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RESEARCH ARTICLE

Effects of obstructive sleep apnea treatment on neurodegenerative biomarker neurofilament light chain and cognitive performance

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Summary

Obstructive sleep apnea is associated with cognitive impairment and increased risk for neurodegenerative diseases. Obstructive sleep apnea treatment with positive airway pressure therapy helps to improve cognitive symptoms and reduces long-term dementia risk. To test whether these treatment effects are due to a reduction in neuronal damage, we examined longitudinal changes in the neurodegenerative serum neurofilament light chain and cognitive performance of patients with obstructive sleep apnea. In this study, 17 patients with obstructive sleep apnea completed baseline and follow-up (9 month after starting PAP treatment) investigation of sleep, daytime symptoms, cognitive testing and serum neurofilament light chain measurements. Depending on treatment adherence and efficacy, participants were assigned either to the effective treatment ($n = 10$) or non-effective treatment group ($n = 7$). As results at baseline lower mean oxygen saturation during sleep was associated with higher serum neurofilament light chain. Patients in the non-effective treatment group showed a significant increase of age-adjusted percentile of serum neurofilament light chain levels at follow-up, whereas serum neurofilament light chain values remained constant in the effective treatment group. At a functional level, effective treatment leads to an improvement in processing speed, which was not the case in the non-effective treatment group. Longitudinal changes of age-adjusted serum neurofilament light chain levels were associated with changes in cognitive performance. To conclude, this longitudinal observational study showed that effective obstructive sleep apnea treatment positively affects the amount of neuronal damage as well as working memory performance. As cognitive symptoms might not only be attributed to obstructive sleep apnea-related sleep deficiency, but also neurodegeneration, our results underline the importance of treatment adherence and efficacy for the prevention of neuronal damage and cognitive consequences.

KEYWORDS
dementia, neurodegeneration, neurofilamant, obstructive sleep apnea, sleep disorder

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is the most common primary sleep disorder in adults, with about a billion estimated cases worldwide (Benjafield et al., 2019). Although the prevalence has significantly increased in our aging and more obese society, OSA remains largely undiagnosed and untreated (Watson, 2016).

Obstructive sleep apnea is characterized by recurrent complete or partial collapses of the upper airway during sleep, resulting in airflow reduction and either fall in blood oxygen saturation or arousal (Strollo & Rogers, 1996). This pathophysiological mechanism results in chronic intermittent hypoxia, sympathetic hyperactivity and sleep fragmentation (Kapur et al., 2017). Typical symptoms include excessive daytime sleepiness, contributing to impaired work performance, increased motor vehicle crash risk and reduced quality of life (Young et al., 2002). Moreover, untreated OSA is associated with an increased risk for cardiovascular (e.g. hypertension, heart failure and coronary heart disease), metabolic (e.g. diabetes type 2) and neurological diseases (e.g. stroke, dementia; Gagnon et al., 2014; Javaheri et al., 2017; Punjabi et al., 2009). Therefore, the consistent and effective therapy of OSA aims at both the treatment of acute concomitant symptoms and the prevention of secondary diseases. Positive airway pressure (PAP) therapy is currently the first-choice treatment of OSA, and is generally considered the most effective treatment (ET) to improve daytime sleepiness, quality of life, hypertension and cognitive performance. Adequate therapy adherence for at least 4 hr per night is commonly defined as the minimum treatment duration per night for effective therapy.

Effective OSA treatment by PAP therapy has both immediate effects on cognitive performance and long-term effects on dementia risk reduction. Improvement of sleep efficiency and consecutively daytime alertness may be an important factor for better executive function. However, PAP treatment and adherence are independently associated with lower risk for Alzheimer's dementia in older adults (Dunietz et al., 2021), also indicating a long-term effect on the pathomechanism of neurodegenerative diseases. Recently it is has been shown that PAP treatment in patients with OSA lead to improvement in cognition and global increase of glucose metabolism in ^{18}F-FDG-PET (Fernandes et al., 2022). However, it remains uncertain whether PAP therapy improves neuronal integrity and function or even counteracts neurodegeneration. The intermittent hypoxaemia and sleep fragmentation associated with OSA leads to a cascade of pathophysiological processes, including oxidative stress, systemic and neuronal inflammation, which may be responsible for neuronal damage and consequently cognitive dysfunction (Daulatzai, 2015; Douglas et al., 2010; Snyder et al., 2017; Unnikrishnan et al., 2015; Zhou et al., 2016).

