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Obstructive sleep apnea treatment, slow wave activity, and amyloid- β

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Abstract

Obstructive sleep apnea (OSA) increases risk of dementia, a relationship that may be mediated by amyloid-beta ($A\beta$) and downstream Alzheimer's Disease pathology. We previously showed OSA may impair $A\beta$ clearance and affect the relationship between slow wave activity (SWA) and $A\beta$. In this study, SWA and CSF $A\beta$ were measured in participants with OSA before and 1–4 months after treatment. OSA treatment increased SWA, and SWA was significantly correlated with lower $A\beta$ after treatment. Greater improvement in OSA was associated with greater decreases in $A\beta$. We propose a model whereby OSA treatment may affect both $A\beta$ release and clearance.

Introduction

Obstructive sleep apnea (OSA) is a highly-prevalent sleep disorder in which airway blockage during sleep causes hypoxemia, frequent arousals, and other downstream effects. OSA increases risk of dementia and cognitive decline,^{1–3} suggesting that OSA may promote Alzheimer's Disease (AD) pathogenesis. The effect of sleep on soluble amyloid- β ($A\beta$) may mechanistically link sleep disorders with AD. Sleep deprivation increases $A\beta$ levels, primarily through increased release of $A\beta$ by neurons into the interstitial fluid (ISF).^{4–5} Preliminary studies suggest slow wave activity (SWA) may modulate soluble $A\beta$: selective SWA deprivation increases $A\beta$,⁶ while partial sleep deprivation with preserved SWA does not affect $A\beta$.⁷ Cross-sectionally, in the normal population, increased SWA is associated with lower $A\beta$ levels.^{8–9} While insoluble amyloid plaques in AD exert a “sink” effect causing abnormally low soluble $A\beta$ levels,^{10,11} prior to any plaques, higher soluble $A\beta$ levels increase risk of amyloid plaque formation.¹² Herein we focus on $A\beta$ levels during mid-life prior to AD pathology, when theoretically lower $A\beta$ indicates lower risk of developing AD pathology.

We previously found SWA is decreased in moderate-to-severe OSA, yet $A\beta$ is decreased compared to people without OSA, and there is no association between $A\beta$ and SWA.⁸ Other

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groups have shown reduced SWA and abnormal dissipation of SWA overnight in mild OSA.¹³ We found that other CNS-derived proteins were decreased in the cerebrospinal fluid (CSF), suggesting there was reduced clearance from the ISF to the CSF.⁸ The glymphatic system facilitates clearance from the ISF to CSF,¹⁴ and is affected by pulsations related to respiration,¹⁵ and we hypothesized that the pressure fluctuations during apneas and secondary effects on venous drainage impede normal glymphatic clearance in OSA. Subsequently, another group has also found decreased A β levels in OSA.¹⁶ Decreased clearance of A β would lead to increased ISF A β which, over time, hypothetically increases risk of amyloid plaques and subsequent AD pathology.¹²

In this study, we examined the effect of treatment of OSA on A β and SWA.

Methods

Participants from the Saint Louis, Missouri community were included if they were age 35–65 years, had body (BMI) 18–40 kg/m², had no subjective cognitive decline, reported sleeping “about the same” or “slightly worse” in unfamiliar situations, and reported sleep periods from 8PM-midnight to 4AM-8AM. Exclusion criteria were other sleep disorders, prior OSA treatment, co-morbidities except hypertension, neuro-active medications, alcohol >14 drinks/week, and Mini-Mental Status Exam <27. Participants provided informed, written consent.

OSA:

Participants underwent a polysomnogram using standard criteria.¹⁷ Hypopneas were defined as decrease in airflow with 4% desaturation. The apnea-hypopnea index (AHI) determined whether a participant had mild OSA (AHI 5–15) or moderate-to-severe OSA (AHI 15). Participants with 15 (hour⁻¹) periodic limb movements were excluded.

