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Original Article

Sleep spindle activity correlates with implicit statistical learning consolidation in untreated obstructive sleep apnea patients

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ABSTRACT

Objective/Background: The aim of this study was to examine the relationship between overnight consolidation of implicit statistical learning with spindle frequency EEG activity and slow frequency delta power during non-rapid eye movement (NREM) sleep in obstructive sleep apnea (OSA).
Patients/Methods: Forty-seven OSA participants completed the experiment. Prior to sleep, participants performed a reaction time cover task containing hidden patterns of pictures, about which participants were not informed. After the familiarisation phase, participants underwent overnight polysomnography. 24 h after the familiarisation phase, participants performed a test phase to assess their learning of the hidden patterns, expressed as a percentage of the number of correctly identified patterns. Spindle frequency activity (SFA) and delta power (0.5–4.5 Hz), were quantified from NREM electroencephalography. Associations between statistical learning and sleep EEG, and OSA severity measures were examined.
Results: SFA in NREM sleep in frontal and central brain regions was positively correlated with statistical learning scores ($r = 0.41$ to 0.31, $p = 0.006$ to 0.044). In multiple regression, greater SFA and longer sleep onset latency were significant predictors of better statistical learning performance. Delta power and OSA severity were not significantly correlated with statistical learning.
Conclusions: These findings suggest spindle activity may serve as a marker of statistical learning capability in OSA. This work provides novel insight into how altered sleep physiology relates to consolidation of implicitly learnt information in patients with moderate to severe OSA.

1. Introduction

Sleep plays a role in consolidating explicitly learnt information for later recall [1]. Sleep spindles, and slow–wave activity (SWA), are two key electroencephalography (EEG) micro-architecture characteristics during non-rapid eye movement (NREM) sleep

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putatively involved in memory processes [2,3]. Sleep spindles are discrete waxing-and-waning EEG oscillations which occur mainly in N2 stage of NREM sleep [4,5]. Sleep spindle frequency activity (SFA) typically falls within the sigma EEG range (11–16 Hz) when using power spectral analysis to quantify EEG micro-architecture [6]. SWA is comprised of high amplitude, slow frequency EEG activity, typically quantified in the delta frequency range that occurs predominantly in slow wave sleep. Studies have consistently shown that greater sleep spindle frequency and SWA during NREM sleep are associated with improved declarative and procedural memory consolidation overnight [7].

Implicit learning is the learning of information without conscious awareness, or intention to do so. One variant of implicit learning is 'statistical learning', which refers to the brain's ability to detect statistical regularities from visual, auditory, and tactile stimuli [8,9]. This ability to extract repeated patterns allows people to categorise and segment continuous information, predict upcoming events, and develop basic mechanisms of perception and action [10,11]. Statistical learning appears to be independent of general intelligence or working memory ability [11] but relies on multiple underlying components including attention, processing speed and memory [8]. Importantly, sleep appears to consolidate statistical learning and the detection of hidden regularities [12].

An overnight sleep period between exposure to the stimuli and recognition resulted in higher levels of statistical learning compared to those who performed the test phase 30 min after exposure [13]. A longer duration of slow wave sleep (SWS) was associated with better statistical learning performance, however, no quantitative analysis of sleep EEG micro-architecture was performed [13]. Analysis of sleep EEG micro-architecture showed higher fast spindle activity (13–16 Hz) in the right hemisphere fronto-central regions during overnight sleep was associated with better statistical learning [14], however, this study did not examine SWA during NREM sleep as a possible correlate of implicit learning.

As these studies were conducted in healthy participants, the effects of sleep disorders on statistical learning are unknown. Obstructive sleep apnea (OSA) is a common sleep disorder which affects approximately 20% of the middle-aged population [15]. OSA leads to significant intermittent hypoxemia and sleep fragmentation, resulting in daytime dysfunction and cognitive impairment in some individuals [16]. In untreated OSA, there is evidence of abnormalities in NREM sleep micro-architecture, with reported deficits in sigma EEG power (sleep spindle frequency) as well as reduced SWA and altered SWA dynamics compared to controls [17]. Recent studies suggest that on a group level, OSA does not impair statistical learning compared with healthy controls [18,19]. Nevertheless, there appeared to be wide inter-individual variability in statistical learning performance within the OSA group as shown by relatively large standard deviations. While there is evidence in healthy subjects that fast sleep spindle activity partly explains the individual variability in statistical learning [14], this has not been explored in OSA, a disorder that markedly impacts sleep macro (sleep stages) and micro-architecture (EEG oscillations).