Neurofilament light chain (NfL) is the most prevalent intermediate filament in neurons, and is important to maintain axonal stability. As a consequence of axonal damage, it is released into cerebrospinal fluid (CSF) and consequently blood circulation. The Single Molecule Array (SIMOA) technology allows a sensitive detection of very low NfL concentrations in blood, that highly correlate with CSF levels (Kuhle et al., 2016). Serum NfL (sNfL) levels increase in normal aging (Benkert et al., 2022); moreover, neurodegenerative diseases like Alzheimer's disease and amyotrophic lateral sclerosis are associated with strongly increased NfL levels in CSF and serum (Elmers et al., 2023; Gaiottino et al., 2013).

If OSA treatment counteracts neurodegenerative processes, this should also be evident at the level of neurodegenerative biomarkers like sNfL and cognitive performance in dependence of treatment effectiveness (efficacy and adherence). In this prospective longitudinal observational study, we examined changes in sNfL levels, cognition and subjective treatment effects in patients with OSA at time of diagnosis and after several months of treatment considering treatment efficacy and adherence.

2 | METHODS

Twenty patients with OSA initially agreed to participate in the study at the Interdisciplinary Sleep Center in Dresden. The study was approved by the local ethic committee "Ethikkommission der TU Dresden" (EK 394102018).

In our study, OSA was defined as a minimum apnea–hypopnea index (AHI) of 15 per hour. The presence of dementia and other neurodegenerative diseases was the relevant exclusion criteria at screening. For polysomnography (PSG), the standards of the American Academy of Sleep Medicine were applicated. One single rater was employed to analyse all PSG measurements.

The time of OSA diagnosis by diagnostic PSG is considered the baseline (BL). In all 20 patients, OSA treatment was initiated during a second therapeutic PSG that followed the day after the diagnosis. During PSG, the following sleep parameters were evaluated: AHI; mean oxygen saturation (O_2mean); oxygen desaturation index (ODI); arousal index; periodic limb movement index (PLM-Index); sleep efficacy (SE); relative amounts of different sleep stages (N1, N2, N3 or rapid eye movement [REM] sleep).

An interim follow-up (FU) investigation was performed 2 months after treatment start, and the final FU investigation was in a median of 9 months after treatment start (range 7.5–11 months). Assessment of adherence and effectiveness of the used therapy were evaluated via ambulant cardiorespiratory polygraphy and compliance data of PAP device at interim analysis, and via compliance data of PAP device and patient interview at the final FU investigation.

Three patients were lost or not eligible for FU. Of the remaining 17 patients, 10 patients were assessed with an ET in terms of sufficient adherence as they met both criteria, namely mean PAP use ≥ 4 hr per night and AHI < 10 per hr (according to published recommendations; Riha et al., 2023) at the final FU investigation. The others were assessed as non-effective treatment (nET), if they used the PAP device less than 4 hr per night or discontinued between 2 months and the final FU visit, although AHI was < 10 per hr during the short therapy intervals.

Serum was drawn at the day after diagnostic PSG (BL), and after 2 and 9 months. NfL levels were measured in serum using the commercially available sNfL assay for SIMOA and measured on a HD-X

Analyser (SIMOA, Quanterix, Lexington, MA, USA). Due to the post hoc group allocation based on treatment adherence, a comparable age distribution in the two groups could not be expected. Because the serum NfL value is known to increase with age, we considered it necessary to convert the absolute NfL values into age-adjusted units (percentiles). Therefore, age-adjusted measures were derived from a statistical model referring to a database of 4532 samples from control persons (Benkert et al., 2022). Age-adjusted percentile values of sNfL were calculated for each separate time point. To illustrate the longitudinal dynamics of sNfL changes as a function of treatment adherence and efficiency, the difference of the age-adjusted sNfL values between 2 and 9 months FU was calculated for each participant. At BL and FU, sleep questionnaires (Pittsburgh Sleep Quality Index [PSQI], Epworth Sleepiness Scale [ESS], Fatigue-Severity Scale [FSS], Patient Health Questionnaire-9 [PHQ-9]) were completed, and cognitive tests (Symbol Digit Modalities Test [SDMT], Montreal Cognitive Assessment Test [MoCA]) were performed. Age-, gender- and education-adjusted values were estimated for the measured

TABLE 1 BL characteristics.

