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Sleep EEG oscillation associations with plasma amyloid-β42 in apneic adolescents: a cross section study

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Abstract Obstructive sleep apnea (OSA) is very serious and multifactorial sleep disorder in both adults and children. Growing evidence suggests some pathophysiological links between OSA and cognitive decline or Alzheimer's disease (AD). Based on associations between sleep homeostasis alteration in OSA and cognition, here we evaluated potential relationships between plasma Aβ42 levels with biophysical properties of slow wave sleep (SWS) and sleep spindles (SSs) in adolescent samples which different in weight and the presence of OSA. One-night in-lab polysomnography and morning blood collection were performed to estimate sleep EEG oscillation patterns and measure plasma Aβ42 levels. SWS was significantly negatively correlated with plasma Aβ42 in OSA patients only (with and without obesity). Despite a significant association between all SSs parameters and Aβ levels in both obese group (OSA + and OSA−) stronger correlations were observed in obese OSA + patients. So, spindle number, density and duration were positively correlated with Aβ42 levels, and spindle amplitude and frequency were negatively correlated with they. There was only one strong positive correlation between plasma amyloid and spindle number in the OSA non-obese adolescents. Altered SW and spindles activity during sleep in OSA may represent an early dysfunction related to amyloid, possibly reflecting brain damage through hypoxia and metabolic stress, or increased amyloid secretion and reduced Aβ clearance. So, SWA and SSs play important role in neuroplasticity and memory consolidation and they may represent a putative mechanism by which amyloid impairs cognition, as well as rendering it potentially new biomarkers for early neuronal dysfunction in young age.

1 Introduction

Obstructive sleep apnea (OSA) is a chronic condition characterized by repetitive collapse of the upper airway during sleep leading to intermittent hypoxemia, excessive arousals and disrupt of sleep homeostasis [1]. It prevails, particularly among middle-aged and elderly men with obesity; however, its cases in women (e.g., in menopause) as well as in individuals with normal body weight (NBW) increasingly reported [2, 3]. OSA prevalence in children is 2–4% [4], in adolescents at least 2%, and it is increasing within 24–61% in cases of obesity [5]. OSA is a heterogeneous sleep disorder with multifactorial pathophysiology [6]. Wherein the most common cause of pediatric OSA has been recognized overgrowth of the tonsils and adenoid tissue [7], while in adolescence obesity comes to the fore [5]. Unfortunately, a large percent of OSA patients remain undiagnosed and adequately untreated even in countries where this disorder is widely recognizable [8]. Wherein, without treatment OSA may lead to increased cases of cardiovascular diseases, type 2 diabetes, metabolic syndrome, strokes, and neurocognitive impairment [9, 10]. A number of large epidemiological researches have suggested some pathophysiological links between OSA and Alzheimer's disease (AD) or dementia [11, 12]. Mechanisms by which sleep disturbances may affect cognitive deficits not clear yet. Researchers has been recognized the protective role of "good" sleep, which may be critical in AD pathogenesis. It is well known, that the neuropathologic hallmark of AD is cerebral atrophy, β-amyloid (Aβ) plaques, and tau protein tangles [13]. A glymphatic system to remove potentially neurotoxic metabolic waste, e.g., Aβ, was recently described [14]. Has been shown that this system is optimized during sleep [15;16]. Authors has been shown that the level of soluble Aβ in the cerebrospinal fluid (CSF) increases during wakefulness and decreases during sleep, while

