], 4 studies assessed the influence of PAP treatment on the level of AD biomarkers [29,31,41,42], 11 studies measured the impact of PAP treatment on cognitive function in OSAHS [1,4,14,43-50] and 10 studies measured the impact of PAP treatment on cognitive function in OSAHS and aMCI/AD [7, 8,17,20,21,51-55].

4. Discussion

To address the aim of this review, the impact of PAP treatment on sleep fragmentation and intermittent hypoxia will be discussed on 1) the functioning of the glymphatic system; 2) the brain fluid diffusivity and volume changes in white and grey matter structures via magnetic resonance imaging (MRI); 3) levels of biomarkers for AD in the CSF and blood and 4) cognitive function in OSAHS patients with and without aMCI.

4.1. *Sleep fragmentation, intermittent hypoxia, and the glymphatic system.*

The importance of sleep for optimal function of the glymphatic system has been previously reported in humans [23,28-32,34].

It has been hypothesised that the glymphatic system is most effective during slow wave sleep; with the purpose of CSF influx into the brain, mixing with the interstitial fluid containing the metabolic waste such as amyloid beta (Aβ), which accumulates during wakefulness. The combined fluid containing the proteins are washed out of the parenchyma into the CSF and the blood stream via the blood brain barrier, for elimination through the kidneys and liver [23,28,30,31,34,56].

Therefore, if the glymphatic system is most effective during sleep then fragmented sleep, a sleep pattern observed in those with OSAHS, causes deficiencies in the glymphatic clearance. This supports the amyloid cascade theory, a persuasive model for the development of AD [6]. This relates to the discrepancy in the production and clearance of Aβ, which is secreted mainly by neurons, and subsequently the effectiveness of the glymphatic system [6,56]. If this pattern of sleep fragmentation persists and glymphatic clearance is impaired, there will be an increase in the accumulation and aggregation of insoluble Aβ peptides which form extracellular plaques [29,30,34].

The mechanism of increased extracellular tau proteins in the brain is less characterised [56]. It has been suggested that tau is a product of axonal loss mainly due to increase in hyperphosphorylated tau which cannot bind to the microtubules of the axon. Therefore, support from tau is no longer available causing axon instability and neuronal death leading to neurodegeneration (Figure 1a) [11,29,31,35,57,58]. This is likely to be caused by intermittent hypoxia leading to inflammation in the brain (Figure 1a).

To add insult to injury, intermittent hypoxia, another feature of OSAHS, also contributes to neurodegeneration by several physiological mechanisms including inflammation, due to an increase in oxidative

stress [49]. An increase of free radical formation and hence an imbalance between antioxidants is a consequence of oxidative stress, which increase release of inflammatory factors and endothelial cell damage (Figure 1b) [12,24,25,26,27,33]. Oxidative stress can cause an increase in the microglia (immune cells of the central nervous system) and astrocyte (subtype of glial cells) activity [49,59]. There is essentially a role reversal of these cells. For example, instead of the protective function that microglia provide by clearing Aβ proteins, when the cells are overactivated they can produce harmful amount of neurotoxic pro-inflammatory factors such as tumour necrosis factor alpha, interleukin [48,49,59]. These substances have been shown to be harmful to neurons, can cause an increase in inflammation and may influence tau pathology [49,59].

