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Impact of Obstructive Sleep Apnea on Sleep-Wake Stage Ratio

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Abstract—**Patients with obstructive sleep apnea (OSA) experience fragmented sleep and exhibit different sleep architectures. While polysomnographic metrics for quantifying sleep architecture are studied, there is little information about the impact of OSA on the ratio of different sleep-wake stages (wake, W; rapid eye movement, REM; non-REM stages 1 to 3, N1 to N3). This study, therefore, aims to investigate the relationship between apnea-hypopnea index (AHI, a measure of OSA severity) and all possible ratios of sleep-wake stages. Sleep architectures of 24 adult subjects with suspected OSA were constructed according to the American Academy of Sleep Medicine scoring manual, and subsequently analyzed through various correlation (Pearson, Spearman, and Kendall) and regression (linear, logarithmic, exponential, and power-law) approaches. Results show a statistically significant positive, linear and monotonic correlation between AHI and REM/N3, as well as between AHI and N1/W (p-values < 0.05). These findings imply that patients with increased severity of OSA may spend more time in REM than deep sleep, and in light sleep than wake (or less time in deep sleep than REM, and in wake than light sleep). A power-law regression model may possibly explain the relationships of AHI–REM/N3 and AHI–N1/W, and predict the value of AHI using REM/N3 or N1/W.**

I. Introduction

Obstructive sleep apnea (OSA) is the most prevalent condition among the sleep-related breathing disorders, affecting 9–24% of men and 4–9% of women in the United States population aged 30–60 years [1]. Among them, the occurrence of OSA with daytime hypersomnolence is 4–5% and 2–3% in men and women, respectively, which is comparable to the affliction in Asian men and women ranging from 4.1–7.5% and 2.1–3.2%, respectively [2]. OSA is characterized by repetitive pharyngeal airway obstruction for at least 10 seconds, with oxyhemoglobin desaturation and heart rate reduction, despite continuous chest and abdominal movements [3]. Recurrent airway occlusion during sleep results in an augmented corrective inspiratory effort, which often triggers a transient arousal that causes sleep fragmentation and disruption to a normal pattern of sleep stages comprising of rapid eye movement (REM), non-REM (NREM) stages 1 (N1), 2 (N2), and 3 (N3). N1 and N2 can be referred to as light sleep, while N3 as deep sleep [4, 5].

Polysomnography is the gold standard for diagnosing OSA [3]. It quantifies the severity of OSA by computing the number of apneas and hypopneas per hour of sleep, known as apnea-hypopnea index (AHI), and provides quantitative measures of sleep architecture, such as sleep efficiency (ratio of total sleep time to total time in bed), REM latency (time taken from sleep onset to first epoch of REM sleep), and distribution of time spent in the four sleep stages (REM, N1, N2, and N3) [4, 5].

Bianchi *et al.* [6] found significant differences in percentages of REM, N2, and N3, but not in sleep efficiency and N1, across mild and severe OSA patients. Conversely, Ratnavadivel *et al.* [7] reported that patients with OSA had considerably more N1, lesser deep sleep, and longer REM latency than those without OSA. A higher transition frequency for wake (W)-to-REM and REM-to-W was also noted in patients with OSA [8]. While the polysomnographic metrics are used to quantify sleep architecture between apneic and benign patients, there is little information about the impact of OSA on the ratio of different sleep-wake stages. For instance, how does the severity of OSA influence the ratio of W to REM? Do patients with moderate OSA spend more, less, or equal time in N1 than N3, as compared to those with severe OSA?

This study, therefore, aims to investigate the relationship between AHI and all possible ratios of sleep-wake stages through various correlation and regression approaches. To the best of our knowledge, this is the first study to address the association of AHI and sleep-wake stage ratio. This paper is organized as follows. Section II describes the experimental setup and methods including the dataset, ratio of sleep-wake stages, correlation statistics of Pearson, Spearman, and Kendall, as well as regression models of linear, logarithmic, exponential, and power-law functions. Subsequently, results are presented in Section III and discussed in Section IV. All analysis in this study was performed within MATLAB (MathWorks, Release 2011b) unless otherwise stated.