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the rate of Aβ clearance has the opposite relationship. Brain burdens of aggregated Aβ have been linked with a reduced sleep intensity, as indexed by the production of activity in 0.5–4.0 Hz frequency range occurring during NREM sleep (so called, slow waves (SW)) [17, 18]. Given the fact that Aβ accumulation plays the key role in AD pathology, sleep alteration and sleep fragmentation (disturbance in the production of SW) in OSA have lent considerable weight to contributing toward this disease. Wherein, such pathophysiologic hallmark of OSA as intermittent hypoxemia has also been associated with increased production and reduced clearance of Aβ [19–21]. It should be noted that the relationship between brain and plasma Aβ levels has been the subject of debate for many years. This protein can enter the bloodstream from the brain through the blood–brain barrier, the glymphatic system, and the blood-liquor barrier. However, there are data on the production of amyloid by platelets. The protein that enters the blood can be cleared in the periphery (in the liver, kidney, gastrointestinal tract, and skin), thereby reducing the Aβ amyloid burden. If the capacity of Aβ clearance is decreased or disturbed amyloid penetrates back into the brain tissue, and finally leading to the formation of Aβ deposits. Some authors present results confirming the similarity of amyloid levels in the periphery with its content in cerebrospinal fluid, as well as associations with the accumulation of this protein in the brain parenchyma according to positron emission tomography. In addition, a change in the plasma Aβ levels, as well as its structural organization, has been proven in patients several years before the clinical manifestation of cognitive deficit and AD [22–25]. These data suggest that the Aβ blood test can be used as a minimally invasive, affordable, cost-effective, and rapid tool for screening of cognitive decline and early AD stages as a funnel for further more invasive and expensive tests (cerebrospinal fluid assays, positron emission tomography or magnetic resonance imaging).

It is known that sleep spindles (SSs), in particular fast frequency SSs, are reduced in AD, but the mechanisms of this deficit remain unclear [26]. Cortical SSs are 11–16 Hz bursts of activity generated within the thalamo-cortical network that occur during non-rapid eye movement (NREM) sleep and have been defined as slow or fast based on their spectral frequency [27]. Sleep microstructure elements, such as SW and SS, are essential correlates of the cognitive functions of sleep, and has been linked to a better motor learning and memory consolidation [28, 29]. The spectral electroencephalographic (EEG) power as well as coupling of SS and SW has been reported to be altered in aging, and to predict overnight memory retention [30–32]. A decrease in these neuroplasticity-promoting processes could lead to the spread of dementia.

It is known that the clinical manifestation of AD usually occurs with cognitive deficits in elderly patients [33, 34]. Wherein, we found only two studies, highlighting AD-related biomarkers in OSA young children, but no adolescents [35, 36]. However, there is a significant transformation of sleep architecture associated with the ongoing reorganization of the brain through adolescence [37]. The most obvious change in the macrostructure of sleep, described by a number of authors, is a decrease in SW activity, and a shift in the SS frequency range toward fast SSs. These changes are associated with active synaptic elimination, but the remaining synapses become more complex and efficient [38]. Adolescence is characterized by the rapid development of cognitive functions, and the adolescent's brain is particularly vulnerable to developmental declines (e.g., OSA) that impact functioning through adulthood [39].

Despite the pilot study highlighted such AD-biomarker as Aβ42 in adolescence if OSA and/or obesity are present was already provided by us, further researches any associations between this specific protein and some brain patterns is absolutely needed.

Based on the above mentioned information, the aim of this cross section study was to investigate whether SS and SW activity during the sleep are associated with plasma Aβ42 levels in adolescents with different weight and OSA status. We hypothesized that in the each study group these associations will be different due to the effect of nocturnal hypoxia or altered sleep homeostasis or obesity. At the same time, the association of OSA and obesity will increase the chances of significant correlations.

2 Materials and methods

Both obese and non-obese male subjects aged 15–17 years were consecutively included in this study between October 2019 and May 2022. Study participants were recruited from patients referred to the Children's Clinic of Scientific Centre for Family Health and Human Reproduction Problems (SC FHHRP, Irkutsk, Russian Federation).

The adolescents underwent a standard screening including physical examinations, survey questionnaire, polysomnography (PSG), and laboratory tests, including Aβ42 level. Study participants required meeting the following inclusion criteria: 15 to 17 years old; zBMI $>$ 2 for to be obese; zBMI ≥ -2 to $+$ 1 for to be normal body weight (NBW); no concomitant psychiatric or neurologic diseases; no intake of sleep-promoting pills; signed informed consent. Exclusion criteria were as follows: neuromuscular diseases and craniofacial anomalies; treated OSA; overweight or underweight (zBMI $>$ $+$ 1 but $\leq$ $+$ 2 and ≤ -2, accordingly); unwillingness to participate in the study. Moreover, all patients underwent a comprehensive neuropsychological testing (but these results have not been shown in this article).