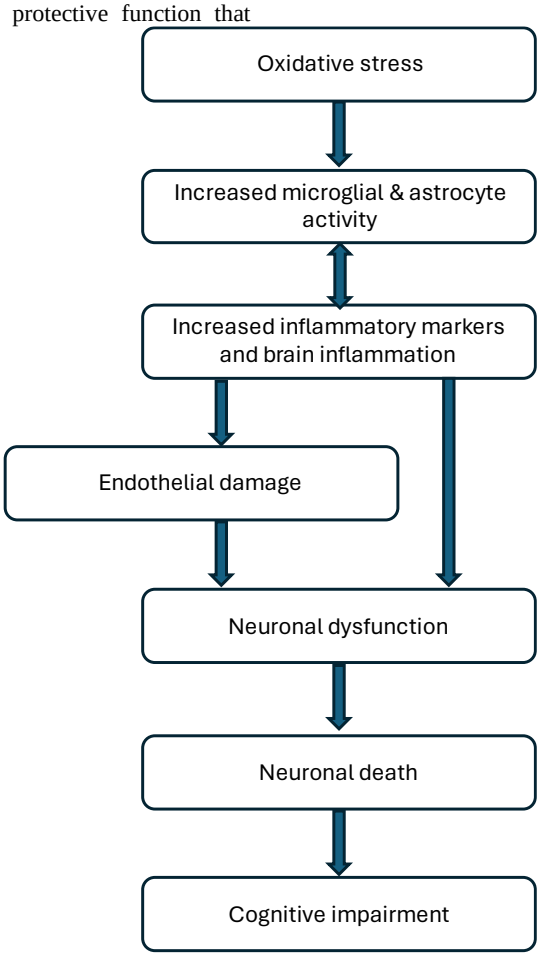

Figure 1b. Proposed physiological changes in OSAHS leading to increase in oxidative stress and cognitive impairment [49]. Oxidative stress has been proposed to cause an increase in the microglial and astrocyte activity, which in response release pro-inflammatory factors causing inflammation in the brain [48,59]. Increase in the inflammatory factors further promotes immune cell and release of inflammatory factors [59]. In addition, inflammation, oxidative stress, and blood flow surges can cause endothelial damage and changes in the blood-brain barrier integrity [56,57]. This reduces permeability of the blood brain barrier, allowing easy access of foreign agents into the brain [56]. Both the inflammation and the endothelial damage can lead to neuronal dysfunction and neuronal death and ultimately cognitive impairment [12,26,49,56].

Unstable levels of oxygen in the blood cause a rise and fall in blood pressure, the resultant blood pressure swings may cause hypertension [29]; a known risk factor for AD and comorbidity of OSAHS. Furthermore, the repetitive nature of respiratory events causes surges in

the intracranial and intrathoracic pressure (Figure 1a). These high-pressure swings may impede the glymphatic flow due to increased resistance and hence impede drainage efficiency from the glymphatic system [28,60].

This demonstrates the complex and intricate relationship that can result in the accumulation of Aβ and cellular death, which are key features of AD, through the two overarching mechanisms of intermittent hypoxia and

sleep fragmentation; both of which are commonly experienced in OSAHS.

4.2. *Effect of positive airway pressure treatment on the glymphatic system.*

As previously discussed, intermittent hypoxia has been hypothesised to contribute to neuroinflammation ultimately leading to widespread neuronal damage and brain atrophy (Figure 1,1a,1b). It has been observed that OSAHS patients demonstrate a reduction in the diffusivity volume in the brain [37,39,61-63] suggesting alterations in the brain structure of the grey and white matter. Structural changes due to cellular membrane destruction can occur, in addition, inflammation can cause an increase in water diffusivity and blood vessel damage [37]. All of which may hinder fluid flow across the brain and therefore reducing glymphatic clearance [62]. This suggests the presence of intracellular cytotoxic oedema and increased production of microglial and astrocyte activity [62], as previous discussed in section 4.1. This will further contribute to the accumulation of Aβ.

The effects of PAP treatment on brain fluid diffusivity have been observed using MRI. Albeit there are very few studies that have assessed the full impact of PAP as an intervention on the glymphatic function in

OSAHS patients. Nonetheless, five longitudinal studies using MRI measures were identified.

In a group of 17 severe OSAHS male patients using PAP therapy for 3 months, Canessa et al [36] found the reversal of grey matter volume in the hippocampal and frontal cortex regions of the brain. Supporting these findings, Rosenzweig et al [38] found a reduction in fibres in the left hippocampus, bilateral globus pallidus, and mid-posterior part of the corpus callosum in OSAHS patients. After using PAP for 1 month these observations were no longer found, suggesting adaptation of the neuroplastic structures which also correlated to reduced somnolence and improvements in attention and memory.

The importance of glymphatic drainage was demonstrated by Wang et al [40]. They found enlarged perivascular spaces in the bilateral frontal cortex and basal ganglia in OSAHS patients and even more prominently so in the severely hypoxic OSAHS patients. Both of which improved with PAP treatment [36,37,40]. These findings suggest that PAP may help to restore brain structure and glymphatic function and consequently improve cognitive impairment because of restoring sleep architecture and improving cerebral perfusion [16].

