The Correlation between Phase Coherence of Respiratory Sinus Arrhythmia and Slow Wave Brain Activity is Altered in Depressed patients with and without Obstructive Sleep Apnea during Sleep.

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Abstract

Phase coherence between respiratory sinus arrhythmia (RSA) and respiratory movement has been proposed to be a predicator of slow wave sleep (SWS) in healthy subjects. The aim of this study is to investigate whether this prediction is still valid on OSA patient with and without major depression disorder (MDD), and if it is not valid, how does it differ from healthy subjects. Overnight electroencephalogram (EEG), electrocardiograms (ECG), and breathing using plethysmography were recorded from control subjects (17 CONT),OSA subjects with MDD (17 OSAMDD+) and OSA subjects without MDD (17 OSAMDD-). Slow wave activity was computed by the amplitude envelope of the EEG δ-wave(0.5–4 Hz). The interbeat intervals (RRI) and respiratory movement were extracted from ECG. RRI and respiration were resampled at 10 Hz, and the band passed filtered (0.10–0.4 Hz) before the Hilbert transform was used to extract instantaneous phases of the RSA and respiration. Then the phase coherence(λ) between RSA and respiration were quantified. Using cross-correlation analysis, we found that overnight profiles of λ and δ-wave were correlated in only CONT groups, with significant cross-correlation coefficient (0.36±0.06). This coefficient correlation were significantly higher than that obtained for OSAMDD+(0.26±0.09) and OSAMDD-(0.27±0.07) groups. In addition, the fluctuation in λ precedes the δ-wave changes by 4 minutes only in Control, while such delay was lost in both OSAMDD+ and OSAMDD- groups. These results suggest that the association between λ and δ-wave has been disturbed in OSA patients. Therefore, the correlation between phase coherence (λ) and slow wave sleep can be used as trait marker for distinguishing between healthy and OSA patients.

Introduction

Obstructive sleep apnea (OSA) is a condition characterized by frequent obstructions in the upper airway during sleep, resulting in either reduced breathing or complete cessation of breathing, known as hypopnea and apnea, respectively. A metric known as the apnea-hypopnea index (AHI) is used by sleep experts and medical professionals to categorize a patient's breathing [**1**]. The AHI quantifies the number of hypopneas and apneas per hour of sleep.

OSA is often associated with other medical conditions, most notably cardiovascular complications, cognitive decline, and hypersomnia. Significantly, there is a strong connection between OSA and depression, with reported depression prevalence among OSA patients ranging from 5 to 63 percent **[2]**. Depression is another common condition, and as such, could potentially coincide with OSA, but whether that relationship is causal one way or another is a trickier question altogether.

From literature, we know that both OSA and depression have a noticeable effect on heart rate variability (HRV), the latter causing a simple reduction [3] and the former an increase due to the increased arousal due to cessation of breathing [4]. Respiratory sinus arrhythmia (RSA) is characterized by synchronicity of HRV with respiration causing a reduction in R-R intervals (RRI) in inhalation and the opposite in exhalation. It is generally associated with the high frequency (HF) component of the HRV and parasympathetic activity **[5]**.

Cardiorespiratory phase synchronization or phase coupling is becoming a large area of interest in individuals with OSA, as described in our previous work [6]. Studies also show that sleep stages play a critical role in the characterization of OSA by making use of RSA and phase coupling. Studies show that OSA patients display elevated cardiorespiratory synchronization during non-rapid eye movement (NREM) sleep in contrast to rapid eye movement (REM) sleep, possibly due to interference from higher brain regions during REM sleep **[7]**. Research into phase coherence between RSA and the respiratory system under induced mental stress has shown a positive correlation with vagal activity **[5]**. Furthermore, Phase coherence between respiratory sinus arrhythmia (RSA) and respiratory movement has been proposed to be a predicator of slow wave sleep (SWS) in healthy subjects [8].