II. Experimental Setup and Methods

A. Dataset

Sleep architectures of 24 adult subjects with suspected OSA (20 males; 4 females; mean ± standard deviation of age = 50 ± 10 years, range 28–68 years; AHI = 23.8 ± 20.6 events/h, range 2–91 events/h; body mass index = 31.7 ± 4.1 kg/m^2, range 25.1–42.5 kg/m^2), who entered all five sleep-wake stages (W, REM, N1, N2 and N3) during an overnight polysomnography (duration = 7.0 ± 0.5 h, range 5.9–7.7 h) were obtained from the St. Vincents University Hospital / University College Dublin sleep apnea database in the PhysioBank archives [9].

As the initial sleep-wake stages were scored in accordance with Rechtschaffen and Kales rules proposed in 1968 [4], we modified the stages using the recent American

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Academy of Sleep Medicine scoring manual published in 2007 [5]. The modifications made were:

- replacing Rechtschaffen and Kales nomenclature of stage 3 and stage 4 sleep with N3; and
- labeling an epoch with major body movement or muscle artifact as W.

B. *Ratio of Sleep-Wake Stages*

There are five stages of vigilance during sleep, namely W, REM, N1, N2, and N3. Given these five sleep-wake stages, 20 possible stage ratios can be derived. On equation,

$$\mathrm{R}_{xy} = E_x / E_y \quad (1)$$

is the ratio of the number of epochs scored as x to the number of epochs scored as y, where x and y are specific sleep-wake stages (W, REM, N1, N2, or N3), $E_x > 0$, $E_y > 0$, and $x \neq y$. For ease of discussion,

$$x/y = \mathrm{R}_{xy}. \quad (2)$$

For example, W/REM refers to the ratio of the number of W epochs to the number of REM epochs, which in layman's terms represents, for every duration of REM, how long there is of W.

C. *Correlation Coefficients*

To quantify the relationship between AHI and ratio of sleep-wake stages, we computed correlation coefficients of Pearson's product-moment (r_m), Spearman's rho (r_s), and Kendall's tau (t_k) [10]. r_m measures the degree of a linear association between two variables (AHI and R_{xy}, in this case), and is defined as the covariance of the two variables divided by the product of their standard deviations:

$$r_m = \frac{\mathrm{cov}(\mathrm{AHI}, \mathrm{R}_{xy})}{\sigma_{\mathrm{AHI}}\, \sigma_{\mathrm{R}xy}}. \quad (3)$$

Unlike r_m, r_s is a nonparametric measure of monotone association between two variables, given by

$$r_s = 1 - \frac{6\sum d^2}{n(n^2 - 1)} \quad (4)$$

where d is the differences between the ranks of corresponding values of AHI and R_{xy}, and n is the number of pairs of values (AHI, R_{xy}). It can be regarded as the r_m between the ranked variables.

Similar to r_s, t_k is a nonparametric measure between two variables; however, it compares the relative ordering of ranks rather than their numerical difference.

$$t_k = \frac{n_c - n_d}{\sqrt{[n(n-1)/2 - n_a][n(n-1)/2 - n_b]}} \quad (5)$$

where n_c and n_d are the number of concordant pairs and discordant pairs, respectively, whilst n_a and n_b are the number of pairs tied on AHI and R_{xy}, respectively.

Regardless of parametric or nonparametric correlation measures, r_m, r_s and t_k fall in the range of -1 and +1, where the negative or positive sign indicates a negative or positive association, respectively, together with the magnitude reflecting the strength of association. A correlation coefficient of zero indicates no systematic co-varying exists between the two variables [10]. In this study, we considered a p-value below 0.05 as statistically significant.

D. *Regression Models*

Besides quantifying the direction and magnitude of association between AHI and ratio of sleep-wake stages, we attempted to identify the relationship between AHI (dependent variable) and sleep-wake stage ratio (R_{xy}, independent variable) through fitting the scatter plot of AHI versus stage ratio using regression models with linear and nonlinear functional forms:

- linear, $\mathrm{AHI} = a\,(\mathrm{R}_{xy}) + b$
- logarithmic, $\mathrm{AHI} = a + b \log(\mathrm{R}_{xy})$
- exponential, $\log(\mathrm{AHI}) = a + b\,(\mathrm{R}_{xy})$
- power-law, $\log(\mathrm{AHI}) = a + b \log(\mathrm{R}_{xy})$

where a and b are constants, and log refers to logarithm function with base 10.

Goodness-of-fit statistics, in terms of coefficient of determination (R^2) and residual standard deviation (RSD), were also computed to determine if the regression model is satisfactory [11]. R^2 calculates the proportion of variance in AHI that is predictable from stage ratio, while RSD calculates the standard deviation of the differences between the observed and predicted AHI values. The value of R^2 ranges from 0 to 1, which signifies the extent to which AHI is predictable from stage ratio. $R^2 = 0$ means AHI cannot be predicted, whereas $R^2 = 1$ means AHI can be predicted with no errors.