The primary aim of this study was to examine the relationship between statistical learning and SFA and SWA in NREM sleep in untreated OSA. We hypothesised that higher SFA and higher SWA in NREM sleep would correlate with better statistical learning. The secondary aim of this study was to examine the relationship between statistical learning and OSA disease severity markers such as apnea hypopnea index (AHI), lowest oxygen saturation (SpO_2%), and EEG arousal index. We hypothesised that more severe OSA severity would correlate with worse statistical learning performance. The tertiary aim of this study was an exploratory analysis of sleep macro-architecture and statistical learning. Of interest were the percent of stage N2, N3, and REM, as well as total sleep time and sleep efficiency.

2. Materials and methods

Data was analysed from patients enrolled in a larger study conducted to identify potential biomarkers of neurobehavioral dysfunction in the OSA population (NHMRC #GNT1028624). Ethics approval was granted by the Sydney Local Health District Human Research Ethics Committee (X12-0028). All participants provided written informed consent and the trial was registered on the Australian and New Zealand Clinical Trials Registry (ANZCTR No:12613001171707).

2.1. Participants

Male and female participants aged 25–65 years with screening PSG confirmed diagnosis of untreated OSA (defined by an apnea hypopnea index (AHI) $\geq$ 15/hr and 3% oxygen desaturation index (ODI) $\geq$ 10/hr) were invited to participate in the study. Participants also had to weigh less than 150 kg (the limit was for the brain MRI required for the primary study), be able to read and speak English, and perform neurobehavioral tests. Participants were either identified by treating physicians or were recruited through community advertisement. Participants with other sleep disorders or any clinically significant or uncontrolled comorbidity that required continuous medical care (eg cardiac failure, hypertension, hypercapnia, chronic obstructive pulmonary disease, type 1 diabetes) were excluded. Other exclusion criteria included: a history of head injury or psychiatric/neurological disorders, current use of CNS active medications/drugs (eg anti-depressants, anti-psychotics, opiates, antihistamines), or current heavy alcohol consumption, current shift work or irregular sleep/wake routine, or current smokers.

2.2. Study protocol

Participants attended the sleep laboratory at the Woolcock Institute of Medical Research, Sydney, Australia. Participants arrived at 5:30 pm. The statistical learning task familiarisation phase (exposure to the stimuli) occurred at 6:30pm in the evening prior to an overnight PSG. The test phase occurred at the same time in the evening 24 h later under the same conditions. All participants remained in the controlled environment of the sleep laboratory for the entire 24 h period as part of the larger trial.

2.3. Assessments

2.3.1. Statistical learning task

The statistical learning task was originally created for use in studies with child populations [20] and has subsequently been validated in studies with adults [21,22]. The statistical learning task was divided into two phases; the familiarisation phase, followed by the test phase. The stimuli were 18 cartoon-like alien pictures (see Appendix Figure A.1 for the pictures). The pictures did not resemble real-world animals, people, or popular cartoon characters. Six pictures were used only for instruction and practice. The practice alien pictures were pink in colour and different from those used in the familiarisation and test phases to ensure no unintentional priming to the statistical regularities. The pictures in the familiarisation phase were divided into four groups of triplets (ABC, DEF, GHI, and JKL; with each letter representing a different picture, see Appendix Figure A.1 for full description of the task). The statistical learning task was programmed using E-Prime (v2.0, Psychology Software Tools, Sharpsburg, PA., U.S.A.).

After the completion of the familiarisation phase, participants were told there would be no further testing involving this task. This was so participants did not unintentionally reminisce on the pictures, which potentially could have explicitly reinforced the triplet

boundaries. Participants were only informed of the test phase immediately prior to the test, ensuring participants did not attempt to explicitly remember patterns during the interceding 24 h. Immediately prior to the instructions of the test phase, participants were asked if they recognised any pattern with the pictures, and if so, to describe them. After this question, participants were informed there were hidden triplets, and were provided instructions on the test phase. Participants received a different random order for the test trials. Statistical learning was expressed as a percentage of the number of triplets the participant identified correctly (test score/64 test trials x 100).

2.3.2. Polysomnography

Full overnight PSG was conducted using Embla Titanium system (Natus, CA, USA) with an 8-h time in bed opportunity (10pm to 6am). PSG included EEG, left and right electrooculogram (EOG), chin electromyogram (EMG), electrocardiogram (ECG), nasal airflow pressure (nasal cannula), thoracic and abdominal respiratory effort, finger pulse oximetry (SpO_2%), body position, and leg EMG measurements. EEG was recorded at the following scalp positions and referenced to the contralateral mastoid: F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1, and sampled and stored at 512 Hz.

Sleep staging and scoring were performed using standardised assessment criteria by registered sleep technologists [23]. PSG recordings were exported into standardised digital European Data Format (EDF) prior for all subsequent quantitative EEG analyses.