Participants were provided auto-titrating PAP machines (REMstar Auto, Philips-Respironics) set at 4–20 cmH₂O. Following usage for 2 weeks, settings were changed to continuous PAP at the 90th percentile delivered pressure. For participants (N=3) with difficulty tolerating continuous PAP, the mode was reverted to auto-titrating, with the range set from the median to the 90th percentile pressures from the initial auto-titrating period. One participant sought clinical care and underwent polysomnogram for PAP titration, and continued in this study using the identified optimal PAP pressure. Participants had up to 4 months to demonstrate adherence to PAP, defined as usage 4 hours on 70% of 30 preceding nights recorded by PAP machine. Interval between polysomnograms was 1–4 months.

CSF was obtained by lumbar puncture at 9:30–10AM following polysomnograms, and A β 40, A β 42, total tau and total protein levels were assessed as previously described.⁸ Individuals (N=4) with abnormally low A β 42 levels (<608 pg/mL) indicating amyloid plaques were excluded from analyses of A β 40 or A β 42.¹⁰

SWA was quantified by electroencephalographic spectral power in the delta (0.5–4 Hz) frequencies, averaged during non-REM sleep.^{6,8}

Statistical analyses were performed with SPSS 24 (IBM). Continuous variables were compared with Student's T-tests if normally-distributed, and Mann-Whitney-U tests or Wilcoxon-Signed rank tests if not. Categorical variables were compared with Chi-squared tests. Correlations were assessed with Spearman's correlation coefficient.

Results

Of 35 participants with OSA, 18 were adherent to PAP and completed the study. OSA severity was mild in 7, and moderate-to-severe in 11. Participants were 56.9 ± 8.3 years old on average, 67% (12) were male, and 72% (13) were Caucasian. BMI was 30.4 ± 4.6 kg/m², and 28% (5) reported having hypertension. Final PAP settings were 9.2 ± 2.0 to 9.7 ± 2.2 cm H₂O. Participants used PAP for >4 hours on $88\% \pm 12\%$ of nights during the 30 days preceding the second polysomnogram, for $6:18 \pm 0:57$ hours per night. PAP treatment was effective, as shown by normalized AHI and decreased time in hypoxemia. While total sleep time and sleep efficiency did not change, SWA increased after treatment, there was shift of sleep time from light N1 sleep to deeper N3 sleep, and the frequency of arousals decreased. (Table 1)

Prior to PAP, there was no statistically significant correlation between SWA and A β that is seen in normal individuals (Figure 1A, 1C). After PAP treatment, we found a significant negative correlation between SWA and A β , whereby higher SWA is significantly correlated with lower A β (Figure 1B, 1D). Tau and total protein were not associated with SWA before or after PAP.

As a group, there was no significant change in A β with PAP treatment (Table 1). We performed correlational analyses between the degree of OSA improvement and the degree of change in A β and other proteins. We found that greater improvement in OSA was associated with greater decrease in A β 40 and A β 42 (Figure 2A-D). Additionally, we found that change in tau negatively correlated with OSA improvement, but no such relationship with total protein (Figure 2E-H). Notably, we observed that participants who had a small improvement in OSA had increases in A β 40, A β 42, and tau.

Discussion

We found that treatment of OSA was associated with increased SWA, and that after PAP treatment, there was a negative association between SWA and A β as described in normal individuals. We previously described a lack of association between SWA and A β in moderate-severe OSA,⁸ and here we found the same after including participants with mild OSA. Since our participants had objectively-confirmed high adherence to treatment for 1–4 months, we believe the elevation in SWA is sustained and not due to “first night” treatment rebound effects.¹⁸ Greater improvement in OSA was associated with more decrease in A β and tau, however participants with minimal improvement in OSA had increased A β and Tau. In combination with our prior finding that CNS-derived proteins are decreased in moderate-severe OSA,⁸ we propose a two-factor model for the relationship between OSA and A β (Figure 2I). Due to decreased SWA, there would be relatively increased release of A β into the ISF. However, as OSA severity worsens, pressure effects of obstructive respiratory events