Interestingly, Zhang et al [39] compared sleepy and non-sleepy OSAHS patients treated with PAP for one month, both groups demonstrating an adequate adherence of ≥6 hours per night. They found that the white matter measured by mean diffusivity was higher in the sleepy group when compared to the non-sleepy group. However, optimisation of PAP treatment only relied on PAP reported AHI, other variables influencing PAP effectiveness such as interface leak was not reported. The severity of white matter damage before treatment for each group was not measured, and therefore it is unknown if groups were comparable before starting treatment. Although speculative, the amount of white matter damage may improve after a longer period using PAP treatment.

The arbitrary follow up periods of one and three months are often used. This may stunt potential alterations in the white and grey matter. This was highlighted in a controlled prospective study by Castronovo et al [37]. They found that impaired cognitive function was associated with white matter structural changes measured via fractional ansiotropy and mean diffusivity in the OSAHS group pre-treatment. Reductions in fractional ansiotropy and hence white matter integrity was found in several brain regions including the parietal, frontal, and prefrontal cortical areas. This suggests that OSAHS has a significant impact on white matter in the patient's brain. However, after 12 months of PAP treatment, repeat measurements of fractional ansiotropy and mean diffusivity demonstrated more notable changes in the reversal in white matter integrity when compared to three month follow up measurements. This suggests the repair of neuronal injury from intermittent hypoxia is a longer process. This was also correlated with improvements in attention, executive function, and memory.

4.3. *Effect of positive airway pressure treatment on levels of biomarkers for AD in OSAHS patients.*

There is a proposed bidirectional relationship between OSAHS and AD relating to protein accumulation of Aβ and tau and reduced slow wave sleep (Figure 1a) [5]. It has been established with suggested that a lack of slow wave sleep contributes to the formation of Aβ plaques [6, 10, 11], the accumulation of Aβ in turn hinders slow wave sleep, generating a vicious cycle of events [64]. The mechanisms behind this two-way relationship remain unclear however, it has been proposed to be influenced by inflammation [5,6,64] as described in section 4.1. This proposed relationship further supports the amyloid cascade theory (Section 4.1) [6] which leads to neurodegeneration and AD pathology.

According to Mullins et al [16], the number of papers demonstrating the effect of PAP on levels of CSF and blood AD biomarkers is sparse. Nonetheless, PAP has been shown to alter sleep macrostructure in OSAHS patients, particularly slow wave sleep duration and sleep efficiency. Improvements in levels of pathological Aβ and tau biomarkers when OSAHS patients have been using PAP is thought to be due to the restoration of slow wave sleep [5]. Similar findings were found in several papers and are discussed below.

A study by Madaeva et al [31] demonstrated an increase in slow wave sleep positively correlated to plasma Aβ42 levels in a group of moderate and severe OSAHS treated with PAP for three months. Restoring the sleep architecture to a standard pattern by increasing the sleep quality and duration due to PAP treatment may improve glymphatic drainage.

In support of these findings, Liguori et al [29] demonstrated higher levels of Aβ42 in the CSF of those using PAP compared to non-PAP users. This suggests that the PAP group were more likely to experience consolidated sleep and thus less sleep fragmentation which favoured a more efficient clearance of Aβ from the brain. Interestingly, they also supported the influence of intermittent hypoxia on cognition and neurodegeneration by demonstrating that lower levels of Aβ in the CSF correlated with poorer cognitive function and lower oxygen saturations.

A similar study by Liu et al [42] compared plasma biomarkers Aβ42 and T-tau in PAP and non-PAP OSAHS patients. Those using PAP treatment demonstrated a significantly reduced level of both biomarkers compared to the non-PAP group after 3 months of treatment. The individuals assigned to each group was by self-selection, and therefore motivational bias to use PAP therapy may have been present. Those in the PAP group also demonstrated higher baseline in the Epworth sleepiness score compared to the non-PAP group supporting a further motivational influence. Nonetheless, the physiological change in biomarkers supports that PAP treatment may be effective in reducing cognitive dysfunction.

Furthermore, Ju et al [41] findings support the proposed bidirectional relationship and found that PAP treatment significantly increased slow wave sleep duration which correlated with improved pathological levels of Aβ42 in the CSF. Surprisingly, this was the only study found that used auto-titrating PAP to ascertain the 90th percentile pressure over a ≥2-week period. Thus, allowing for the monitoring of night-to-night variation as opposed to a split night or depending on a single night titration study [7,21,51-53]. Titrating over a longer period will argueably improve the efficacy of treatment.