Anthropometric parameters were assessed when adolescents they underwent a screening. The standing body height was measured to the nearest 0.1 cm using a stadiometer and the body weight was measured to the nearest 0.1 kg using scales. Subjects were clothed only underwear and without shoes during the measurements. BMI was calculated as kg/m2 and further analyzed

as zBMI using the AnthroPlus calculator according by World Health Organization (WHO) references [40].

Participants completed the Adolescent Sleep Habits Survey (a previously validated questionnaire [41]) about their sleeping habits. The questionnaire consisted of questions on sleep/wake rhythms, apnea, snoring, daytime sleepiness, and some others. Returned questionnaires were entered into a computerized database and analyzed.

Both nonsnoring adolescents as well as snoring subjects were invited to the Sleep Center for an overnight PSG assessment (GRASS-TELEFACTOR Twin PSG, Comet, USA) and OSA diagnosis. The standard parameters were interpreted by a blinded sleep medicine physician, using the American Academy of Sleep Medicine (AASM) scoring rules [42]: total sleep time (TST), NREM sleep stages 1 and 2 (S1–S2), SW sleep (SWS) overnight portion and number of its episodes, REM sleep (REM) stages, arousal index (AI), AHI, and oxygen hemoglobin saturation (SaO2). OSA was determined by nocturnal PSG, performed according to AASM criteria [41]. We defined obstructive apnea as at least a 90% reduction of respiratory airflow and hypopnea as the reduction at least 30% that was associated with an arousal or oxygen desaturation of 3%. Both apnea and hypopnea must continue for 10 and more seconds. OSA was identified if AHI $\geq$ 2 n/h [43].

SSs were detected automatically on artifact free NREM epochs in F3, F4, Fz, Cz, C3, C4, O1, and O2 scalp derivations referred to linked earlobes as F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, and O2-A1. Cz was the reference and Fz was the ground. Data were bandpass filtered from 11 to 16 Hz [44]. SSs were detected as a narrow conical shape waves reaching duration criterion (at least 0.5 s). Five SSs characteristics were derived: number (total of SSs in NREM sleep, N_SSs); density (number of SSs per minutes of NREM sleep, expressed in number/minute, SSs_den); maximum amplitude (peak-to-peak difference in voltage, expressed in μV, SSs_amp); mean duration (average duration of SSs, expressed in seconds, SSs_dur), and mean frequency (number of oscillations per second, expressed in Hz, SSs_f).

The following morning after PSG all participants underwent a blood draw. Fasting blood samples were drawn by venipuncture into tubes with EDTA. Blood samples were centrifuged for 10 min at 1.500g at 4 °C, and plasma samples were stored at − 80 °C until assay. Aβ42 levels (pg/ml) were examined using commercial enzyme-linked immunosorbent assay (ELISA) kits «Amyloid-beta (1–42) High Sensitive» (IBL International GmbH, Hamburg, Germany) on the ELx808™ Absorbance Microplate Reader (BioTek Instruments, Inc., VT, USA).

This study was conducted in accordance with ethical principles of the Declaration of Helsinki (1964, ed. 2013) and the study protocol was approved by the local Ethics Biomedical Committee. Patients and controls provided their informed consent to this study.

Statistical analysis was performed using the Statistica 10.0 software (Statsoft Inc, USA). The Shapiro–Wilk (W) test was used to check for normal distribution of the screening data. One-way analysis of variance (ANOVA), Kruskal–Wallis (K-W H), chi-square, t test or Mann–Whitney (M-W U) test were used for the statistical comparisons between groups where appreciate. Data were presented as means ± standard deviation (SD) or as Me [25th; 75th percentile]. Spearman correlation testing was conducted to evaluate association between several study parameters, including plasma Aβ42 levels and SWS, N_SSs, SSs_den, SSs_amp, SSs_dur, and SSs_f. The critical significance level was taken as 5% (0.05).