2.4. Quantitative EEG analysis

2.4.1. EEG artefact processing

All night PSG recordings were subjected to automated EEG artefact processing. An algorithm identified and rejected artefactual EEG data at a resolution of 5-s epochs based on artefact detection threshold parameters previously validated to detect sleep EEG artefacts against artefacts manually scored by three experienced technologists (reference standard) in overnight PSGs recordings from participants with and without sleep disordered breathing [24]. In the validation study, the algorithm had a high level of accuracy of 94.3, 94.7 and 95.8% for detecting artefacts during the entire PSG, NREM sleep and REM sleep, respectively. Contaminated 5-s epochs identified as containing artefact were subsequently excluded from EEG analysis. Quantitative EEG (qEEG) measures were derived from all artefact-free sleep EEG recordings during overnight PSG.

2.4.2. Power spectral analysis

Artefact-free epochs were analysed using a standard fast Fourier transform (FFT) with a rectangular weighted window for each non-overlapping 5-s epoch of EEG for frontal (F3-M2, F4-M1) and central (C3-M2, C4-M1) channels. The absolute spectral power (μV^2) was calculated for EEG activity within 0.5–35 Hz range. Delta EEG power (0.5–4.5 Hz) was used as a measure of SWA. Spindle activity typically occurs in 11–16 Hz range [6] and based on this we calculated slow (11–13 Hz) and fast (13–16 Hz) spindle frequency activity (SFA). The EEG power for each sleep-staged epoch was calculated by averaging data from up to six artefact-free 5-s epochs of EEG that comprised that 30-s recording segment. The weighted-average spectral power within the defined frequency bands was then computed for NREM sleep stages (N2 and N3).

2.5. Statistical analysis

Forty-seven (44 males) of 58 participants enrolled in the main study completed the statistical learning task and were included in this present secondary analyses. Analyses were conducted using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Descriptive data are presented as mean ± standard deviation unless otherwise stated. All data were checked for normal distribution, and where necessary, were normalised using a $\log_{10}$ transformation. For statistical learning, a one-sample t-test with effect size was used to determine whether performance was significantly above chance level of 50%. Statistical significance was set at $\alpha = 0.05$.

Parametric correlations were performed between statistical learning test phase scores and the primary qEEG outcomes: slow and fast SFA and SWA in NREM sleep. Secondary outcomes included OSA disease severity: apnea hypopnea index (AHI, events per hour), lowest oxygen saturation (SpO_2%), and EEG arousal index (events per hour). Tertiary outcomes included PSG derived sleep macro-architecture: total sleep time (TST, mins), sleep efficiency (%), stage N2 (%), N3 (%), and REM (%) sleep.

Case-wise regression diagnostics were performed to detect any potential outliers and high leverage data points, by using Studentized Residuals for outliers, Leverage Values for extreme values, and Cook's D for highly influential values. Cases that exceeded these values were removed, and correlations were rerun. These are presented in the Appendices, Table A.1.

Post-hoc analysis using Fisher's Z-transformation was performed to determine if correlation coefficients were significantly different from each other for disease severity measures (AHI, EEG arousal index, lowest SpO_2 vs SFA, SWA).

Following the correlation analysis, backward stepwise multiple linear regression models were used to determine if spindle variables were significant predictors of statistical learning while controlling for potentially important confounders. The confounder variables were selected according to 1) variables that were considered clinically important for OSA and may influence statistical learning and, 2) variables that were significant correlates with the statistical learning outcome at $p < 0.05$. A separate set of models were also conducted to account for the level of education. As such the main models always included age, Epworth sleepiness scale (ESS), AHI, sleep onset latency, and SFA variables of interest. Models accounting for education always included age, ESS, sleep onset latency, years of education and SFA variable of interest. It important to note that only sleep onset latency and the spindle variable met the significance criteria 1 above and were significantly correlated with statistical learning outcome (both $p < 0.01$). All other predictor variables were included based on clinical significance criteria 1 above, with none significantly correlated with statistical learning at the univariate level (all $p > 0.2$) All predictor variables were log transformed if they were not normally distributed. All predictors were not correlated with one another and were tested for collinearity (tolerance and variance inflation factor (VIF) were all within normal range) to ensure this was not a problem in the final models.

3. Results

3.1. Participant characteristics and baseline polysomnography

Demographics and standard sleep study measures of the 47 participants included in this analyses are presented in Table 1. On average, participants were middle-aged, obese and had moderate to severe untreated sleep apnea. Sleep macro-architecture showed that the duration of total sleep time was 402.3 min and was comprised of 60% stage N2, 16.5% stage N3 and 19.3% stage REM sleep (see Appendices Table A.1 for full overnight polysomnography data).