	Diagnostic PSG	PSG with PAP treatment	
	n = 20	*n* = 20	
	Mean (± SD)	Mean (± SD)	*p*-Value
Demographics			
Age (years)	59.92 (11.06)		
BMI (kg/m^{-2})	30.17 (4.78)		
Gender (% female)	40.0		
PSG parameters	Naive	Treatment	
AHI (per hr)	33.04 (11.98)	10.85 (8.52)	<0.001
O_2mean (%)	92.55 (1.69)	93.80 (0.94)	<0.001
ODI (per hr)	32.62 (11.42)	10.59 (8.29)	<0.001
Arousal-Index (per hr)	26.56 (16.05)	20.65 (16.46)	0.12
PLM-Index (per hr)	29.62 (33.03)	21.76 (23.43)	0.05
SE (%)	75.82 (15.68)	76.33 (12.78)	0.96
N1 (%)	26.33 (20.20)	15.34 (12.46)	<0.01
N2 (%)	47.58 (16.47)	40.59 (12.36)	0.08
REM (%)	10.91 (6.98)	18.40 (5.74)	<0.001
N3 (%)	14.87 (11.42)	23.61 (13.15)	<0.01
Questionnaires/PUI			
PSQI	7.05 (4.42)		
ESS	7.85 (4.40)		
FSS	31.90 (17.02)		
PHQ-9	6.90 (6.57)		
PUI	5.78 (1.92)		
Cognition			
SDMT	47.42 (10.66)		
SDMT percentile (%)	27.78 (32.37)		
MoCA	27.95 (2.12)		
Neurofilament			
sNfL (pg ml^{-1})	10.16 (4.03)		
sNfL percentile (%)	41.13 (30.65)		

Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; FSS, Fatigue-Severity Scale; MoCA, Montreal Cognitive Assessment Test; N1, N2, N3, REM, relative amounts of sleep stages non-rapid eye movement (REM)-sleep 1, non-REM-sleep 2, non-REM-sleep 3 or REM-sleep; O_2mean, mean oxygen saturation; ODI, oxygen desaturation index; PAP, positive airway pressure; PHQ-9, Patient Health Questionnaire-9; PLM-Index, periodic limb movement index; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; PUI, pupillary unrest index; SDMT, Symbol Digit Modalities Test; SDMT percentile, age-, gender- and education-adjusted Symbol Digit Modalities Test; SE, sleep efficacy; sNfL, serum neurofilament light chain; sNfL percentile, age-adjusted serum neurofilament light chain.

SDMT scores referring to normative data recently published for the oral version of the SDMT (Strober et al., 2020). For these values corresponding percentile values were calculated. Additionally, the pupillary unrest index (PUI) was collected with the pupillographic sleepiness test (AMTech Pupilknowlogy GmbH, Dossenheim, Germany) to objectively measure daytime sleepiness.

Statistical analyses were performed using the IBM SPSS software (version 28.0, IBM Corporation, Armonk, NY, USA), and data were visualized using GraphPad Prism (version 8; GraphPad Software, La Jolla, CA, USA). Values are displayed as mean and standard deviation or standard error of the mean. Inter-group analyses of BL characteristics were performed using the *t*-test or chi-square test for gender differences, and in-group longitudinal analyses were performed using the paired *t*-test or ANOVA with post hoc Bonferroni test for more than two repeated measurements (sNfL levels, sNfL percentile values). Correlation analyses were performed via Spearman test. A value of $p < 0.05$ was considered as statistically significant.

3 | RESULTS

3.1 | BL characteristics

Twenty patients with 20 OSA were initially enrolled in the study. BL characteristics are displayed in Table 1. After OSA treatment initiation, significant improvements in AHI, O_2mean and ODI could be achieved. Regarding sleep parameters, an increase in the relative amounts of sleep stage N3 and REM, and a resulting decrease in the relative amounts of sleep stage N1 and N2 occurred. No changes in Arousal-Index and SE were investigated.