3 Results

3.1 Participant characteristics

A total of 127 male adolescents were recruited in the study, and 102 of them completed all study procedures (47 participants who did not snore and had not have PSG evidence of OSA, and 55 participants who had snore as well as PSG evidence of OSA). Twenty-five participants were lost for the study: 10 adolescents had incomplete questionnaire data and/or refused PSG and/or blood testing; 15 adolescents had some sleep disorders other than OSA on PSG (habitual snoring, insomnia, restless leg syndrome, sleepwalking or/and sleep talking, sleep terrors or nightmares). In the results of all study procedures have been formed four study groups: OSA obese patients (OSA + OB, $n = 35$, mean age 16 [16;17] years), non-OSA obese patients (OB, $n = 27$, mean age 16 [15;17] years), OSA lean patients (OSA, $n = 20$, mean age 16 [16;17] years), and non-OSA lean participants (Control, $n = 20$, mean age 16[16;17] years).

According to the survey data whole sample ($n = 102$), there were 42.16% ($n = 43$) of the adolescents who showed sleep duration less than 8 h on weekdays, but there were not none on weekends. Regarding self-assessment of sleep, 43.14% ($n = 44$) of the respondents had sleep problems. There were free main reported factors that led to their emergence: poor sleep hygiene (in 30.39% of the cases, $n = 31$), psychological stress (in 18.63% of the case, $n = 19$), relationship problems with family or friends (in 16.67% of the cases, $n = 17$). It is important that 18.63% ($n = 19$) of the adolescents had a combination of these factors. Daytime dysfunction was the main respondents' complaint (in 76.47% of the cases, $n = 78$). About one-fourth of adolescents had snoring (in 23.53% of the cases, $n = 24$) and about one-tenth had sleep breathing pauses (in 9.8% of the cases, $n = 10$). There were not significant differences between the four groups in weekday/weekend total sleep time and bedtime/wake time. Whereas significant differences between groups were found in daytime dysfunction and snoring ($p = 0.002$ and $p < 0.001$, accordingly).

Table 1 shows the baseline demographic and clinical data, sleep variables with sleep spindles detection, and plasma Aβ42 levels of these groups. There was differences respect both to age and BMI between some study

Table 1 Participant's characteristics

Parameters	OSA + OB ($n = 35$) 1	OB ($n = 27$) 2	OSA ($n = 20$) 3	Control ($n = 20$) 4	p	p		
						1–2/ 3–4	1–3/ 2–4	1–4/ 2–3
Age, years	16 [16;17]	16 [15;17]	16 [16;17]	16 [16;17]	0.738	0.749 ($Z = 0.319$)/0.892 ($Z = 0.135$)	0.506 ($Z = -0.664$)/0.471 ($Z = -0.721$)	$0.536^{\#}$ ($Z = -0.472$)/ < 0.360 ($Z = -0.914$
BMI, kg/m2	34.6 ± 5.13	30.61 ± 0.85	21.66 ± 2.37	21.57 ± 1.68	0.000**	$0.00^{\#\#}$/0.89	$0.000^{\#\#}$/$0.000^{\#\#}$	$0.000^{\#\#}$/$0.000^{\#\#}$
z-BMI	2.97 [2.49;3.21]	2.5 [2.5;2.68]	0.23 [− 0.59;0.97]	0.23 [− 056;0.62]	0.000*	$0.00^{\#}$ ($Z = 3.513$)/0.482 ($Z = 0.703$	$0.000^{\#}$ ($Z = 6.115$)/$0.000^{\#}$ ($Z = 5.799$)	$0.000^{\#}$ ($Z = 6.115$)/$0.000^{\#}$ ($Z = 5.799$)
AHI, events/hour	9.27 [4.2;13.9]	1.03 [0.7;1.3]	5.71 [3.35;7.4]	0.87 [0.55;1.1]	0.000*	$0.000^{\#}$ ($Z = 6.701$)/$0.000^{\#}$ ($Z = 5.396$)	0.041 ($Z = 1.951$)/0.305 ($Z = 1.022$)	$0.000^{\#}$ ($Z = 6.115$)/$0.000^{\#}$ ($Z = -5.798$)
SaO_2 nadir, %	88.6 [88;92]	95.38 [95.0;96.0]	89.92 [88.5;92.25]	95.72 [95;96.17]	0.000*	$0.000^{\#}$ ($Z = -6.687$)/$0.000^{\#}$ ($Z = -5.248$)	$0.036^{\#}$ ($Z = -0.909$)/0.161 ($Z = -0.366$)	$0.000^{\#}$ ($Z = -6.106$)/$0.000^{\#}$ ($Z = 5.605$)
SWS, minutes	58.91 [54;65]	86.94 [84;89]	61.62 [56;65.25]	105.42 [98;113]	0.000*	$0.000^{\#}$ ($Z = -6.488$)/$0.000^{\#}$ ($Z = -5.013$)	$0.41^{\#}$ ($Z = -0.822$)/ $0.000^{\#}$ ($Z = -5.315$)	$0.000^{\#}$ ($Z = 6.115$)/$0.000^{\#}$ ($Z = -5.153$)
Number of SSs (n)	1972.83 [1786;2176]	564.48 [487;623]	1876.25 [1722;2014]	459.85 [416;511]	0.000*	$0.000^{\#}$ ($Z = 6.701$)/$0.000^{\#}$ ($Z = 4.303$)	0.124 ($Z = 1.539$)/ $0.000^{\#}$ ($Z = 5.396$)	$0.000^{\#}$ ($Z = 6.115$)/$0.000^{\#}$ ($Z = 5.799$)