3.2. Statistical learning performance

The detection of repeated pictures during the familiarisation phase was 91.6 ± 8.0% (range: 70.8–100.0%). The average performance score in the test phase of the task, which assessed the level

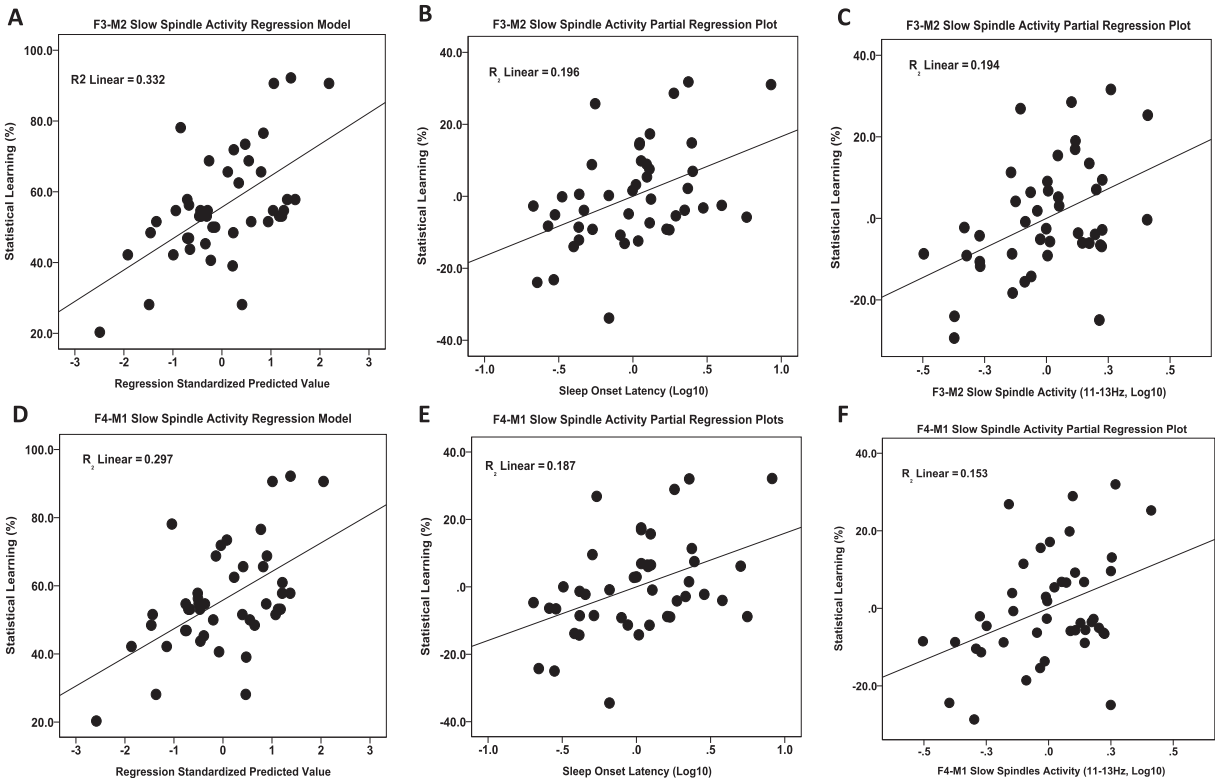

Fig. 1. Linear regression scatter plots showing the overall model summary with the regression standardised predicted value vs Statistical Learning (%) for the A - C Frontal F3-M2 and D–F Frontal F4-M1 models. Panel B, E and C, F represent the partial regression plots for the individual predictors, sleep onset latency and slow spindle activity vs statistical learning at the frontal F3-M2 and F4-M1 sites.

of implicit learning, was 55.4 ± 15.1% (range of scores: 20.3–92.2%). This was significantly above chance level ($t_{46} = 2.45$, $p = 0.018$, Cohen's $d = 0.72$). Furthermore, when asked immediately prior to the test phase, no participants reported they noticed any patterns with the order of the pictures.

3.3. Relationship between spindle frequency activity in NREM sleep and statistical learning

Of the 47 participants, sleep qEEG measures were attained in 44 participants for the frontal and central sites (see Appendices Table A.2 for NREM sleep qEEG measures). Correlation coefficients between normalised spindle activity measures in NREM sleep and statistical learning scores (test phase) are presented in Table 2. There were positive correlations between statistical learning performance and slow (11–13 Hz) spindle activity at frontal (F3 and F4) and central (C3 and C4) brain regions. Fast spindle activity (13–16 Hz) at frontal and right central (C4) regions were significantly correlated with statistical learning ($p < 0.05$), with a trend observed at C3 ($r = 0.292$ [95% CIs 0.001 to 0.537], $p = 0.054$).