III. Results

A. *Correlation Analysis*

Table I summarizes the correlation statistics of Pearson, Spearman, and Kendall between AHI and ratio of sleep-wake stages. Four out of 20 stage ratios have statistically significant linear and monotonic relationship with AHI (p-values < 0.05); they are REM/N3 (r_m = 0.7118, r_s = 0.6186, t_k = 0.4571), N1/W (r_m = 0.5061, r_s = 0.4506, t_k = 0.3254), N3/REM (r_m = -0.4640, r_s = -0.6186, t_k = -0.4571), and W/N1 (r_m = -0.4550, r_s = -0.4506, t_k = -0.3254). REM/N3 and N1/W exhibit positive association with AHI, being stronger in the former than in the latter, whereas N3/REM and W/N1 exhibit negative association with AHI.

In contrast, W/N3, N1/REM, N1/N2, N1/N3, and N2/N3 possess only significant linear relation, while REM/N2 and N2/REM possess only significant monotonic relation. The remaining nine stage ratios (W/REM, W/N2, REM/W, REM/N1, N2/W, N2/N1, N3/W, N3/N1, N3/N2) have no significant relation with AHI (p-values ≥ 0.05).

TABLE I. CORRELATION COEFFICIENTS BETWEEN APNEA-HYPOPNEA INDEX AND SLEEP-WAKE STAGE RATIO

Stage Ratio	Correlation Coefficient		
	r_m	r_s	t_k
W/REM	-0.2921	-0.3783	-0.2815
W/N1	-0.4550*	-0.4506*	-0.3254*
W/N2	0.0224	-0.1128	-0.0768
W/N3	0.6692*	0.0461	0.0037
REM/W	0.0332	0.3783	0.2815
REM/N1	-0.0842	0.1881	0.1572
REM/N2	0.1240	0.4763*	0.3547*
REM/N3	0.7118*	0.6186*	0.4571*
N1/W	0.5061*	0.4506*	0.3254*
N1/REM	0.4432*	-0.1881	-0.1572
N1/N2	0.5723*	0.3087	0.2304
N1/N3	0.7199*	0.3966	0.2889
N2/W	0.0239	0.1128	0.0768
N2/REM	-0.3267	-0.4763*	-0.3547*
N2/N1	-0.1815	-0.3087	-0.2304
N2/N3	0.6791*	0.1763	0.1134
N3/W	-0.1306	-0.0461	-0.0037
N3/REM	-0.4640*	-0.6186*	-0.4571*
N3/N1	-0.3804	-0.3966	-0.2889
N3/N2	-0.0963	-0.1763	-0.1134

W refers to wake; REM, rapid eye movement; N1, non-REM stage 1; N3, non-REM stage 3; r_m, Pearson's product-moment; r_s, Spearman's rho; t_k, Kendall's tau. Asterisk indicates statistically significant (p-value < 0.05).

B. Regression Modeling

Table II lists the four linear and nonlinear functional forms of regression models for AHI–REM/N3 and AHI–N1/W, along with the two goodness-of-fit statistics (R^2 and RSD) and the values of REM/N3 and N1/W for predicting AHI values of 15 and 30 events/h. The regression model of power-law function seems to best fit both the scattering plots of AHI versus REM/N3 (R^2 = 0.5635, RSD = 0.2549) and AHI versus N1/W (R^2 = 0.3463, RSD = 0.3120) in comparison to linear, logarithmic, and exponential regression models. On the contrary, the logarithmic function is possibly the least favorable for describing the relationships of AHI–REM/N3 and AHI–N1/W because it yields the smallest R^2 and the largest RSD.

For predictive AHI values of 15 events/h (moderate OSA) and 30 events/h (severe OSA), the corresponding values of REM/N3 are 0.9126 and 2.2812, and of N1/W are 0.5474 and 1.4456, according to the devised power-law regression models that are depicted as linear regression on log-log scatter plots in Fig. 1.