Table 1 (continued)

Parameters	OSA + OB ($n = 35$) 1	OB ($n = 27$) 2	OSA ($n = 20$) 3	Control ($n = 20$) 4	p	p		
						1–2/ 3–4	1–3/ 2–4	1–4/ 2–3
SSs density (n/60 s. N2 stage)	4.57 [4.3;5]	1.31 [1.1;1;5]	4.35 [3.9;4.85]	0.99 [0.9;1.1]	0.000*	$0.000^{\#}$ ($Z = 6.701$)/$0.000^{\#}$ ($Z = 5.396$)	0.125 ($Z = 1.531$)/ $0.000^{\#}$ ($Z = 4.539$)	$0.000^{\#}$ ($Z = 6.115$)/$0.000^{\#}$ ($Z = -5.799$)
SSs maximum amplitude (μV)	19.86 [19;21]	32.7 [31.5;34]	20.42 [19;21.5]	30.87 [29.5;82]	0.000*	$0.000^{\#}$ ($Z = -6.701$)/$0.000^{\#}$ ($Z = -5.396$)	$0.139^{\#}$ ($Z = -1.461$)/ $0.002^{\#}$ ($Z = 3.131$)	$0.000^{\#}$ ($Z = -6.115$)/$0.000^{\#}$ ($Z = 5.799$)
SSs duration (s)	1.32 [0.9;1.7]	1.11 [0.7;1.5]	1.14 [0.9;1.5]	1.03 [0.6;1.4]	0.0578*	0.027 ($Z = 2.193$)/0.341 ($Z = 0.947$)	0.13 ($Z = 1.505$)/ 0.356 ($Z = 0.882$)	0.02 ($Z = 2.309$)/ < 0.721 ($Z = -0.355$)
S Ss frequency (Hz)	11.21 [11;12.1]	13.57 [13;14]	11.61 [11.1;12.5]	14.17 [13;15]	0.000*	$0.000^{\#}$ ($Z = -6.63$)/$0.000^{\#}$ ($Z = -4.923$)	0.282 ($Z = -1.058$)/ 0.031 ($Z = -2.108$)	$0.000^{\#}$ ($Z = -6.115$)/$0.000^{\#}$ ($Z = 5.067$)
Aβ42 levels, pg/ml	4.2 [3.1;5.6]	2.1 [1.2;2.9]	3.1 [2.3;4.0]	1.55 [1.2;2.1]	0.000*	$0.000^{\#}$ ($Z = 5.232$)/$0.000^{\#}$ ($Z = 4.03$)	$0.003^{\#}$ ($Z = 2.887$)/0.203 ($Z = 1.269$)	$0.000^{\#}$ ($Z = 5.881$)/$0.062^{\#}$ ($Z = -1.721$)

Data are shown as mean ± SD or Me [25%;75%]