4.4. *Positive airway pressure treatment and cognitive function in OSAHS and in OSAHS and aMCI.*

In recent years there has been an increased interest in the cognitive effects of PAP treatment in those with OSAHS. However, more research is needed to assess PAP as an intervention in those with OSAHS and cognitive impairment. There have been few longitudinal and randomised controlled trials assessing the effects of PAP treatment on cognition specifically in OSAHS patients with aMCI. Nevertheless, randomised controlled trials have shown cognitive improvements in OSAHS patients with AD when using PAP treatment [20,51-53]. Findings from these studies demonstrated significant improvements in slow wave sleep, mood, cognition, and sleepiness; suggesting that aMCI and AD patients with OSAHS may benefit from PAP treatment.

Studies have hypothesised that intermittent hypoxia and sleep fragmentation is associated with cognitive impairment due to reduced SWS and REM, oxidative stress, and intrathoracic pressure swings (Figure 1), all contributing to neurodegeneration and thus aMCI (Figures 1a and 1b) [1,2,18]. PAP treatment may therefore improve cognitive impairment by consolidating sleep and normalising nocturnal oxygen levels, and consequently restore the sleep architecture and reduce daytime somnolence [3]. In support, Dandan-Zong et al [1] found a reduction in the inflammatory marker's interleukin 6 and interleukin 8 in PAP users compared to pre-treatment, which also correlated with improved cognitive function assessment scores. Ou et al [49] also demonstrated improvements in inflammatory markers (TAR DNA-binding protein 43, histone deacetylase 6 and peroxiredoxin-1) and cognitive function in

patients with severe OSAHS using PAP treatment for 12 weeks. Furthermore, Zong et al [48] has shown that 12 weeks of PAP treatment can reduce levels of inflammation and oxidative stress by preventing the intermittent hypoxia and hence the repetitive deoxygenation and reoxygenation nature of OSAHS [48]. Consequently, the inflammatory proteins involved in neuro-inflammation and oxidative stress pathway are reduced, improving endothelial dysfunction allowing for unrestricted blood flow and hence improves cognitive impairment in OSAHS (Figure 1b) [48].

A study by Ferini-Strambi et al [43] showed an improvement in attention and somnolence levels after 15 days of PAP treatment with titration over one night using polygraphy, in 16 severe OSAHS patients. However, these findings should be interpreted with caution as the study was underpowered due to the small sample size with a predominantly male cohort and only severe OSAHS cases were included in the study. No further enhancements in cognition were found after 4 months of PAP treatment, and the OSAHS group did not achieve full resolution of cognitive deficits. This supports the hypothesis that intermittent hypoxia causes irreversible hypoxic injury to areas of the brain such as the hippocampus and frontal cortex [15,65]. This is likely to exhibit the most extreme influence of intermittent hypoxia and sleep fragmentation [22,32,45]; and hence is likely to generate a more adverse impact including levels of oxidative stress, inflammation, intrathoracic pressure swings, reduction in slow wave sleep. Overall, this causes neuronal death with irreversible damage in the brain structure and function (Figures 1a and 1b). Consequently, the effects of PAP treatment are limited once significant neuronal death has happened. This suggests the timing of PAP treatment is imperative for prevention of irreversible damage and may be more effective as a preventative treatment for neurodegeneration when initiated early in those with OSAHS.

In support, a systematic review by Bubu et al [4] concluded PAP treatment improves attention and vigilance in OSAHS patients, but other cognitive domains such as visuospatial organisational skills and mental set-shifting performance, tend to remain impaired. Similarly, a meta-analysis by Wang et al [66] showed only attention and processing speed improved with PAP. In contrast, two meta-analyses by Olaithe and Bucks [45] and Pollicina et al [47] found an improvement in executive function with PAP treatment. Whereas Lajoie et al [55] found multiple areas of cognition improved with PAP treatment including global cognition, psychomotor speed, and executive function.