impede the clearance of A β and tau out of the interstitial space, resulting in lower levels in the CSF, and an inverse U-shaped curve. In this model, a small improvement in OSA may result in an increase in A β or tau, whereas a larger improvement in OSA—that ameliorates both SWA and clearance mechanisms—will result in a decrease in A β and tau. The inverse U-shaped curve is expected in the lumbar CSF, while it is hypothesized that A β would be increased in the ISF for all severities of OSA.

Strengths of our study include carefully selected participants, outstanding PAP adherence at effective settings, and intra-individual analyses to maximize power. Our study is the first to examine the effect of OSA treatment on SWA and A β levels in individuals without AD. A single case report described the reversal of AD biomarkers with OSA treatment.¹⁹ We tested individuals *without* any AD pathology as assessed by CSF A β 42, a highly-sensitive biomarker of amyloid plaques.¹¹ This means our study findings can be extrapolated to the large population of people with OSA, many of whom are middle-aged or younger, and have many years to accrue benefit from AD risk reduction.

Due to the study design, untreated participants were excluded, therefore the trajectory of A β and tau in untreated OSA is unknown, nor can we determine if our findings are attributable to the “first night” effect during the first polysomnogram. Therefore we are unable to draw causal inference from our findings. Hypoxia may separately affect A β release and clearance. However, since changes in arousals, hypoxemia, and AHI were highly correlated, we could not separate any individual effects of changing these variables, particularly due to the small data set.

In summary, we found that PAP treatment for OSA was associated with increased SWA, higher SWA was correlated with lower A β , and greater improvement in OSA was associated with greater decreases in A β and tau levels. The effect of OSA on SWA and A β —and possibly tau—is a probable proximal step in a cascade whereby OSA increases the risk of AD. Furthermore, once amyloid plaques are present, OSA is associated with accelerated increase in plaque burden longitudinally.²⁰ Given the high prevalence of OSA, if the effects on A β could be mitigated with treatment, improving OSA diagnosis and treatment could potentially reduce AD risk on a broad scale.

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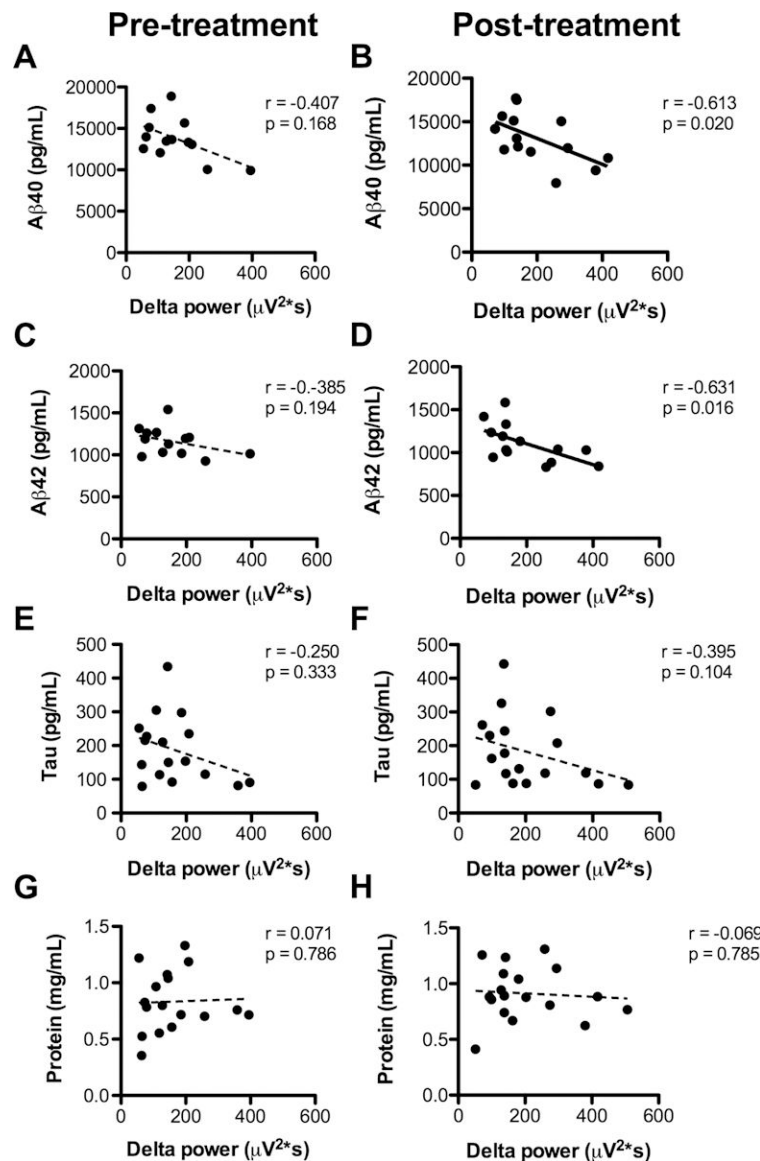


