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Original Article

The relationship between pre-sleep arousal and spontaneous arousals from sleep in subjects referred for diagnostic polysomnograms

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Abstract

Background: To explore the relationship between pre-sleep arousability and spontaneous arousals from sleep, we conducted a cross-sectional study.
Methods: Four hundred and four outpatients with suspected sleep-disordered breathing who had received diagnostic polysomnograms were enrolled. Spontaneous arousals from sleep were identified by electroencephalogram and scored according to the criteria of the American Academy of Sleep Medicine. Pre-sleep arousals were evaluated with the Pre-sleep Arousal Scale.
Results: After controlling for confounders, the Cognitive subscale was correlated with spontaneous arousal indices during non-rapid eye movement sleep ($b = 0.41$, $p = 0.01$). Among patients with apnea-hypopnea index < 40/hour, a relationship between the Cognitive subscale and spontaneous arousal indices was found during both non-rapid eye movement and rapid eye movement sleep. In contrast, among patients whose apnea-hypopnea index was ≥ 40/hour, this relationship was not present ($b = 0.25$, $p = 0.35$).
Conclusion: Pre-sleep cognitive hyperarousal is associated with increasing spontaneous arousals from sleep. Severity of sleep-disordered breathing may modulate this relationship.

Keywords: Arousal; Electroencephalography; Severity of illness index; Sleep-disordered breathing; Sleep deprivation

1. Introduction

Fragmented sleep results in the impairment of cognitive function, vigilance, metabolism, and hemodynamic/autonomous nervous system abnormalities.[1−3] Traditionally, it has been thought that arousal from sleep is a sudden, transient elevation of the vigilance level because of arousal stimuli or spontaneous vigilance level oscillation.[4] Although debates exist on the definition and the function of arousal, a scoring system that is independent of the rules of Rechtschaffen and Kales was developed to record the phasic change in sleep electroencephalogram (EEG) by the American Sleep Disorder Association (ASDA) in 1992.[5] The conceptual basis of the ASDA criteria is that an arousal is the brain's response to stimuli, a transient intrusion of wakefulness into sleep, and is harmful.[6]

Nicassio and colleagues, using self-reported questionnaires, found that a correlation existed between pre-sleep hyperarousal and sleep fragmentation.[7] Indeed, both physiological[8−10] and cognitive[11−15] hyperarousal have been found to be causes of sleep disturbance rather than epiphenomena of poor sleep. Because the major manifestation of sleep fragmentation found in EEGs is arousal from sleep, whether EEG arousals from sleep mediate the relationship between pre-sleep arousals and sleep fragmentation remains unknown.

EEG arousals derived from various causes fragment human sleep. The daytime neurobehavioral deficits of primary sleep disorders have a close relationship with sleep disruption secondary to event-related EEG arousals.[16,17] Sleep is also fragmented by spontaneous EEG arousals, which occur without

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evident sources of stimuli during sleep. Spontaneous arousals are normal components of sleep physiology, and everyone experiences them.[18,19] Indeed, mechanisms by which post-sleep arousal-inducing stimuli disrupt sleep consolidation have been demonstrated.[20,21] However, the effect of pre-sleep arousal on the manifestation of spontaneous EEG arousals remains unclear.

We hypothesized that spontaneous arousals from sleep are associated with pre-sleep arousal. This study examined this relationship and further explored the impact of severity of sleep-disordered breathing on arousal from sleep.

2. Methods

2.1. Participants

Consecutive patients who visited the sleep clinic in a medical center because of excessive daytime sleepiness or observed sleep apnea were eligible subjects. Only those patients who underwent polysomnography were enrolled. From March 2005 to February 2006, a total of 404 patients provided consent to participate. The study was approved by the Human Research and Review Committee of the Shin-Kong Wu Ho-Su Memorial Hospital.

2.2. Measurement instruments

The Pre-sleep Arousal Scale (PSAS) was used to measure pre-sleep arousal.[7] The PSAS is a 16-item self-reported questionnaire comprising both cognitive and somatic manifestations of arousal, with eight items in each subscale. Two subscale scores ranging from 8 to 40 were computed separately. In taking the PSAS, subjects were asked to describe how intensely they generally experienced each component as they attempted to fall asleep in their own bedroom by selecting an appropriate rating of: 1 = not at all, 2 = slightly, 3 = moderately, 4 = a lot, or 5 = extremely. Both the cognitive and the somatic subscales correlated positively with severity of anxiety, depression and the general indices of sleep disturbance. Two dimensions of arousal differentiated insomniacs from normal sleepers and increased with sleep latency. Thus, the PSAS is a good instrument for exploring pre-sleep arousal among subjects with sleep disturbance and for screening insomniacs. The participants in the present study completed the PSAS just before polysomnography was performed.