Correlations repeated after removing outliers and highly influential cases identified as part of the case wise regression diagnostics did not change the results except that the trend observed with fast spindle activity at C3 became statistically significant ($r = 0.453$ [95% CIs 0.237 to 0.672], $p = 0.003$); and thus all spindle frequency activity measures at both frontal and central sites were positively correlated with statistical learning performance (see Appendices Table A.3).

3.4. Relationship between SWA in NREM sleep and statistical learning

Correlation coefficients between normalised SWA in NREM sleep and statistical learning scores (test phase) are presented in Table 2. Whilst frontal SWA demonstrated a trend for positive correlations with statistical learning performance (F3, $r = 0.264$ [-0.007 to 0.490], $p = 0.083$], no EEG sites were statistically significant.

3.5. Relationship between OSA severity metrics, polysomnography sleep macro-architecture measures and statistical learning

Correlations between statistical learning performance and OSA severity metrics, as well as PSG-derived measures of sleep macro-architecture, are presented in Table 1.

OSA severity measures (AHI, EEG arousal index, lowest SpO_2%) showed a similar direction of effect with worse severity and poorer statistical learning performance, however, none of these associations were statistically significant. Furthermore, comparisons using Fisher's transformation showed that the associations for AHI with statistical learning were significantly different than the correlations with SFA and SWA ($Z = 2.157$ to 2.605, all $p < 0.05$). Similarly, correlations between EEG arousal index and statistical learning were different than the correlations with all SFA measures at frontal derivations (F3, F4, $z = 2.149$ to 2.493, $p < 0.05$) and for SWA at F3 ($z = 1.727$, $p < 0.05$) but not F4 ($z = 1.55$, *ns*). However, the association between lowest SpO_2 and statistical learning was not different to the correlations observed for SFA measures or SWA ($p > 0.05$). Of note, for this exploratory analysis, comparisons

Table 1
Participant clinical characteristics and baseline polysomnographic measures; and Pearson's correlation coefficients between statistical learning performance and secondary and tertiary outcomes.

	Mean (SD)	Correlation with Statistical Learning	
		Pearson's correlation coefficient	p-value
Clinical measures			
Age (years)	48.8 (8.8)	0.122	0.416
Body Mass Index (kg/m^2)	30.1 (4.3)	0.016	0.912
Epworth Sleepiness Score (/24)	9.9 (4.5)	−0.087	0.562
PSG-derived OSA severity measures			
Apnea Hypopnea Index (/hr)	35.5 (22.7)	−0.054	0.721
Minimum Oxygen Saturation (Lowest SpO_2%)	81.4 (8.2)	0.084ˆ	0.575
EEG Arousal Index (/hr)	30.0 (17.9)	−0.065ˆ	0.665
PSG sleep macro architecture			
Total Sleep Time (mins)	402.3 (41.8)	−0.014ˆ	0.925
Wake After Sleep Onset (mins)	50.4 (26.5)	0.084	0.574
Sleep Efficiency (%)	87.3 (7.0)	−0.143	0.338
Sleep Onset Latency (mins)	6.1 (7.3)	0.394ˆ*	0.006
N1 Sleep (% total sleep)	4.3 (2.3)	0.026	0.863
N2 Sleep (% total sleep)	60.0 (9.8)	0.084	0.575
N3 Sleep (% total sleep)	16.5 (8.0)	0.106	0.477
REM sleep (% total sleep)	19.3 (6.1)	0.283	0.054

N = 47, *p < 0.05, ˆ indicates variables that were not normally distributed and were log transformed for the Pearson's correlational analyses.

Table 2
Correlations between spindle frequency activity and slow wave activity in NREM sleep and statistical learning during the test phase for frontal and central cortical sites. Shaded boxes highlight significant correlation (p < 0.05). Pearson's correlation coefficients (95% confidence intervals).

Brain Region	EEG site	Slow Spindle Activity (11–13 Hz)	Fast Spindle Activity (13–16 Hz)	Slow Wave Activity (delta power, 0.5–4.5 Hz)
Frontal	F3-M2 (n = 44)	r = 0.411 (0.132–0.635) p = 0.006	r = 0.353 (0.070–0.596) p = 0.019	r = 0.264 (−0.007-0.490) p = 0.083
	F4-M1 (n = 44)	r = 0.368 (0.079–0.598) p = 0.014	r = 0.347 (0.021–0.604) p = 0.021	r = 0.228 (−0.070-0.453) p = 0.136
Central	C3-M2 (n = 44)	r = 0.343 (0.068–0.593) p = 0.023	r = 0.292 (0.001–0.537) p = 0.054	r = 0.206 (−0.054-0.417) p = 0.180
	C4-M1 (n = 43)	r = 0.342 (0.048–0.573) p = 0.025	r = 0.309 (−0.009-0.588) p = 0.044	r = 0.247 (0.030–0.438) p = 0.110

between correlations were performed using SFA measures and SWA derived from frontal regions only (F3, F4).