Our main goal in this paper is to focus on a different approach of studying phase coherence to the one presented in our previous work **[6]**; in which we investigated the phase coherence between RSA and respiration in depressed patients with and without OSA

across the sleep stages. In this study, we aim to investigate the correlation between slow wave brain activity and phase coupling between RSA and respiration in OSA patients with and without major depressive disorder (MDD), and *how it differs from healthy subjects*. The goal of that is to gauge the use of this phase coherence in distinguishing between OSA patients with and without depression, and to validate the quality of our dataset compared to other works **[8]**.

2. Method

2.1. Participants and data collection

The dataset we use comprises of overnight polysomnography (PSG) from 34 individuals at the American Center for Psychiatry and Neurology (ACPN) in Abu Dhabi, 17 of which suffered from obstructive sleep apnea and major depression (class named OSAMDD+) and 17 of which suffered from obstructive sleep apnea but not major depression (class named OSAMDD). The dataset of 51 subjects was supplemented with 17 control subjects without obstructive sleep apnea or major depression from the Stanford Technology Analytics and Genomics in Sleep (STAGES) dataset **[9]**. A trained psychiatrist (VL) assessed the degree of clinical depression using the Patient Health Questionnaire-9 (PHQ-9). Total scores on the PHQ-9 range from 0 to 27, with scores of 5, 10, 15, and 20 indicating mild, moderate, moderately severe, and severe depression, respectively **[10]**. In this dataset, individuals with a PHQ-9 score of 10 or higher were classified as having major depression.

The polysomnography signals taken included ECG and piezoelectric belt-based thoracic movement signals, with data recorded at different sampling rates: 100 Hz and 10 Hz for the ACPN data and 200 Hz and 50 Hz for STAGES data.

2.2. EEG and ECG Pre-Processing

The pre-processing steps undertaken with the EEG and ECG signals were similar to those used in Nilzeki and Saitoh's work **[8]**. We begin by identifying the delta waves in the EEG by band-pass filtering the signal from 0.5-40 Hz then we compute the delta wave temporal envelope using the default analytical signal utilized by MATLAB's envelope function, and the trend was obtained by a 1 min median filter. For the ECG, we find the R-peaks and compute the durations between the successive ones to get the beat-to-beat R-R intervals (RRIs). The signal is normalized to zero-mean and a median filter is then used to remove baseline drift, and both the RRI and respiration signals were band-pass filtered from 0.1 to 0.4 Hz and resampled to 10 Hz.

2.3. Phase coupling (λ)

Both RRI and respiration were resampled at 10 Hz and high-pass-filtered at 0.1 Hz, and then, low-pass filtered at 0.4 Hz. Zero-phase digital filtering was performed in which the data was filtered in forward and reverse directions to avoid phase distortion. Hilbert transform was used to calculate instantaneous phases of the RSA [ΦRSA (tk)] and respiration [Φ RESP(tk)]. Then, time dependent phase coherence (λ) between RSA and respiration was obtained through the following equation:

$$\lambda(t_k) = \left| \frac{1}{N} \sum_{j=k-\frac{N}{2}}^{k+\frac{N}{2}} e^{-[\Phi \mathrm{RSA}\,(t_k) - \Phi\,\mathrm{RESP}(t_k)] mod\, \pi 2} \right|^2$$

where N denotes the number of data samples. The λ value is always ≤ 1. The amplitude of RSA (A_{RSA}) was calculated from the average instantaneous amplitude of oscillatory signal of RRI ($v(t)$) **[5,11].**

2.4. HRV

Continuous wavelets transform (CWT) is used to get the HRV spectrum in the high-frequency (HF, frequency range: 0.15–0.40 Hz). Normalized index of HF was also computed by HF/(Total Power) and it is trend was obtained by a 1 min median filter.

2.5. Cross-Correlation Analysis

The cross-correlation functions (CCF) for the entire night were also computed with the same signals to quantify the association between them and the delta waves. The maximum value of CCF (CCFmax) was used to assess the synchronicity or coupling between delta wave and each signal, and the time delay (Td) of the correlation was defined as the difference between the T_{CCFMax} and zero lag.