2.3. Sleep studies

All participants underwent standard overnight polysomnography. The following data were recorded: EEG (C4-A1, C3-A2, O2-A1, O1-A2), submental electromyogram (EMG), nasal flow, respiratory effort by piezoelectric effort bands, right and left anterior tibialis electromyogram, and oximetry. A polysomnographer blinded to the results of the PSAS analyzed sleep data under standard procedures.[22] Sleep staging was performed visually by the rules of Rechtschaffen and Kales using a 30-second epoch.[23] EEG arousals were recognized by the ASDA criteria (ASDA, now the American Academy of Sleep Medicine) put forth in 1992. An arousal was defined as an EEG shift to at least alpha activity from stage 2 to 4 or rapid eye movement (REM). During REM sleep, an increase in EMG activity was required. To score an arousal, it had to last for more than 3 seconds and for less than 15 seconds. At least 10 seconds of uninterrupted sleep was required before an arousal.[5]

2.4. Data analysis

Data were analyzed with SPSS for Windows (Version 8.0, SPSS, Inc., Chicago, IL). In the univariate analyses, the chi-square test and independent t test were used. Pearson correlation coefficients were calculated to examine the relationship between variables. In the multivariate analyses, multiple linear regressions were performed to analyze the relationship between pre-sleep arousal, spontaneous arousals, and apnea-hypopnea index (AHI). In addition to established factors affecting spontaneous arousals, potential confounding variables explored in the univariate analyses were entered into the model for adjusting any confounding effects. To explore the interactive effect of severity of sleep-disordered breathing on the relationship between pre-sleep arousal and spontaneous EEG arousals, we divided the participants, based on AHI, into two groups in advance. We set highest quartile of AHI (AHI: 40/hour) as the cut-off point for grouping because of potential nonlinear effect of severity of sleep-disordered breathing (i.e. AHI) on sleep pressure.

All reported p values are 2-tailed. The p values were considered significant if they were less than 0.05.

3. Results

3.1. Demographic data and clinical characteristics

Table 1 presents the characteristics of 404 participants. The mean age was 45.2 ± 16.6 years. 80% of the subjects were male, and those ranging in age from 41 to 59 years comprised 41.2% of all participants. There was no significant age difference between male and female subjects ($t = 0.17$, $df = 402$, $p = 0.87$).

Among the participants, AHI of 93 subjects (23.0%) were less than 5/hour. The distribution of severity of sleep-disordered breathing was 23.3% ($n = 94$), 19.8% ($n = 80$), and 33.9% ($n = 137$) with respect to mild (AHI: 5–15/hour), moderate (AHI: 15–30/hour) and severe (AHI: $\geq$ 30/hour). Subjects with AHI $\geq$ 40/hour accounted for one-fourth of all participants. Among them, the number of males was significantly greater than females ($p < 0.001$). The mean body mass index (BMI) of subjects with AHI $\geq$ 40/hour (29.4 ± 4.8 kg/m^2) was significantly higher than that of subjects with AHI $<$ 40/hour (25.4 ± 4.6 kg/m^2; $p < 0.001$).

3.2. Polysomnographic data

Data from the sleep studies are shown in Table 1. The mean sleep latency was shorter than 20 minutes (15.7 ± 24.7 minutes),