Regarding our tertiary outcomes, there was no statistically significant associations between statistical learning and PSG-derived sleep macro-architecture measures: TST (mins), sleep efficiency (%), Stage N2 (%), Stage N3 (%), and REM (%).

3.6. Multivariate regression analysis: predictors of statistical learning performance

Table 3 and Fig. 1 shows the results of multivariate stepwise linear regression model results. All models included age, ESS, AHI, sleep onset latency, and the SFA variables of interest. The majority of the models showed that greater spindle frequency activity and longer sleep onset latency were consistently the only significant predictors of better statistical learning performance. Consistent with the univariate correlation analysis, the strongest associations were observed for the slow spindle frequency activity at the frontal electrode sites. Level of education did not make a difference to these outcomes and was not related to statistical learning performance.

4. Discussion

This study examined the relationships between implicit statistical learning and overnight sleep EEG micro-architecture and traditional PSG measures in untreated OSA. Firstly, the results of this study show that higher SFA during NREM sleep in the fronto-central brain regions was consistently correlated with better statistical learning performance. Secondly, traditional OSA severity metrics of AHI, EEG arousal index and minimum nocturnal oxygen saturation levels from overnight PSG were not associated with statistical learning performance. Importantly, correlation comparisons showed that implicit statistical learning is more strongly related to SFA than traditional severity metrics such as the AHI and EEG arousal index. Multivariate linear regression modelling accounting for important clinical confounders have consistently revealed that the two significant predictors of greater statistical learning were higher SFA and longer sleep onset latency.

Our results show that lower spindle frequency activity during NREM sleep in fronto-central brain regions was associated with poorer statistical learning consolidation in this population of untreated OSA patients. Analyses performed on all participants demonstrated slow spindle activity for all frontal and central sites, and fast spindle activity at frontal sites and at C4 were correlates of statistical learning, with a trend observed for fast spindle activity at C3 which became statistically significant after performing case wise regression diagnostics. Furthermore, significant correlations with statistical learning remained after removal of outliers and highly influential values. These data indicate an overall consistent relationship between spindle activity in frontal and central brain regions and statistical learning consolidation.

Only one study, in young, non-OSA healthy volunteers, has examined sleep spindle activity and statistical learning [14], showing higher fast spindle activity in the fronto-central region was associated with better statistical learning. Their participants received multiple exposures to the stimuli (three exposures prior to sleep), compared to only the one exposure in our study. This led to some of their participants becoming partially, and even completely, explicitly aware of the statistical regularities, which was associated with increased slow spindle activity in SWS. Thus, these results suggest that sleep spindles play an important role in learning statistical regularities, regardless of whether learning was implicit or explicit.

Table 3
Multivariate stepwise linear regression model outputs for statistical learning performance. The majority of the models showed that greater spindle frequency activity and longer sleep onset latency were consistently the only significant predictors of better statistical learning performance. All models included age, Epworth sleepiness scale score, apnea hypopnea index, lowest SpO_2%, sleep onset latency and the slow and fast spindle frequency activity at frontal and central EEG electrode placement sites.

Regression Model	Predictors	Standardised β Coefficient	t	p	Adjusted R^2
Slow Spindle Regression Models					
Frontal F3-M2	Slow Spindle Activity (11–13 Hz)	0.400	3.14	0.003	0.300
	Sleep Onset Latency	0.404	3.17	0.003	
Frontal F4-M1	Slow Spindle Activity (11–13 Hz)	0.357	2.72	0.009	0.263
	Sleep Onset Latency	0.402	3.07	0.004	
Central C3-M2	Slow Spindle Activity (11–13 Hz)	0.309	2.30	0.027	0.230
	Sleep Onset Latency	0.386	2.87	0.006	
Central C4-M1	Slow Spindle Activity (11–13 Hz)	0.314	2.32	0.025	0.235
	Sleep Onset Latency	0.395	2.92	0.006	
Fast Spindle Regression Models					
Frontal F3-M2	Fast Spindle Activity (13–16 Hz)	0.316	2.36	0.023	0.235
	Sleep Onset Latency	0.384	2.87	0.006	
Frontal F4-M1	Fast Spindle Activity (13–16 Hz)	0.306	2.27	0.29	0.227
	Sleep Onset Latency	0.379	2.81	0.008	
Central C3-M2	Sleep Onset Latency	0.413	2.94	0.005	0.151
Central C4-M1	Fast Spindle Activity (13–16 Hz)	0.258	1.86	0.071	0.201
	Sleep Onset Latency	0.382	2.73	0.009	