PSG polysomnography, *OSA* obstructive sleep apnea, *OB* obesity, *BMI* body mass index, *z-BMI* z-score BMI, *AHI* apnea–hypopnea index, SaO_2 oxygen saturation, *AI* arousals index, *TST* total sleep time, *REM* rapid eyes movement sleep, *N1* stage 1 of NREM sleep, *N2* stage 2 of NREM sleep, *SWS* slow wave sleep, *SSs* sleep spindle, *N_SSs* number of SSs, *SSs_den* number of SSs per minutes of NREM sleep, *SSs_amp* maximum amplitude of SSs, *SSs_dur* mean duration of SSs, *SSs_f* mean frequency of SSs, *Aβ42* β-amyloid 42, *SD* standard deviation, *Me* median

*Kruskal–Wallis test (K–W H); $^{\#}$Mann–Whitney U Test (M-W U); **ANOVA; $^{\#\#}T$ tests

groups. Age between obese groups (OSA + OB and OB) as well as between lean groups (OSA and Control) were similar ($p = 0.89$ and $p = 0.482$, respectively). BMI and z-BMI scores were similar between lean groups only ($p = 0.082$ and $p = 0.766$, respectively. The highest BMI had boys with OSA and obesity ($p = 0.000$).

There were no significant differences between some PSG parameters in non-OSA groups (OB and Control), including AHI, SaO2 nadir, and SSs duration. Sleep architecture revealed no significant differences between the OSA + OB group and the OSA group. Nevertheless, some sleep parameters as AHI in obese OSA adolescents were significantly higher, and SaO2 nadir was significantly lower than in lean OSA participants ($Z = 1.951$, $p = 0.041$ and $Z = 0.909$, $p = 0.036$, respectively) and both non-OSA groups ($Z = 6.701$, $p = 0.000$ and $Z = 5.248$, $p = 0.000$, respectively). However, as shown in Table 1, there were significant differences between time spent in SWS, as well as between all SSs characteristics in OSA groups versus non-OSA groups ($p = 0.000$), excluding SSs duration between OSA and Control groups ($Z = 0.947$, $p = 0.341$), and between OB and OSA groups ($Z = 0.355$, $p = 0.721$, respectively). Number of SSs and SSs density progressively declined, and SSs amplitude and SSs frequency significantly increased from the OSA groups to the Control group. Differences were statistically significant between both OSA groups and the OB group and the Control group; no statistically significant differences were observed between the OSA groups with no and obesity (Table 1). It should be noted that adolescents in OSA obese group had the most alterations of macro- and microstructure of sleep than participants in other study groups.

As can be seen in Table 1, the concentration of plasma Aβ42 in adolescents with obesity and OSA was significantly higher, both in comparison with adolescents with obesity without OSA, and with lean peers with and without OSA: 4.2[3.1;5.6] pg/mL vs 2.1[1.2;2.9] pg/mL, 3.1[2.3;4.0] pg/mL, and 1.55[1.2;2.1] pg/mL ($Z = 5.232$, $p < 0.0001$; $Z = 2.887$, $p = 0.003$ and $Z = 5.881$, $p < 0.0001$, respectively). There were no significant differences in the content of plasma Aβ42 between the OB and Control groups only, although there was a tendency to increase it in obese patients without OSA ($Z = 1.721$, $p = 0.062$).

Plasma Aβ42 levels, SWS and SSs characteristics were not normally distributed (Shapiro–Wilk (W) test), therefore Spearman correlations were performed for further analysis (Table 2). The plasma Aβ42 level in OSA patients (OB + and OB−) was significant negatively correlated with SW activity during the sleep ($r = -0.373$, $p = 0.027$ and $r = -0.410$, $p = 0.042$, respectively). All SSs characteristics were significantly correlated with plasma Aβ42 level both in OSA + OB and OB groups, and despite the strong correlation in both groups, SSs activity parameters was more strongly associated ($p = 0.000$ for all parameters) with Aβ42 in OSA + OB group than in OB group ($p = 0.000$ for two values only). The correlation coefficient for plasma Aβ42 level and N_SSs only was high in OSA group ($r = 0.490$, $p = 0.028$).