Table 1
Subject characteristics by apnea-hypopnea index

	Total ($n = 404$)	Apnea-hypopnea index <40/hour ($n = 300$)	Apnea-hypopnea index ≥40/hour ($n = 104$)	p
Gender				
Male	326 (80.7)	230 (76.7)	96 (92.3)	<0.001
Female	78 (19.3)	70 (23.3)	8 (7.7)	
Age, yr	45.2 ± 16.6	44.5 ± 17.6	47.3 ± 13.2	0.09
Body mass index, kg/m^2	26.4 ± 4.9	25.4 ± 4.6	29.4 ± 4.8	<0.001
Sleep parameters				
Total sleep time, min	299.5 ± 57.6	299.2 ± 59.5	300.5 ± 52.2	0.84
Sleep latency, min	15.7 ± 24.7	16.5 ± 25.4	13.2 ± 22.4	0.24
Sleep efficiency, %	82.0 ± 14.3	82.0 ± 14.4	82.2 ± 14.1	0.89
Slow-wave sleep, %	20.7 ± 18.6	22.5 ± 19.7	15.3 ± 13.4	<0.001
Rapid eye movement sleep, %	14.2 ± 6.9	14.8 ± 7.0	12.6 ± 6.2	0.006
Apnea-hypopnea index (number/hour)	25.9 ± 25.1	13.4 ± 11.0	61.9 ± 18.6	<0.001
Arousal index (number/hour)				
Associated with respiration	5.4 ± 6.4	3.0 ± 3.6	12.5 ± 7.2	<0.001
Spontaneous				
Total	32.3 ± 22.1	32.5 ± 23.8	31.8 ± 16.2	0.76
Rapid eye movement sleep	28.6 ± 21.1	28.5 ± 21.7	28.9 ± 19.2	0.87
Nonrapid eye movement sleep	32.2 ± 20.0	32.3 ± 21.0	32.0 ± 16.8	0.89
Pre-sleep Arousal Scale				
Somatic subscale	14.2 ± 5.6	14.3 ± 5.5	13.9 ± 5.8	0.53
Cognitive subscale	17.7 ± 7.8	18.2 ± 7.9	16.4 ± 7.5	0.05

Data are presented as n (%) or mean ± standard deviation.

the mean sleep efficiency reached 80% (82.0 ± 14.3%), and the mean spontaneous arousal indices were 32.3 ± 22.1/hour. Sleep parameters were compared by the severity of sleep-disordered breathing. Subjects with AHI ≥ 40/hour had a significantly lower percentage of slow-wave sleep and REM sleep compared with subjects with AHI < 40/hour. No other significant difference in sleep parameters, including spontaneous arousal indices, was noted between the two subgroups.

3.3. The PSAS scores

The two subscales were moderately correlated ($r = 0.61$, $p < 0.001$), as presented in Table 2. The mean scores of the Somatic subscale and the Cognitive subscale were 14.2 ± 5.6 and 17.7 ± 7.9, respectively. Females had a significantly higher mean score on the Somatic subscale (15.8 ± 6.7) than males (13.9 ± 5.2; $t = 2.83$, $df = 402$, $p = 0.005$). No significant gender differences existed in the Cognitive subscale.

3.4. The correlation between the PSAS subscales and spontaneous arousal indices

In the univariate analyses, spontaneous arousal indices during nonrapid eye movement (NREM) sleep increased with the scores of the Cognitive subscale ($r = 0.16$, $p = 0.001$), but not with the scores of the Somatic subscale ($r = 0.10$, $p = 0.06$). The scores of the Cognitive subscale were negatively associated with AHI ($r = -0.19$, $p < 0.001$). Sleep latency measures increased with the scores of the Cognitive subscale ($r = 0.16$, $p = 0.001$), but not with the scores of the Somatic subscale ($r = 0.02$, $p = 0.64$) (Table 2).

3.5. Factors affecting spontaneous arousal indices

By multiple regression analyses, spontaneous arousal indices during the whole night's sleep increased only with age ($b = 0.18$, $p = 0.007$). Analyses by sleep stages in addition to age revealed that spontaneous arousal indices in NREM as opposed to REM sleep increased with the scores of the Cognitive subscale ($b = 0.41$, $p = 0.01$). On the contrary, spontaneous arousal indices in each sleep stage consistently did not correlate with the scores of the Somatic subscale (Table 3).

The effect of the AHI on the relationship between the scores of the Cognitive subscale and the spontaneous arousal indices in two sleep stages is shown in Table 4. The relationship between the spontaneous arousal indices and age existed only in the subgroup with AHI < 40/hour. Similarly, the relationship between the spontaneous arousal indices in NREM sleep and the scores of the Cognitive subscale was noted only in the AHI < 40/hour subgroup ($b = 0.48$, $p = 0.02$). Additionally, there was a weak but significant association between the spontaneous arousal indices in REM sleep and the scores of the Cognitive subscale in the AHI < 40/hour subgroup ($b = 0.43$, $p = 0.048$). In the AHI ≥ 40/hour subgroup, only BMI correlated with spontaneous arousal indices in NREM sleep ($b = -1.00$, $p = 0.01$).