The overall BL sNfL level in our study was 10.2 pg ml^{-1}, which referred to an age-adjusted sNfL percentile of 41.1%. Correlation analysis between BL PSG parameters and sNfL levels revealed a negative association between sNfL level and O_2mean in sleep (Spearman $\rho = -0.535$, $p = 0.015$), but not for age-adjusted sNfL values (not shown).

There were no associations between other OSA-related sleep parameters in the diagnostic PSG (AHI, ODI, SE, relative or absolute amounts of sleep stages N1, N2, N3 or REM sleep) or questionnaire scores and BL age-adjusted sNfL percentiles.

3.2 | FU investigations

Of the 20 included patients with OSA, 17 patients were available for FU investigation after 9 months. On the basis of PAP device recordings, all patients were separated into ET ($n = 10$) and the nET group ($n = 7$). BL values were not significantly different between the two groups (Table 2).

Treatment effectiveness defined as sufficient adherence as well as normalization of AHI under PAP therapy leads to longitudinal changes in different investigated parameters (Table 3). ET led to a 38% reduction in subjective sleepiness score (BL: 9.5; FU: 5.9; $p = 0.008$) and 27% reduction in fatigue score (BL: 30.6; FU 22.2; $p = 0.026$) at FU. Patients assigned to the nET group due to poor adherence did not show any improvement of subjective daytime symptoms. (BL: 7.1; FU: 5.9; $p = 0.188$, respectively, BL: 34.9; FU: 27.0; $p = 0.145$). Objective measurement of daytime sleepiness with the pupillographic sleepiness test revealed no significant differences

TABLE 2 BL characteristics of ET and nET groups.

	ET	nET	
	$n = 10$	$n = 7$	
	Mean (± SD)	Mean (± SD)	*p*-Value
Demographics			
Age (years)	55.87 (13.77)	65.01 (4.72)	0.12
BMI (kg/m^{-2})	30.55 (5.43)	29.86 (5.01)	0.79
Gender (% female)	40.0	57.1	0.49
PSG parameters			
AHI (per hr)	31.31 (12.47)	32.16 (8.19)	0.88
O_2mean (%)	93.05 (1.17)	92.00 (1.66)	0.14
ODI (per hr)	31.94 (11.97)	31.83 (9.73)	0.98
Arousal-Index (per hr)	22.90 (15.17)	21.63 (11.35)	0.86
PLM-Index (per hr)	21.53 (24.91)	47.29 (42.76)	0.15
SE (%)	77.93 (13.49)	80.86 (12.58)	0.67
N1 (%)	23.41 (20.59)	17.53 (6.33)	0.48
N2 (%)	55.82 (17.61)	45.43 (9.83)	0.19
REM (%)	8.36 (6.05)	14.51 (8.02)	0.10
N3 (%)	12.34 (10.25)	21.80 (10.55)	0.09
Questionnaires/PUI			
PSQI	5.30 (2.75)	8.43 (5.22)	0.13
ESS	9.50 (4.45)	7.14 (3.72)	0.27
FSS	30.60 (14.68)	34.86 (21.78)	0.64
PHQ-9	6.70 (7.18)	6.14 (4.67)	0.86
PUI	5.93 (1.28)	5.94 (2.53)	0.99
Cognition			
SDMT	50.50 (7.50)	46.71 (12.65)	0.46
SDMT percentile (%)	28.17 (30.15)	32.80 (40.05)	0.79
MoCA	28.30 (2.36)	28.00 (1.83)	0.78
Neurofilament			
sNfL (pg ml^{-1})	9.25 (4.44)	11.00 (3.04)	0.38
sNfL percentile (%)	39.78 (38.73)	40.68 (20.11)	0.96

Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; ET, effective treatment; FSS, Fatigue-Severity Scale; MoCA, Montreal Cognitive Assessment Test; N1, N2, N3, REM, relative amounts of sleep stages non-rapid eye movement (REM)-sleep 1, non-REM-sleep 2, non-REM-sleep 3 or REM-sleep; nET, non-effective treatment; O_2mean, mean oxygen saturation; ODI, oxygen desaturation index; PHQ-9, Patient Health Questionnaire-9; PLM-Index, periodic limb movement index; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; PUI, pupillary unrest index; SDMT, Symbol Digit Modalities Test; SDMT percentile, age-, gender- and education-adjusted Symbol Digit Modalities Test; SE, sleep efficacy; sNfL, serum neurofilament light chain; sNfL percentile, age-adjusted serum neurofilament light chain.