4 Discussion

There are evidence suggests that sleep disruptions may increase AD-associated protein levels in CSF and/or blood prior in cognitively normal individuals yet. This is related with slowing down clearance process of potentially neurotoxic products, including Aβ42, from the brain [15, 16] that lead to an accumulation of AD-biomarkers in the neural interstitial space. Therefore, intermittent hypoxia, like that found in OSA, may trigger neural amyloidogenesis [45]. So, Jackson and colleagues found that amyloid burden was elevated in OSA patient, particularly in those with severe one, as well as was associated less time spent in stage N3 sleep (so called SWS) [46]. This fact and other growing evidences of elevated of Aβ burden [17, 18] have been linked with a reduced sleep intensity, as indexed by the production of SWA as well as alteration of spindle activity [47]. Chylinski et al. (2022) examined 100 healthy individuals in late-midlife and found that earlier occurrence of SSs on slow-depolarisation SW is associated with higher Aβ burden and is predictive of greater memory decline [48]. In our previous studies we proved alteration of sleep homeostasis and higher plasma Aβ42 levels in OSA adolescents, particularly who had obesity [49, 50], however, associations altered sleep microstructure elements, key to its mnesic function, with amyloid burden in this age group were not early considered. Current study is the first to correlate sleep oscillation-specific associations with Aβ42 burden between obese and non-obese male adolescents with polysomnographically diagnosed untreated OSA and age-matched non-OSA obese and lean controls. We found that patients in OSA + OB group had the highest SSs, SWS and amyloid alterations compared to other groups. Moreover, all SSs parameters had the highest intercorrelations as well as SSs and SW activities were most strongly associated with plasma Aβ42 levels in adolescents with OSA and obesity. There was only one strong negative correlation between plasma amyloid and spindle frequency in the OSA non-obese adolescents. As seen from the above, obesity also may trigger the cascade of pathophysiological processes (e.g., oxidative stress, neuroinflammation, increased blood–brain barrier permeability, insulin resistance) and play a role in dysregulation of spindle properties as well as changing circulating amyloid level, through to putative alter interactions between thalamic reticular, thalamo-cortical, and cortical pyramidal network, and increased transport of Aβ42 to the brain [51–53].

Overall, our results provide compelling evidence that the link between sleep EEG oscillations, Aβ burden, and OSA/obesity-related brain features, involves precise regulation and coupling of two key elements of NREM sleep, spindles and SWA. Our study does indicate, at least in male middle age adolescents that altered biophysical properties of sleep spindles (SSs)

Table 2 Analysis of correlation between plasma Aβ42 level and sleep variables (SWA and SSs) in OSA + OB, OB and OSA groups

Variable	OSA + OB group		OB group		OSA group	
	r	*P* value	*r*	*P* value	*r*	*P* value
SWS	− 0.373	0.027	− 0.001	0.997	− 0.410	0.042
N_SSs	0.729	0.000	0.649	0.000	0.490	0.028
SSs_den	0.606	0.000	0.549	0.003	0.429	0.059
SSs_amp	− 0.755	0.000	− 0.414	0.031	− 0.143	0.548
SSs_dur	0.609	0.000	0.658	0.000	0.280	0.231
SSs_f	− 0.724	0.000	− 0.414	0.032	− 0.362	0.116

OSA obstructive sleep apnea, *OB* obesity, *SWA* slow wave activity, *SWS* slow wave sleep, *SSs* sleep spindles, *N_SSs* number of SSs, *SSs_den* number of SSs per minutes of NREM sleep, *SSs_amp* maximum amplitude of SSs, *SSs_dur* mean duration of SSs, *SSs_f* mean frequency of SSs, *Aβ42* β-amyloid 42, *r* correlation coefficient

and slow wave sleep (SWS) are associated with increase of plasma Aβ42 levels if OSA is present. Altered SW and spindles activity during sleep in OSA may represent an early dysfunction related to amyloid, possibly reflecting brain damage through hypoxia and metabolic stress, or increased amyloid secretion and reduced Aβ clearance. So, SWA and SSs play important role in neuroplasticity and memory consolidation and they may represent a putative mechanism by which amyloid impairs cognition, as well as rendering it potentially new biomarkers for early neuronal dysfunction in young age.

This work was performed with the use of the equipment of Collective Research Centre "Center for the development of progressive personalized technologies for health" SC FHHRP, Irkutsk.

Author contribution statement

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by OB, IM, SB, EU, LS and LR. The first draft of the manuscript was written by OB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability statement The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Declarations

Conflict of interest No financial or non-financial interests and funding.

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