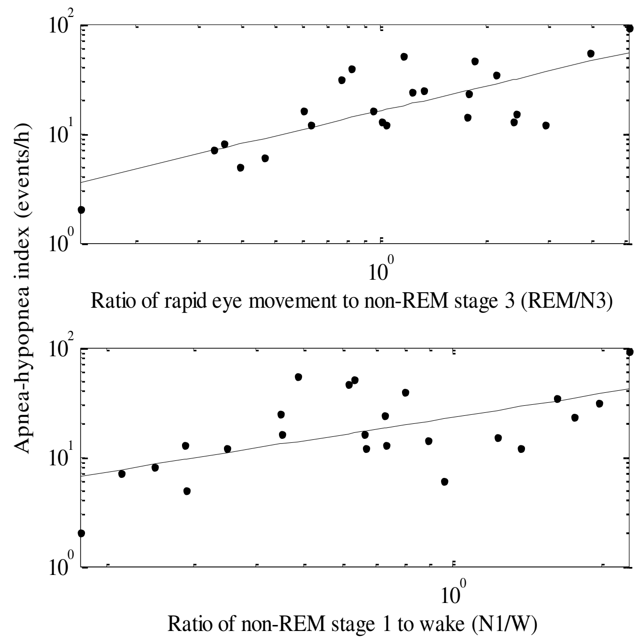

Figure 1. Log-log scatter plots with each a regression line for AHI–REM/N3 (top) and AHI–N1/W (bottom).

IV. DISCUSSION

This study examines the relationship between AHI and sleep-wake stage ratio through (1) determining Pearson, Spearman, and Kendall correlation statistics, and (2) identifying regression models of linear, logarithmic, exponential, or power-law functions that can best interpret their association.

Based on sleep architectures of 24 adult subjects with suspected OSA, we found a statistically significant positive relationship between AHI and REM/N3, which suggests that an increase in OSA severity may lead to a longer time spent in REM than N3 (or a shorter time spent in N3 than REM). In other words, over the course of a period of sleep, patients with severe OSA may experience more REM than deep sleep (or less deep sleep than REM), as compared to those with less severe OSA. This finding lends support to studies showing a reduced proportion or even absent of deep sleep in OSA patients [7, 12]. Reduction of deep sleep may consequently impair memory consolidation and learning [13], which contributes to memory loss, a typical complaint in patients with OSA [3].

Similarly, we also observed a statistically significant positive relationship between AHI and N1/W, which implies that an increase in OSA severity may lengthen the time spent in N1 than W, or equivalently shorten the time spent in W than N1. This is likely due to the fact that a transient arousal caused by apneic attack usually shifts one's sleep stage from deep to light sleep, but rarely to behavioral awakening [14].

TABLE II. REGRESSION MODELS FOR APNEA-HYPOPNEA INDEX (AHI) AND SLEEP-WAKE STAGE RATIOS (REM/N3 AND N1/W)

Regression	Model	R^2	RSD	AHI[a] = 15 events/h		AHI[a] = 30 events/h	
				REM/N3	N1/W	REM/N3	N1/W
Linear	AHI = 12.0435(REM/N3) + 5.8510	0.5066	14.7757	0.7597	-	2.0051	-
	AHI = 17.8266 (N1/W) + 8.9930	0.2561	18.1427	-	0.3370	-	1.1784
Logarithmic	AHI = 22.6169 + 34.3995 log (REM/N3)	0.3920	16.4017	0.6006	-	1.6392	-
	AHI = 29.5908 + 31.6244 log (N1/W)	0.2288	18.4727	-	0.3456	-	1.0302
Exponential	log (AHI) = 0.9407 + 0.1954 (REM/N3)	0.3962	0.2998	1.2048	-	2.7455	-
	log (AHI) = 0.9579 + 0.3300 (N1/W)	0.2609	0.3317	-	0.6612	-	1.5733
Power-law	log (AHI) = 1.2062 + 0.7565 log (REM/N3)	0.5635	0.2549	0.9126	-	2.2812	-
	log (AHI) = 1.3629 + 0.7137 log (N1/W)	0.3463	0.3120	-	0.5474	-	1.4456

W refers to wake; REM, rapid eye movement; N1, non-REM stage 1; N3, non-REM stage 3; R^2, coefficient of determination; RSD, residual standard deviation; AHI[a], predictive apnea-hypopnea index.

The relationships of AHI–REM/N3 and AHI–N1/W may be explained by a regression model with power-law functional form, indicating an existence of a nonlinear power-law relation between AHI and REM/N3, as well as between AHI and N1/W. Although the underlying mechanism between OSA severity and sleep-wake stages has yet to be known, bout durations of REM and NREM demonstrated multi-exponential temporal dynamics, which can be mimicked by a power law distribution [6] describing wake bout durations [15]. Power-law function was also proposed to relate AHI to acoustic properties of snore signals [16, 17].