TABLE 3 Results of BL and FU analyses in ET and nET groups.

	ET			nET		
	n = 10			*n* = 7		
	BL	FU		BL	FU	
	Mean (± SD)	Mean (± SD)	*p*-Value	Mean (± SD)	Mean (± SD)	*p*-Value
Questionnaires/PUI						
PSQI	5.30 (2.75)	4.10 (1.66)	0.19	8.43 (5.22)	6.57 (3.41)	0.22
ESS	9.50 (4.45)	5.90 (3.96)	0.01	7.14 (3.72)	5.86 (3.39)	0.19
FSS	30.60 (14.68)	22.20 (10.75)	0.03	34.86 (21.78)	27.00 (17.55)	0.15
PHQ-9	6.70 (7.18)	3.90 (4.01)	0.08	6.14 (4.67)	5.43 (4.08)	0.41
PUI	5.93 (1.28)	5.31 (1.82)	0.24	5.94 (2.53)	7.62 (3.73)	0.57
Cognition						
SDMT	50.50 (7.50)	55.40 (10.77)	0.02	46.71 (12.65)	48.43 (13.06)	0.12
SDMT percentile (%)	28.17 (30.15)	44.66 (33.44)	0.02	32.80 (40.05)	37.05 (42.00)	0.14
MoCA	28.30 (2.36)	28.30 (1.83)	1.00	28.00 (1.83)	27.00 (3.51)	0.52

Abbreviations: BL, baseline; ESS, Epworth Sleepiness Scale; ET, effective treatment; FSS, Fatigue-Severity Scale; FU, follow-up; MoCA, Montreal Cognitive Assessment Test; nET, non-effective treatment; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; PUI, pupillary unrest index; SDMT, Symbol Digit Modalities Test; SDMT percentile, age-, gender- and education-adjusted Symbol Digit Modalities Test.