2.6. Statistical Analysis

one way analysis of variance (ANOVA) was used to check the differences in the CCFmax and Td in the inter-relationships of indices of δ-wave, λ,nHF and ARSA within and between the three groups (OSA patients with MDD (OSAMDD+), OSA patients without MDD (OSAMDD-), and healthy subjects (CONT)). When a

significant F value was obtained, Bonferroni post hoc tests were used to evaluate pairwise comparisons for the respective variables. Values of $P < 0.05$ were considered as significant.

3. Results and Discussion

Figure 1 demonstrates the analysis performed on the entire sleep profile of a subject with OSA and MDD and obtained results including R-R intervals (RRI), amplitude of RSA (ARSA), phase coupling coefficient (λ), nHF index, and δ-wave activity.

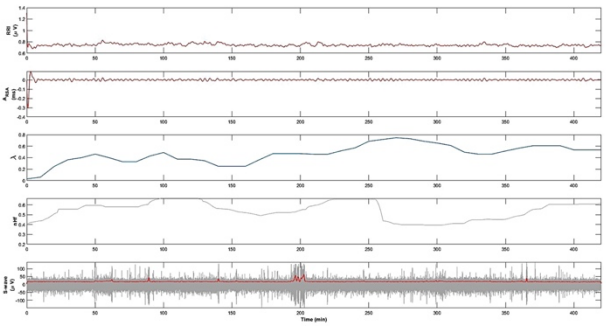

Fig.1 R-R intervals (RRI), amplitude of RSA (ARSA) , phase coupling coefficient (λ), nHF index, and δ-wave activity obtained from the analysis preformed on the entire sleep profile of a subject with OSA and MDD .

Table 1. Demographics of participants. TST (Total Sleep Time). *p<0.05 and ** p<0.01 for OSAMDD+ vs. OSAMDD-; †p<0.05 and †† p<0.01 for OSAMDD- vs Control; ¥ p<0.05 and ¥¥ p<0.01 for OSAMDD+ vs Control.

	OSAMDD+ (17)	**OSMDD- (16)**	**CONT (17)**
Gender(M/F)	**(21/19)**	**(27/13)**	**(12/26)**
Age	**33±6**	**36±12**	**31±7**
BMI (kg/m²)	**42.5±10.4**	**41.4±13.9**	**39.4±17.2**
(AHI /hour)	**24.5±14.6**	**27.6±16.7††**	**1.5±1.3¥¥**
TST(min)	**414±34**	**414±9**	**404±17**

Demographic characteristics and AHI of all subjects are shown in Table 1. Table 1 also showed no significant difference in age and BMI between the three groups, which can eliminate ageing and weight impacts on the results. In addition, Table 1 showed no significant difference on AHI between OSA patients with and without major depression, which can eliminate OSA severity impact on the results.

A comparison of the CCFmax between the groups is shown in Figure 2. The CCFmax of the δ-wave – λ and δ-wave – nHF were significantly higher ($P < 0.05$) compared to the CCFmax of the δ-wave – ARSA in the control group [Cont: 0.36±0.06, OSAMDD-: 0.26±0.09, OSAMDD +: 0.27±0.07]. This result agrees with the literature in which the correlation between δ-wave activity and phase coupling of RSA was comparable to the correlation between δ-wave activity and the normalized HF index, but significantly greater than that the correlation between δ-wave activity and amplitude of RSA [8]. However, such pattern of correlations was lost in patients with OSA. Also, it was found that the CCFmax for the relationship between δ-wave and λ was significantly reduced in both OSAMDD+ and OSAMDD- compared to the control group.

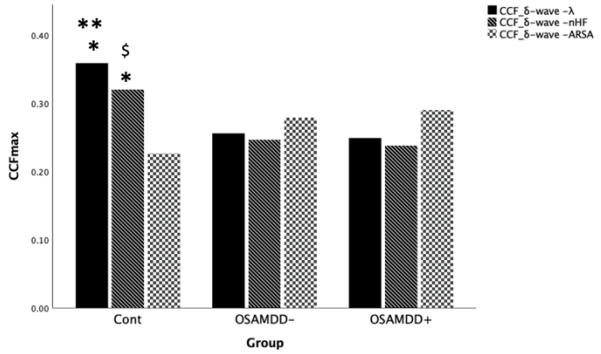

Fig. 2 Maximum values of the cross-correlation function (CCFmax) between δ-wave and λ, between δ-wave and nHF, and between δ-wave and ARSA. *P < 0.05 vs. δ-ARSA, **P < 0.05 vs. OSAMDD+ and OSAMDD-, P < 0.05 vs. OSAMDD+.