In addition, it should not be underestimated the improvement in daytime hypersomnolence when using PAP. Findings from the APPLES study showed subjective and objective improvements in sleepiness in PAP users compared to sham PAP over a 6-month period in OSAHS [44], suggesting a reduction in sleep fragmentation. Although only mild improvements in executive and frontal lobe function were observed when assessed using the Sustained Working Memory Test-Overall Mid-Day Index [2,44].

Another study showed improved cognitive function in OSAHS patients using the objective Montreal Cognitive Assessment tool. It was not specified which cognitive function was improved [50]. Although there was no improvement in subjective cognitive scores. Reassuringly, the respiratory and sleep parameters (total sleep time, sleep latency, wake after sleep onset, sleep stages, mean oxygen saturation, time spent <90%) were also associated with improved cognitive function. These observations were demonstrated over a mean of 12.2 month follow up and it is not known if other lifestyle modifications such as memory games were implemented that may also improve cognition.

Consistent with the APPLES study [44], Chong et al [51] also identified significantly improved somnolence levels in mild to moderate AD patients and OSAHS patients using PAP. These studies show that PAP improves sleep quality which may improve sleep fragmentation and cognitive impairment symptoms and possibly delay aMCI onset. This study also demonstrated that those with mild to moderate AD can tolerate PAP, and a diagnosis of AD should not deter trialling PAP treatment.

Interestingly, Dunietz et al [46] performed a retrospective study over a 2-year period using medical insurance database to identify the association between PAP usage and a diagnosis of MCI/AD in an elderly population of 53,321 people. They found that patients reported to be using PAP treatment was associated with lower odds of also possessing a diagnosis of MCI/AD. Hence PAP users were less likely to also have a diagnosis of MCI/AD. This supports a possible form of protection from using PAP treatment. However, there were potential biases in this report. In addition to the retrospective design, the data was collected through a medical insurance company. Therefore, limiting the data to a population which can afford health insurance and so excluding a key cohort such as low-income elderly individuals. Furthermore, the drive for financial reimbursement from recording effective PAP usage may also produce a bias, and consequently questions the reliability of obtaining accurate PAP usage information from medical insurance records.

This study is supported by Shieu et al [52], who performed a systematic review on the impact of PAP on developing MCI/AD. They found that 9 out of the 11 studies analysed demonstrated a protective mechanism from using PAP in the development of MCI/AD. This was suggested to result from several factors such as a delay in the development of MCI, a reduced rate of diagnosis of MCI/AD, slower decline in cognition or a slower rate of progression to AD. The progression of cognitive decline in the 2 studies that did not demonstrate PAP treatment as a protective mechanism was assessed using a variety of measures including the Trail Making Tests, and the Mini-Mental State Examination score. However, the Clinical Dementia Rating score showed a greater change in the non-adherent to PAP compared to PAP adherent participants. This highlights the impact of using different outcomes of subjective measures and the potential for misinterpretation of the efficacy of PAP treatment on cognition. In addition, half of the studies were classified as high risk or serious for bias in the results of 5 studies due to a lack of randomisation, limited control for confounders and failure to recruit to the target sample size.

A longitudinal study by Troussière et al [8] compared patients with mild to moderate AD and severe OSAHS with and without PAP treatment. They found that the progression of AD was mitigated with PAP intervention compared to those with no PAP treatment over a three-year period. This is supported in a randomised controlled trial by Cooke et al [20], an extension to the Ancoli-Israel et al [53] study. Although the sample size of this study was very small with just five patients per group, it supports the idea that PAP may be associated with improved cognitive function after 13 months of usage in patients with OSAHS and AD. Specifically, this study showed less cognitive decline in the PAP group (moderate to large effect sizes) compared to the non-PAP group, including executive functioning (effect size = 0.7); whereas the non-PAP group were reported to have deteriorated [20].

Ancoli-Israel et al [53] performed a randomised double-blind placebo-controlled trial in a similar cohort. They demonstrated no significant difference in cognitive function after a short trial period of just three weeks of PAP treatment compared to sham PAP. However, the effects of PAP treatment were almost immediate with improvements in sleep architecture demonstrated after just one night of use. Cooke et al [54] found significant alterations in sleep architecture towards normalisation, particularly in wake after sleep onset and slow wave sleep after just three weeks of treatment. This implies that improvements in cognitive impairment are not instantaneous and hence there is a need for a period to rectify the sleep architecture before cognitive changes are evident.