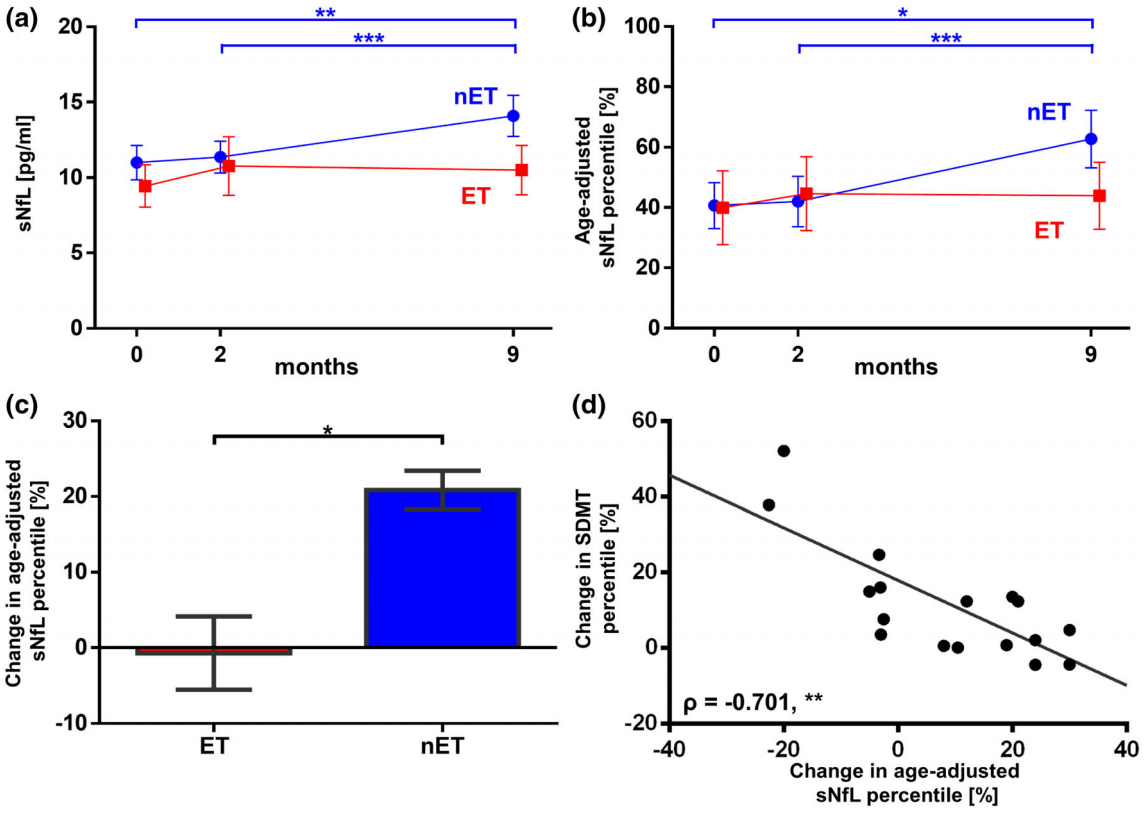

FIGURE 1 (a) Absolute serum neurofilament light chain (NfL) levels at baseline (BL; 0 months) and after 2 months and 9 months in effective treatment (ET, red) and non-effective treatment groups (nET, blue). (b) Age-adjusted serum NfL percentile values at BL (0 months) and after 2 months and 9 months in ET (red) and nET groups (blue). (c) Comparison of the absolute difference in age-adjusted serum NfL percentile values in ET (red) and nET groups (blue) between 2 and 9 months follow-up (FU). (d) Correlation analysis of the absolute difference in age-, gender- and education-adjusted Symbol Digit Modalities Test (SDMT percentile) score and age-adjusted serum NfL percentile values. Error bars indicating standard error of the mean. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

TABLE 4 Results of BL and FU sNfL analyses in ET and nET groups.

	ET			
	n = 10			
	BL	2 months	9 months	
	Mean (± SD)	Mean (± SD)	Mean (± SD)	*p*-Value
Neurofilament				
sNfL (pg ml^{-1})	9.25 (4.44)	10.57 (6.17)	10.30 (5.19)	0.347
sNfL percentile (%)	39.78 (38.73)	44.42 (38.83)	43.72 (35.12)	0.749
	nET			
	n = 7			
	BL	2 months	9 months	
	Mean (± SD)	Mean (± SD)	Mean (± SD)	*p*-Value
Neurofilament				
sNfL (pg ml^{-1})	11.00 (3.04)	11.37 (2.79)	14.10 (3.60)	<0.001
sNfL percentile (%)	40.68 (20.11)	42.00 (22.06)	62.76 (25.24)	0.002

Abbreviations: BL, baseline; ET, effective treatment; nET, non-effective treatment; sNfL, serum neurofilament light chain; sNfL percentile, age-adjusted serum neurofilament light chain.

between the two investigation time points in both groups (ET: PUI BL: 5.9, FU: 5.3, $p = 0.243$; nET: PUI BL: 5.9, FU: 7.6, $p = 0.565$), while for both groups the BL levels lay under the cut-off value of 6.6.

For sleep quality measured by PSQI and depression score evaluated by PHQ-9, no significant changes between BL and FU could be found in both groups (ET group PSQI/ PHQ-9 BL: 5.3, FU: 4.1, $p = 0.193$/BL: 6.7, FU: 3.9, $p = 0.076$; nET group PSQI; PHQ-9 BL: 8.4, FU: 6.6, $p = 0.224$/BL: 6.1, FU: 5.4, $p = 0.411$).

The biomarker analysis of absolute and age-adjusted sNfL values at BL, 2 and 9 months after initiation of PAP therapy revealed a significant increase in the nET group (sNfL: BL: 11.0 pg ml^{-1}; 2 months FU: 11.4 pg ml^{-1}; 9 months FU: 14.1 pg ml^{-1}, $p < 0.001$; sNfL percentile: BL: 40.7%; 2 months FU: 42.0%; 9 months FU: 62.8%, $p = 0.002$), while patients with effective OSA treatment showed stable sNfL levels during the observation period of 9 month (sNfL: BL: 9.3 pg ml^{-1}, 2 months FU: 10.6 pg ml^{-1}, 9 months FU: 10.3 pg ml^{-1}, $p = 0.347$; sNfL percentile: BL: 39.8%; 2 months FU: 44.4%; 9 months FU: 43.7%, $p = 0.749$; Figure 1a,b; Table 4).