The correlation between statistical learning and slow and fast spindle activity in our study of untreated OSA patients is noteworthy of further discussion. The presence of two types of sleep spindles with distinct topographies has been extensively reported with slow spindles more prominent over frontal EEG regions and fast spindles occurring primarily over central and parietal regions [3,7]. Evidence also suggests different putative functional roles for fast and slow spindles with associations observed between fast spindle activity and memory performance but not slow spindles. Studies that have reported associations between memory improvement and fast spindles but not slow spindles assessed declarative [25], visuospatial [26] and procedural/motor memory [27-30]. Our results show slow and fast spindle activity was related to statistical learning, a variant of implicit learning. These discordant findings between studies may be explained by the different type of memory domains assessed. Moreover, fast spindles have been associated with increased activation of the hippocampus and motor cortical areas and are thought to be more related to thalamocortical coupling processes that underlie hippocampal-dependent memory processes than slow spindles [7]. Slower frequency spindle events have been reported in untreated OSA groups [17,31] and it is possible these events, though slower when detected at the surface level EEG recordings may maintain the same functional role as faster frequency spindles detected in healthy subjects. The prior studies assessed correlations between spindles and memory retention in small samples of typically 20–30 or less participants and may have been underpowered to detect any relationship between slow spindles and memory performance. Future larger studies that assess the strength of coupling between fast and slow spindles and slow oscillations [32], determine subject-specific frequencies for slow and fast spindle activity [33], and assess different memory domains in OSA may help elucidate these findings further.

Neuroimaging studies have also shown that the basal ganglia, in particular the striatum, is involved in statistical learning and more generalised implicit learning [34-36]. Sleep spindles are generated in the thalamo-reticular nucleus in the thalamus [37]. Importantly, the basal ganglia encapsulates the thalamus, with dense connections between the thalamus and striatum [38]. It is possible that the association between statistical learning performance and spindle activity may reflect the integrity of the thalamo-striatal connectivity. Moreover, chronic OSA appears to both physically damage the basal ganglia, via reductions in white matter, and disrupt functional connectivity [39,40]. While it is possible that OSA-induced damage to the basal ganglia is one potential mechanism which impairs statistical learning, this cannot be confirmed by the current study and further neuroimaging studies are required.

SWA was not significantly correlated to statistical learning performance in our study, however, the direction of the relationship was similar to that observed with SFA, with a trend for a positive association between frontal SWA and performance. The only other study that directly examined SWA in relation to statistical learning was conducted with 6.5 month old infants, making it very difficult to compare the results [41]. An experimental study that reduced the amount of SWA during slow wave sleep in healthy participants using auditory-induced arousals did not affect the performance of an implicit learning task the following day, but did impair declarative (explicit) memory, as well as vigilance [42]. It is possible that the consolidation of implicitly learnt information may only be sleep spindle dependent, and not SWA (0.5–4.5 Hz) dependent. Further research is needed to address this assertion, as well as the role of slow oscillations of less than 1 Hz, which was not specifically examined in our study.

This study also highlighted that longer sleep onset latency was a predictor of better statistical learning performance and sleep latency explaining approximately 15% of the variance. We speculate that shorter sleep latency would be marker of greater daytime sleepiness in an individual with OSA. There are limited studies examining the relationship between objective PSG measures of sleep architecture and statistical learning performance. In healthy volunteers, of the four studies that have examined sleep stages and timings as correlates of statistical learning performance, none assessed sleep onset latency [13,14,43,44]. Excessive sleepiness has been linked with worse neuropsychological performance in OSA, mainly poorer attention and vigilance [45], however, neither of the studies that examined statistical learning within an OSA population investigated sleepiness-based metrics as a possible correlate for the extraction of hidden statistical regularities [18,19]. Nevertheless, the results of this study suggest that sleep onset latency arguably reflecting daytime sleepiness is an important determinant of statistical learning performance in OSA.

Aside from sleep onset latency, our results showed no significant association between statistical learning and any other sleep macro-architecture measure such as N2 or N3 sleep. Whilst spindles occur primarily during stage N2 sleep, sleep spindles are also present in N3 [46]. Furthermore, there is considerable intra-individual variation in spindle activity. This implies that the amount of stage N2 sleep may not be an accurate indicator of overall spindle activity