Furthermore, a study by Richards et al [21] using a quasi-experimental design and hence randomisation was not used, observed improvements in psychomotor/cognitive processing speed, memory, sleepiness, and daily functioning in MCI and OSAHS patients after PAP treatment for one year. This supports the hypothesis that PAP intervention may slow cognitive

decline. Interestingly, the improvements were observed at different time periods with memory and daily function at 6 months, and attention and sleepiness at 1 year; highlighting the importance of appropriate time milestones during the longitudinal follow up.

There is a similarity in the decline of neuropsychological test outcomes in AD and OSAHS, affecting memory, attention, psychomotor, executive function, and verbal and visuospatial skills [1, 5]. The most affected function is attention in those with OSAHS and is a potential catalyst for impairment in other cognitive domains including memory and executive function [3,15]. Based on findings from these studies, the effect of PAP treatment in cognitive function is still under debate as contrasting evidence has been found. These reviews highlight the heterogeneity of studies, with mostly cross-sectional methodologies, single-centre trials, short treatment follow ups, predominantly male cohorts, diverse age and OSAHS severity ranges used. Therefore, these varying methodologies need to be addressed to obtain more reproducible results.

Although these studies reveal a consensus that PAP treatment can improve cognitive impairment through improving sleep quality and nocturnal oxygenation levels in aMCI/AD patients, there are several methodological flaws. Most studies included patients with moderate to severe OSAHS this is likely to demonstrate as much of an effect as possible, and therefore omitting mild OSAHS. This may, however, be a detriment to the outcome of the results with the more severe the OSAHS, the least reversal in cognitive function potentially occurs. Interestingly, Osorio et al [19] found the age of MCI onset to be younger in those with OSAHS, and PAP treatment delayed MCI onset comparable to those with no OSAHS. This suggests that PAP treatment may have a protective influence on cognition and hence possibly more effective in younger patients over a longer period. This emphasises the importance of treating OSAHS early including those with mild OSAHS, before OSAHS severity increases, and irreversible damage in the brain is experienced [5,15,66,67].

There was also a lack of quality assurance of PAP treatment, such as reviewing interface leak, comfort, and oxygen and sleep parameters when using PAP. Suboptimal treatment can not only impair the effectiveness, but also the tolerability of PAP and ultimately the adherence [68,69]. This may dilute the potential positive effects of the treatment on intermittent hypoxia and sleep fragmentation and ultimately the impact on cognition.

In support, a retrospective study by Costa et al [17] demonstrated the impact of suboptimal PAP adherence. They compared cognition with PAP adherence after 2-12 months of usage in MCI patients with OSAHS. Despite the non-adherent group (<4 hours/night) still using PAP, the adherent group (≥4 hours/night) demonstrated significant improvements in cognition, particularly visuospatial/executive functioning. Though the cohort was not specific for aMCI and included vascular MCI and AD.

Conversely, a retrospective study by Skiba et al [7] found no difference in cognition between PAP adherent (≥6 hours/night) and non-adherent MCI patients. However, there were limitations that may explain the lack of significance including a 20-month discrepancy in the cognitive assessment between groups and the PAP cohort exhibiting higher intelligence levels. This yields to the cognitive reserve theory whereby those with a higher intelligence or IQ may provide 'protection' against cognitive decline [15,45]. This is thought to be due to possessing a larger cognitive reserve, or better compensation and hence using different areas of the brain to maintain normal function [70]. This may influence PAP effectiveness when measured using neuropsychological assessments which may not be sensitive enough to detect changes in those with higher intelligence [3].

Therefore, the lack of a standardised definition of PAP adherence is arguably the most discernible methodological discrepancy with a very wide range included. The arbitrary threshold of ≥4 hours, 70% of the nights is commonly used, but studies may also define their own criteria [17,53,56]. A complication to standardising the threshold may be that it is dependent on the outcome being measured such as memory or daytime sleepiness [56]. Overall, this limits the interpretation of findings about the effectiveness of PAP treatment on cognitive function.