Absolute changes of age-adjusted sNfL levels between 2 and 9 months follow-up differed significantly between the nET and ET groups ($p = 0.002$; Figure 1c). General cognitive performance measured by MoCA did not significantly change, but processing speed performance in the SDMT improved in patients with an effective PAP treatment but did not change when OSA treatment was ineffective (BL: 50.5, FU: 55.4, $p = 0.016$, respectively, BL: 46.7, FU: 48.4, $p = 0.119$). Even after adjusting SDMT scores for age, gender and education (SDMT percentile values), the divergent trajectories of cognitive performance in the two groups remained detectable (BL: 28.2, FU: 44.7, $p = 0.015$, respectively, BL: 32.80, FU: 37.05, $p = 0.138$).

The longitudinal dynamics of the increase of age-adjusted sNfL negatively correlated with change in age-, gender- and education-adjusted cognitive performance in terms of less sNfL increase or sNfL decrease was associated with higher improvement in processing speed and working memory (Spearman's $\rho = -0.701$, $p = 0.002$; Figure 1d).

4 | DISCUSSION

Obstructive sleep apnea has been increasingly linked to cognitive impairment and neurodegenerative diseases such as AD (Lal et al., 2022). The underlying mechanisms and the impact of ET on neurodegeneration remain largely unclear. This study aimed to evaluate neurodegeneration using the serum biomarker NfL, and to assess cognitive function in patients with OSA before and after therapy, focusing on therapy efficacy and adherence.

Serum NfL levels are highly age-dependent, and increase by a mean of 2.2% per year between the ages of 18 years and 70 years (Disanto et al., 2017). When accounting for this increase by using age-adjusted percentile values, we found that the concentrations in the OSA cohort were, with an average percentile value of 41.1%, very similar to values in the reference database of healthy controls (i.e. the 50th percentile; Benkert et al., 2022). These findings are consistent with a previous cross-sectional study that observed no significant difference in sNfL levels between normal individuals and patients with OSA. However, we observed a negative correlation between O_2mean in the naïve PSG at BL and sNfL levels, indicating that lower oxygen saturation during sleep is associated with a higher amount of neuronal damage. Even though this correlation was no longer detectable in our small cohort using the age-adjusted percentile values, the results are in line with previous findings of a positive correlation between sNfL levels and sleep time with oxygen saturation below 90% and ODI in mild and moderate–severe OSA groups (Arslan et al., 2021). This supports the hypothesis that OSA-related intermittent hypoxic stress

might contribute to neuronal damage and cognitive dysfunction (Daulatzai, 2015; Snyder et al., 2017). Recently, this interaction was investigated in a mouse model, which provided evidence that the cholinergic neurodegeneration causative for cognitive impairment is mediated by the accumulation of nuclear hypoxia inducible factor 1 alpha (Qian et al., 2022).

There were no further significant associations between other objective or subjective sleep parameters and sNfL levels at BL in our cohort. However, in patients with ongoing neurodegenerative disease like AD, NfL levels in CSF seem to be modulated by sleep quality, as relative amounts of time spent in light and deep sleep have an opposite effect on NfL levels (Targa et al., 2021). Patients with more severe changes of sleep quantity and quality like chronic insomnia have increased sNfL levels that are associated with insomniac severity and are partially reversible after ET (Zhang et al., 2018). Thus, hypoxaemia as well as disturbed sleep seem to contribute to neuronal damage at least in the presence of neurodegenerative disease or severe and chronic sleep disturbance.

In summary, the extent of neurodegeneration in OSA appears to be the result of the complex interaction between sleep disturbance and hypoxaemia.

In addition, it is important to consider that neurodegenerative diseases themselves lead to sleep disorders, so there could be a bidirectional relationship leading to a vicious cycle (Guarnieri & Sorbi, 2015).