Figure 1 – Association of slow wave activity and amyloid-β

Before treatment (left column), there is no significant correlation between slow wave activity as measured by delta power, and (A) Aβ40, (C) Aβ42, (E) tau, or (G) total protein in CSF. After treatment (right column), there is a significant negative correlation between SWA and (B) Aβ40 and (D) Aβ42; there is no correlation with (F) Tau or (H) total protein. Linear regression lines are shown for illustrative purposes; since the data were not normally distributed, correlations were assessed with Spearman’s correlation coefficient ($r=\rho$) and associated p values.

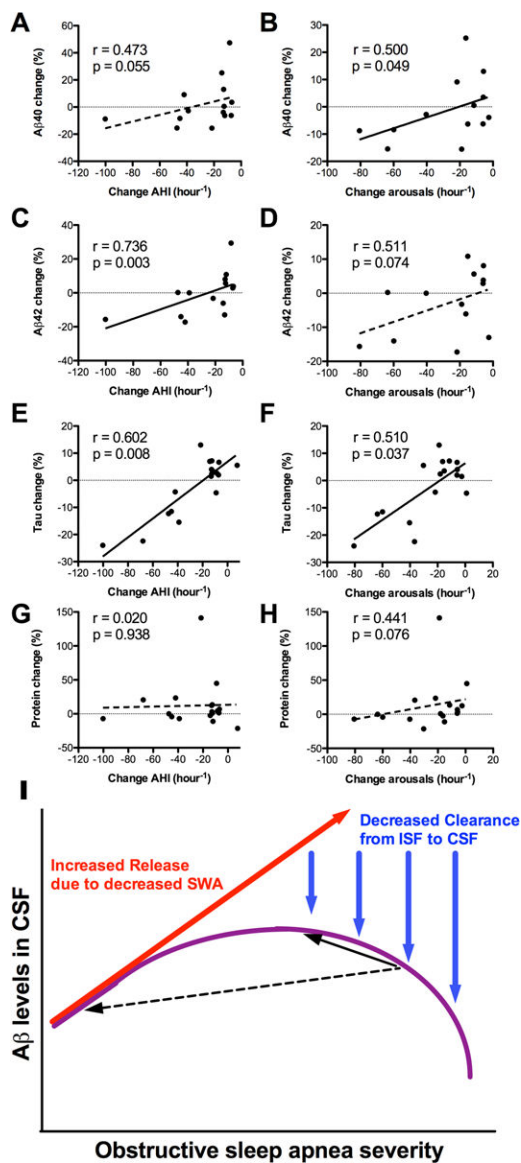


Figure 2 –. Change in amyloid-beta associated with change in OSA severity. Improvement of OSA is shown on the X-axes, with more leftward values indicating greater improvement. The graphs in the left column show change in AHI, while the graphs in the right column show change in arousals per hour. Greater improvement in OSA was associated with decreased (A,B) Aβ40, (C,D) Aβ42, and (E,F) Tau, but not (G,H) total protein. Linear regression lines are shown for illustrative purposes; since the data were not normally distributed, correlations were assessed with Spearman’s correlation coefficient (r=rho) and associated p values. (I) A schematic illustrates two interacting effects of OSA on CSF Aβ levels. With increasing arousals and sleep disruption related to OSA, SWA decreases; this leads to increased Aβ release into the interstitial space (red arrow). However, with worsening OSA severity, there is reduced glymphatic clearance from the ISF to CSF, due to abnormal pressure fluctuations during obstructive respiratory events (blue arrows). The combination of these two effects is hypothesized to result in an inverse U-shape of Aβ in the