4. Discussion

The brain is never completely isolated from the outside environment. Even when strictly controlling external conditions, some internal unexpected factors will exert an influence on sleep.[18] The combined effect of the intensity of stimuli, sleep stages, and sleep propensity affects the EEG

Table 2
Correlations between subject characteristics with spontaneous arousal index and Pre-sleep Arousal Scale

Variables	Spontaneous arousal index				Pre-sleep Arousal Scale			
	Nonrapid eye movement sleep		Rapid eye movement sleep		Somatic subscale		Cognitive subscale	
	Correlation coefficient	*p*	Correlation coefficient	*p*	Correlation coefficient	*p*	Correlation coefficient	*p*
Spontaneous arousal index (number/hour)								
Nonrapid eye movement sleep	1		0.61	<0.001	0.10	0.06	0.16	0.001
Rapid eye movement sleep	0.61	<0.001	1		0.08	0.12	0.07	0.14
Pre-sleep Arousal Scale								
Somatic subscale	0.10	0.06	0.08	0.12	1		0.61	<0.001
Cognitive subscale	0.16	0.001	0.07	0.14	0.61	<0.001	1	
Age, yr	0.19	<0.001	0.15	0.003	0.06	0.23	0.05	0.37
Body mass index, kg/m^2	−0.13	0.79	0.04	0.43	0.07	0.57	−0.07	0.19
Apnea-hypopnea index (number/hour)	0.01	0.87	−0.04	0.44	−0.01	0.79	−0.19	<0.001
Sleep latency, min	0.06	0.27	0.06	0.27	0.02	0.64	0.16	0.001

manifestations of arousal-inducing stimuli.[24] The present study was conducted among subjects referred for diagnostic polysomnograms (PSG) and regarded subjective pre-sleep arousal as a potential, nonorganic, endogenous source of stimuli to sleep. The results suggested that increased pre-sleep cognitive arousal predicted more sleep fragmentation in NREM sleep. In addition, severity of sleep-disordered breathing may modify this relationship.

In the present study, females had higher mean scores on the Somatic subscale than males. This differs from the findings reported in the original PSAS validation study, in which no gender differences were noted.[7] Different study subject characteristics are the most likely explanation. In the original validation study, normal sleepers and chronic insomniacs were enrolled. In contrast, subjects with more diverse conditions, both with and without sleep-disordered breathing, participated in the present study.

Among insomniacs, the PSAS is a useful tool to describe the pre-sleep state. Cognitive and somatic pre-sleep arousal dimensions have been shown to be empirically discriminable. The relationship between the subjective pre-sleep arousal state and sleep-onset difficulties has been established.[7] In the present study, we further demonstrated, using objective measurements, the utility of the PSAS among subjects referred for diagnostic PSG. Because the major manifestation of sleep fragmentation on EEG is arousals, our findings also offer the theoretical justification for a direct relationship between the PSAS and self-reported sleep fragmentation noted in the original validation study. In addition, the results also showed the greater relevance of pre-sleep cognitive arousal to sleep disturbance. Problematic insomnia symptoms were reported by 50% of patients with sleep-disordered breathing.[25] The PSAS may be a useful tool for future research that seeks to determine to what extent insomnia symptoms interfere with the manifestation and treatment of sleep-disordered breathing.

Sleep deprivation is chronic, naturally occurring in essence among patients with sleep-disordered breathing. The AHI $\geq$40/hour subgroup in this study may represent patients whose sleep has been chronically and seriously deprived. In this subgroup, an association between pre-sleep cognitive arousal and EEG spontaneous arousals was not found. Furthermore, consistent with previous normative data, age independently increased spontaneous arousal indices among all subjects.[26] This finding supported the concept that the aging process physiologically fragments sleep.[19] Similarly, the relationship mentioned above failed to appear in the AHI $\geq$40/hour subgroup.