Several studies have demonstrated the cardiorespiratory synchronization in OSA patients during sleep [4,6,7]. They found that OSA patients exhibited a relatively lower cardiorespiratory synchronization than healthy individuals. This is because OSA patients are characterized with higher sympathetic activities than healthy individuals caused by repetitive cycles of apnea-hypopnea [4]. This might explain why we observed lower association between δ-wave activity and phase coupling (λ) in OSA patients.

Furthermore, Figure 2 showed that the CCFmax between δ-wave and nHF in OSAMDD+ was reduced compared to that calculated in OSMDD- and control groups [Cont: 0.32±0.07, OSAMDD-: 0.27±0.012, OSAMDD+: 0.22±0.07]. This might be due to the impact of depression in reducing the HRV [3] and cortical δ-wave activities [12]. Future investigation in the oscillatory behavior of SWS activity and nHF index signals may provide explanation of this observation in OSA patients with depression.

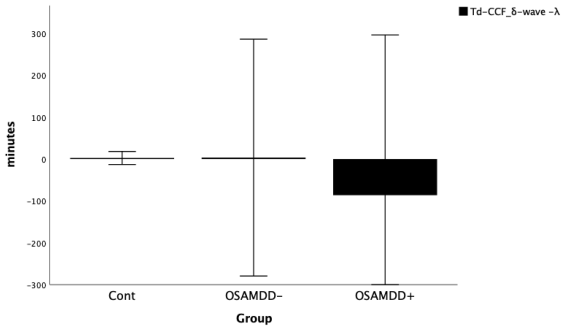

Fig. 3 Time delay (Td) of the δ-wave from the changes in λ.

Figure 3 shows that the time delay of δ-wave from the changes in the phase coupling (λ). We found that λ had a positive time delay around 4 min in control group, suggesting that the changes in EEG δ-activity lagged the

changes in the λ by 4 mins in healthy individuals. Our findings is consistent with earlier observation [8], which reported a tight temporal correlation between δ-wave and phase coherence of RSA (λ) in healthy subjects, with variation of λ preceding the onset of the δ-wave by ∼3min. It was postulated that this interaction may be mediated by the neural pathway connection between cardiovascular medullary center and thalamocortical regions. The cortical deactivation during onset of sleep lags thalamic deactivation by few minutes, suggesting that the deactivation of cerebral cortex function is necessary for falling asleep, and is preceded by thalamus deactivation. Presumably, the brainstem which regulates parasympathetic nervous function transmits a signal to thalamus neurons through ascending pathway. Then, the cortex may gradually harmonize with thalamus such that EEG activity follows cardiorespiratory pattern [13].

We also found that this delay between vagal and cortical δ-wave activities disappeared in OSA patients with Td around 13.7 ± 122 and -69.7±183 min for OSAMDD- and OSAMDD+, respectively. OSA is known to have higher sympathetic activities than healthy individuals as well as their HRV being changed, primarily with substantial increase in the VLF caused by repetitive cycles of apnea-hypopnea [4]. This may disturb the linkage between autonomic nervous activity and cortical activity and explain the absence of the delay between phase coherence ((λ) and cortical δ-wave activity in OSA patients.

In this study, we conclude that OSA syndrome could disturb the pattern of correlation between slow wave brain activity and phase coupling between RSA and respiration. We also conclude that the time delay of δ-wave from the changes in the phase coupling (λ) which existed in healthy individuals is absent in OSA patients with and without MDD. Our findings suggest that the correlation between slow wave brain activity and phase coupling between RSA and respiration could be used as a trait marker for distinguishing between OSA patients and healthy subjects. Further investigations in sleep stages and the correlation between phase coupling of RSA and SWS activity may provide useful evidence to distinguish between depressed and nondepressed OSA patients.

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