This study examined a modest sample size of 24 patients (20 males and 4 females). Thus, future work should involve a larger sample size, preferably with age- and gender-matched, to ascertain the results of this study. Despite of this limitation, we found statistically significant positive relationships of AHI–REM/N3 and AHI–N1/W that may be interpreted by a power-law regression model.

REFERENCES

[1] T. Young, M. Palta, J. Dempsey, J. Skatrud, S. Weber, and S. Badr, "The occurrence of sleep-disordered breathing among middle-aged adults," *N. Engl. J. Med.*, vol. 328, no. 17, pp. 1230–1235, 1993.

[2] B. Lam, D. C. Lam, and M. S. Ip, "Obstructive sleep apnoea in Asia," *Int. J. Tuberc. Lung Dis.*, vol. 11, no. 1, pp. 2–11, 2007.

[3] K. Banno, and M. H. Kryger, "Sleep apnea: clinical investigations in humans," *Sleep Med.*, vol. 8, no. 4, pp. 400–426, 2007.

[4] A. Rechtschaffen, and A. Kales, *A Manual of Standardized Terminology, Techniques and Scoring System of Sleep Stages in Human Subjects*. Los Angeles: BIS/BRI, University of California, 1968.

[5] C. Iber, S. Ancoli-Israel, A. Chesson, and S. F. Quan, *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specification*. Westchester, IL: American Academy of Sleep Medicine, 2007.

[6] M. T. Bianchi, S. S. Cash, J. Mietus, C. K. Peng, R. Thomas, "Obstructive sleep apnea alters sleep stage transition dynamics," *PLoS One*, vol. 5, no. 6, art. no. e11356, 2010.

[7] R. Ratnavadivel, N. Chau, D. Stadler, A. Yeo, R. D. McEvoy, P. G. Catcheside, "Marked reduction in obstructive sleep apnea severity in slow wave sleep," *J. Clin. Sleep Med.*, vol. 5, no. 6, pp. 519–524, 2009.

[8] B. J. Swihart, B. Caffo, K. Bandeen-Roche, and N. M. Punjabi, "Characterizing sleep structure using hypnogram," *J. Clin. Sleep Med.*, vol. 4, no. 4, pp. 349–355, 2008.

[9] C. Heneghan, St. Vincent's University Hospital / University College Dublin Sleep Apnea Database, *Physionet*, 2011. [Online] Available: http://physionet.org/pn3/ucddb/.

[10] D. J. Sheskin, *Handbook of Parametric and Nonparametric Statistical Procedures*. Chapman and Hall / CRC, 2011.

[11] T. P. Ryan, *Modern Regression Methods*. Wiley, 2009.

[12] D. N. F. Fairbanks, S. A. Mickelson, and B. T. Woodson, *Snoring and Obstructive Sleep Apnea*. Lippincott Williams and Wilkins, Philadelphia, 2003.

[13] B. Rasch, C. Buchel, S. Gais, and J. Born, "Odor cues during slow-wave sleep prompt declarative memory consolidation," *Science*, vol. 315, no. 5817, pp. 1426–1429, 2007.

[14] Atlas Task Force of the American Sleep Disorders Association, "EEG arousals: scoring rules and examples," *Sleep*, vol. 15, pp. 173–184, 1992.

[15] C. C. Lo, T. Chou, T. Penzel, T. E. Scammell, R. E. Strecker, H. E. Stanley, and P. Ch. Ivanov, "Common scale-invariant patterns of sleep-wake transitions across mammalian species," *Proc. Natl. Acad. Sci. USA*, vol. 101, no. 50, pp. 17545-17548, 2004.

[16] A. K. Ng, T. S. Koh, E. Baey, T. H. Lee, U. R. Abeyratne, and K. Puvanendran, "Could formant frequencies of snore signals be an alternative means for the diagnosis of obstructive sleep apnea?" *Sleep Med.*, vol. 9, no. 8, pp. 894–898, 2008.

[17] A. K. Ng, T. S. Koh, U. R. Abeyratne, and K. Puvanendran, "Investigation of obstructive sleep apnea using nonlinear mode interactions in nonstationary snore signals," *Ann. Biomed. Eng.*, vol. 37, no. 9, pp. 1796–1806, 2009.