CSF with increasing OSA severity (purple curve). The black arrows illustrate the direction of change in CSF A β following treatment of OSA. If OSA is improved a small degree (solid black arrow), CSF A β levels may increase, whereas if OSA is improved a large degree (dashed black arrow), CSF A β may decrease.

Table 1 –

Effect of PAP treatment

	Pre-treatment	Post-treatment	P value
Sleep characteristics			
Total sleep time (minutes)	377 ±69	377 ±82	0.988
Sleep efficiency (%)	78 ±13	78.7 ±15	0.956
Latency (minutes) ^a	6.5 ±17.5	12.5 ±19.3	0.306
Rapid eye movement sleep latency (minutes) ^a	76.5 ±82.3	74.5 ±63.3	0.144
Wake time after sleep onset (minutes)	81 ±46	75 ±48	0.507
Rapid eye movement sleep (minutes) [% of total sleep time] ^a	62 ±40 [16% ±7%]	79 ±25 [21% ±6%]	0.170
Non-rapid eye movement sleep (minutes) ^a	302 ±107.5	312 ±64	0.267
N1 (minutes) [% of total sleep time] ^a	48 ± 35 [12% ±12%]	22 ± 16 [6% ±5%]	0.004
N2 (minutes) [% of total sleep time]	240 ± 65 [62% ±11%]	233 ±71 [63% ±12%]	0.741
N3 (minutes) [% of total sleep time] ^a	1 ± 21 [0% ±6%]	21 ± 60 [5% ±16%]	0.005
Awakenings	7 ±4	6 ±4	0.222
OSA-related variables			
AHI ^a (hour ⁻¹)	18 ±30	1.1 ±4	<0.001
SaO2 nadir ^a	82.5% ± 8%	91% ±6%	0.001
Time with SaO2 below 90% (minutes) ^a	5.1 ±11.3	0.1 ±1.4	0.007
Arousals (hour ⁻¹)	35 ±23	10.9 ±5.0	<0.001
Spectral power			
Delta ^a	143 ±127	152 ±158	0.004
Theta ^a	11.6 ±5.5	14.5 ±9.3	0.004
Alpha ^a	6.8 ±3.1	7.2 ±5.1	0.177
Beta ^a	2.9 ±2.5	3.5 ±2.7	0.407
18–50 Hz ^a	2.6 ±1.3	6.6 ±1.8	0.093
CSF			
Aβ40 (pg/mL)	12033 ±3972	12059 ±3560	0.944
Aβ42 (pg/mL)	987 ±329	977 ±319	0.733
Tau (pg/mL)	184 ±96	182 ±102	0.602
Protein (mg/mL)	0.857 ±0.279	0.912 ±0.235	0.197

Mean ±standard deviation shown with p value for paired t-test between pre- and post-treatment conditions.

^aNot normally distributed variables. Median and interquartile range shown, and p value is for Wilcoxon Signed Rank test between pre- and post-treatment conditions.