Thirty percent to 40% of patients with OSA show nET mainly due to scarce use of PAP therapy or residual high AHI (Rotenberg et al., 2016). This prompted us to focus on how OSA therapy effectiveness affects biomarkers of neurodegeneration and cognitive performance.

Longitudinal assessment revealed that patients with non-effective PAP therapy exhibited a significant increase in absolute and age-adjusted sNfL, and we could demonstrate significant differences in the longitudinal dynamics of sNfL increase, indicating higher neuronal damage likely due to persisting sleep-related hypoxaemia and sleep disturbance. Conversely, ET demonstrated stable absolute and age-adjusted sNfL levels and improvements in age-, gender- and education-adjusted cognitive function (speed and working memory measured by SDMT). These findings highlight the positive impact of OSA treatment on cognitive dysfunction, neuronal integrity and dementia risk (Ismail et al., 2020; Lal et al., 2022).

Studies focusing on longitudinal changes and treatment effects on sNfL levels in sleep disorders are rare. One study on insomniac patients has shown a reduction of sNfL levels after adequate treatment (Zhang et al., 2018). Others investigated effects of full or partial sleep deprivation over 1 or 5 days on neurodegeneration markers including NfL in CSF or serum, but did not find any significant change (Benedict et al., 2020; Olsson et al., 2018, 2019). In contrast to other studies, we determined age-adjusted percentile values of sNfL levels using a large sample of healthy controls (Benkert et al., 2022) to account for age-related changes in absolute values as well as higher longitudinal dynamics at older ages. We here described for the first time an association between age-adjusted longitudinal changes in sNfL and cognitive performance in patients with OSA as a function of treatment effectiveness.

Because the study was designed as an observational pilot-study, relevant limitations arise. Due to the small number of participants, the statistical analyses allow rather a descriptive evaluation. Beside the small sample size, the main limitations result from the post hoc group allocation based on treatment adherence leading to inevitable unequal distribution of age and BL sleep parameters in the two groups studied, even if the differences were not statistically significantly different. However, the increase of sNfL levels in the nET group as well as group differences of longitudinal sNfL changes were also detectable when possible age effects were excluded by using age-adjusted percentile values of sNfL. For the same reason, the second observation variable, cognitive performance, was also adjusted for age, gender and education in order to minimize possible confounders. BL sleep parameters revealed a trend to more NREM 3 and REM-sleep in the nET group, which should not be responsible for the observed effect, as a higher proportion of deep and REM sleep is rather associated with lower NfL values (Targa et al., 2021; Zhang et al., 2018). In our study, evaluation of treatment efficiency was based on read-out PAP-device data, which means AHI values were achieved with different methods at BL and FU. Because PAP devices are less sensitive to detect respiratory events than PSG, we could not exclude a relevant residual OSA with certainty. However, we consider this uncertainty, which exists across both groups, to be negligible because there was no direct comparison of the AHI and therapy adherence is ultimately more decisive for the success of the therapy. With this in mind, it can even be an advantage to use criteria by which efficient and non-efficient therapies are distinguished in everyday clinical practice, to better reflect real-world situations.

5 | CONCLUSION

In conclusion, our study provides new findings supporting the importance of efficient OSA therapy in reducing disease-related neurodegeneration, as measured by the sNfL biomarker, and improving cognitive performance. Failure to adhere to or benefit from therapy may lead to increased axonal damage and higher conversion rates to dementia symptoms. Future studies with larger patient cohorts, more detailed cognitive testing and longer observation periods will contribute to a more differentiated view of individual therapy effects and the extent to which changes in sleep and cardiorespiratory parameters influence neurodegenerative biomarkers and cognitive performance.

AUTHOR CONTRIBUTIONS

Tony Sehr: Conceptualization; methodology; formal analysis; investigation; resources; writing – original draft; writing – review and editing; visualization. **Katja Akgün:** Methodology; resources; investigation; writing – review and editing. **Pascal Benkert:** Methodology; writing – review and editing; resources. **Jens Kuhle:** Writing – review and editing. **Tjalf Ziemssen:** Conceptualization; writing – review and editing; resources; methodology. **Moritz D. Brandt:** Conceptualization; resources; methodology; writing – original draft; writing – review and editing; formal analysis.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT CONSENT STATEMENT

The study participants agreed to participate in the study and gave written consent.

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