[47]. We did not observe any relationship between the percentage of SWS (N3) and statistical learning. Previous studies have shown SWS is associated with the consolidation of auditory statistical learning [13,43,44]. Along with differences in modalities, the familiarisation phase in these studies was immediately followed by the first of two test phases, with the second test phase occurring after a nap or an overnight PSG. Whilst participants were not informed of their performance in the initial test phase, participants were made aware of a regular pattern in the stimuli, which introduced an element of explicitness into their learning. Importantly, SWS plays an important role in consolidating explicit memory [2], thus potentially explaining differences in results between our study and theirs. Other studies have utilised a visual statistical learning task known as the 'weather prediction task' (WPT) [48-51]. One study showed the amount of REM sleep during a 90-min nap was associated with improved visual statistical learning performance [48]. In contrast, another study showed the amount of SWS was strongly correlated with visual statistical learning performance, whereas stage N1 and N2 were weakly correlated. Participants in this study, however, were exposed to the WPT 14 times over seven days (once each morning and evening) [51]. Sleep variables were an average of the seven nights. Two more studies showed no correlates between visual statistical learning performance and any sleep stage [49,50]. [49]; however, had participants perform the test phase immediately after the familiarisation phase (before sleeping) and then again after overnight sleep. Interestingly, WPT learning prior to sleep correlated to the amount of REM sleep, whereas post-sleep WPT learning was not correlated to any sleep metric. Overall, the lack of similarities in correlates between our study and these studies may be explained by differences in the modalities of the tasks employed (auditory vs. visual), the presence of an immediate test phase after exposure to the stimuli, and in the healthy young vs the middle-aged clinical populations across studies.

AHI, EEG arousal index, lowest SpO_2%, were not correlated with statistical learning. Previous studies examining statistical learning in OSA patients did not examine relationships between OSA severity metrics and statistical learning, making our findings novel [18,19]. Whilst our results seemingly suggest OSA severity itself does not affect statistical learning, there is need for more research to confirm these findings, as OSA metrics have been shown to be inconsistent and unreliable correlates of the neurobehavioral deficits [52,53].

This is the first study to examine statistical learning and associations with sleep macro- and micro-architecture in patients with OSA. The study assessed statistical learning in the largest clinical group of well-characterised patients with moderate-severe OSA to date and uses routine PSG to derive quantitative EEG measures. Furthermore, it uses a validated statistical learning task to examine the relationship between implicit learning capacity and sleep micro-architecture. Limitations include the lack of healthy control comparator group and a baseline night. However, the approach used in this study attempts to explain the substantial individual variability in statistical learning capacity and how this relates to sleep EEG micro-architecture within OSA patients. Moreover, a baseline measure of statistical learning would not have been possible as this would have exposed the implicit nature of the memory task. Without a baseline night, we are not able to draw any conclusions about the direction of effect or for example, whether individuals who may already have a greater number of spindles at baseline are better at statistical learning. The timing of the testing phase of the performance task occurred 24 h after the familiarisation phase, a similar paradigm used in prior studies of statistical learning [13,21,43]. Though testing administered in the morning would have been closer temporally to the preceding sleep period, the advantages of the 24-h testing paradigm include testing at the same time of day and adjusting for the influence of circadian phase on performance, although the effect of circadian phase on implicit learning performance has yet to be explored. This study did not include discrete sleep spindle events but rather focused on EEG spectral power as a proxy of sleep spindles. Using 62 channel high-density EEG, the topographies of sigma power were consistent with spindle density and peak spindle amplitude, and sigma power profiles were more stable across nights than density measures suggesting meaningful information can be provided by spectral measures of spindle activity [33]. Moreover, automated methods to detect spindle events have the potential to miss relevant spindle activity as they rely on arbitrary thresholds for spindle identification [35,54]. Individual differences in the topography and frequency of slow and fast spindles during N2 and N3 sleep highlight the need for future studies to employ methodological approaches to identify spindles at the individual level to further our understanding of their functional role.

We showed that sleep spindle activity deficits derived from EEG signals collected during routine PSG were correlated with worse statistical learning. Shorter sleep-onset latency possibly indicating greater sleepiness was also a significant predictor of statistical learning performance. Traditional OSA severity measures derived from PSG such as the AHI were not related to cognitive outcomes. This highlights the utility of sleep EEG microarchitecture measures, to provide more sensitive markers of cognitive dysfunction than traditional metrics of disease severity in OSA.

High-density EEG during sleep may provide further insights into topographical brain activity during sleep [55] and how regional deficits in sleep EEG activity in untreated OSA [56] may relate to statistical learning processes. Discrete slow oscillations (<1 Hz) and spindle events and their coupling appear to be important for consolidation of declarative memories [57], but it is currently unclear how implicitly learnt information is governed by these dynamics and is thus an area for future work.

5. Conclusions

Sleep spindle activity derived from all-night polysomnography and sleep-onset latency were significant predictors of implicit learning performance, whereas indices of OSA disease severity were not. This work provides novel insight into how altered sleep physiology relates to consolidation of implicitly learnt information in patients with moderate to severe OSA. These findings support the use of quantitative EEG markers as stronger correlates of OSA-related cognitive deficits than traditional measures such as the AHI.

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Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.01.035.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2021.01.035.

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