For example, Troussière et al [8] deemed good adherence as >5 nights/week, whereas both Costa et al [17] and Ancoli-Israel et al [53] accepted low adherence with PAP being used just 35% and 32% of the time, respectively. The adherence was also self-reported in some studies introducing further bias [19,71]. This may dilute the effect of PAP treatment on cognitive domains and therefore hinder any conclusions that can be made on the effects of PAP intervention on cognitive impairment.

There have been two recent systematic reviews on PAP adherence [56,72]. Lajoie et al [56] determined the PAP adherence threshold and the effects of adherence level on cognition in patients with OSASHS and neurodegenerative diseases (MCI, AD, Parkinson's disease, and multiple system atrophy). Using 8 studies, the MCI and AD group demonstrated a wide range of adherence (28-61%) and overall, those with aMCI/AD typically demonstrated lower adherence [56]. Oliver et al [72] found approximately half of the participants with OSAHS and MCI/AD reached the threshold of ≥4 hours, 70% of the nights in all 5 studies included. However, in 3 out of 5 studies, a wide adherence range was reported from 3.2 to 6.3 hours per night [72]. Despite this, it was found that PAP adherence in the OSAHS population with MCI/AD did not differ to the general elderly population.

An example of a study demonstrating acceptable adherence is Richards et al [55]. They found those with aMCI were able to tolerate PAP treatment with 73% of the cohort achieving adherence of ≥4 hours for 70% of the nights. Though this level of adherence may have been higher due to the behavioural support provided throughout the study including social support and motivational enhancements which helped to reinforce the participants health related goals. The number of behavioural support sessions attended and the severe severity of OSAHS was associated with increased adherence. Nonetheless, this study has shown that adherence in this cohort is possible.

Influencing factors of the level of adherence includes the time given to adapt to treatment. Across several studies the range varied from 3 weeks to 3.3 years. Another factor is motivation to continue the treatment. For example, it has been shown that unmarried patients were more likely to abandon PAP treatment [21,56]. Finally, at what point PAP treatment is introduced to a patient with aMCI/AD should also be considered. Although Skiba et al [7] found no difference in adherence in those with and without aMCI, the APPLES study [44] and Chong et al [51] both demonstrated that those with moderate AD can tolerate PAP treatment, therefore there may come a point in the AD pathway when PAP acceptance is more difficult.

5. Limitations

Limitations of the review include the use of studies with small sample sizes, which included predominately male participants and a lack of ethnic diversity. There is an urgent need for studies where equal representation of different populations is included. This will demonstrate the full impact of PAP treatment in the general population.

Further limitations of the studies included in this review are the variability of methodologies including different adherence thresholds for PAP, and a lack of clarity in the optimisation of PAP such as leak level. Providing information on the PAP parameters will help determine PAP efficacy. There are also different follow up periods, and a mixture of qualitative and quantitative measurement tools used for cognition and sleep architecture. Finally, the different baseline severities of OSAHS and aMCI/AD selected is also present across studies. Such heterogeneity poses difficulty comparing study outcomes and the interpretation of PAP treatment on cognition.

6. Conclusion

PAP has been used for the treatment of OSAHS for several decades, and despite the compelling results of the association between OSAHS and AD, the evidence concerning PAP effectiveness in improving cognitive impairment has been varied. PAP treatment correlates well with attention and somnolent levels. PAP intervention has shown to improve sleep architecture, increase Aβ clearance and improve brain function and fluid diffusivity in OSAHS patients and in those with OSAHS and aMCI/AD.

Unfortunately, the results are often marred by methodological differences across the studies and hence the heterogeneity restricts the generalisability of the results. There is much discrepancy in the level of acceptable adherence of PAP use. In addition, the reliance on self-reported data of the adherence of PAP treatment as opposed to objective measures is less robust. The full effects of PAP treatment may also be dependent on age, OSAHS severity, when the treatment started, and aMCI/AD severity of the patient. Nonetheless, evidence implies that PAP treatment may slow aMCI/AD development and progression in patients with OSAHS.

Therefore, future research should focus on longitudinal studies to fully understand the complex relationship between OSAHS and AD neuropathology and specifically the effect of intermittent hypoxia and sleep fragmentation influence in neurodegeneration, the long-term efficacy of PAP to revert key features of AD such as the progression of cognitive decline. It is equally important to establish the optimal protocols of PAP adherence required to obtain maximum protective effect and identify the time threshold to start PAP treatment for slowing aMCI progression.

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