Heightened sleep pressure after sleep deprivation may account for the interactive effect of AHI on the relationship

Table 3
Multiple regression analysis for variables predicting spontaneous arousal index by sleep types

	Spontaneous arousal index								
	Total			Nonrapid eye movement sleep			Rapid eye movement sleep		
	b	SE	*p*	b	SE	*p*	b	SE	*p*
Pre-sleep Arousal Scale									
Somatic subscale	−0.01	0.25	0.97	−0.01	0.23	0.97	0.14	0.24	0.57
Cognitive subscale	0.31	0.18	0.10	0.41	0.16	0.01	0.16	0.18	0.37
Age, yr	0.18	0.07	0.007	0.22	0.06	<0.001	0.18	0.06	0.005
Gender (male/female)	3.90	2.85	0.17	2.27	2.54	0.37	0.25	2.73	0.93
Body mass index, kg/m^2	−0.24	0.26	0.35	−0.21	0.23	0.37	0.01	0.25	0.96
Apnea-hypopnea index (number/hour)	0.01	0.05	0.92	0.02	0.05	0.62	0.02	0.05	0.75
Sleep latency, min	0.02	0.05	0.64	0.02	0.04	0.65	−0.05	0.04	0.22

Table 4
Multiple regression analysis for variables predicting spontaneous arousal index in different sleep types by apnea-hypopnea index

	Spontaneous arousal index											
	Nonrapid eye movement sleep						Rapid eye movement sleep					
	Apnea-hypopnea index<40/hour			Apnea-hypopnea index ≥40/hour			Apnea-hypopnea index <40/hour			Apnea-hypopnea index ≥40/hour		
	b	SE	*p*	b	SE	*p*	b	SE	*p*	b	SE	*p*
Pre-sleep Arousal Scale												
Somatic subscale	0.10	0.29	0.73	−0.25	0.35	0.47	−0.05	0.30	0.87	0.49	0.41	0.23
Cognitive subscale	0.48	0.20	0.02	0.25	0.27	0.35	0.43	0.22	0.048	−0.48	0.31	0.13
Age, yr	0.23	0.07	0.001	0.07	1.31	0.59	0.20	0.08	0.009	0.10	0.15	0.50
Gender (male/female)	0.94	2.85	0.74	12.11	6.57	0.07	−1.24	3.01	0.68	12.06	7.64	0.12
Body mass index, kg/m^2	−0.01	0.28	0.97	−1.00	0.39	0.01	0.12	0.30	0.70	−0.55	0.46	0.23
Apnea-hypopnea index (number/hour)	0.05	0.13	0.67	0.14	0.10	0.19	0.05	0.13	0.69	0.08	0.12	0.50
Sleep latency, min	0.06	0.05	0.23	−0.10	0.08	0.19	−0.03	0.05	0.57	−0.13	0.09	0.14

between stimuli and spontaneous arousals. Previous experimental studies on short-term sleep deprivation have shown rebound sleep pressure in the recovery nights that follow.[27,28] EEG microarousals were suppressed in the follow-up recuperative sleep. However, these suppression effects lasted only one night.[28] Diminished associations between potential arousal-inducing stimuli (i.e. aging, pre-sleep cognitive arousal) and EEG arousals may reflect the long-term effect of persistent sleep deprivation on the arousal threshold.[29,30] This finding may explain why some patients with severe sleep-disordered breathing did not report difficulties in sleep maintenance.

We found that BMI was independently, negatively associated with spontaneous arousal indices in NREM sleep in the AHI $\geq$ 40/hour subgroup. In this study, subjects with AHI $\geq$ 40/hour were apparently obese (mean BMI: 29.4 kg/m^2) for ethnic Chinese people. In fact, obesity is independent from sleep-disordered breathing as a risk factor for excessive daytime sleepiness among clinical and community populations.[31,32] In addition, the prevalence of excessive daytime sleepiness increases dramatically among subjects who are overweight or obese.[31] A recent animal study successfully demonstrated that obese mice who gained weight from high-fat food had increased sleep pressure and difficulties in maintaining wakefulness during the active phase.[33] That evidence suggests that obesity increases sleep pressure by itself. Therefore, sleep pressure from obesity, and severity of sleep-disordered breathing may play an important role in modulating the relationship between potential arousal-inducing stimuli and spontaneous arousals.

Spontaneous arousals during sleep increase when organs are stimulated or psychiatric disorders exist.[4,34] As we know, in the absence of apnea or hypopnea, respiratory effort-related arousals are increased in the sleep of subjects with sleep-disordered breathing as a reaction of the sleeping brain to a repetitive breathing disturbance.[4] Because esophageal pressure data were not available in the present study, we were unable to differentiate true spontaneous arousals from respiratory effort-related arousals. Although no significant difference of spontaneous arousal indices was noted between the different AHI subgroups, we still allowed AHI as a covariate in the multiple regression analyses to adjust for potential confounding factors derived from subtle obstructions of the upper airway during sleep. We did not evaluate other confounding psychopathologies, such as depression or anxiety. Broman and colleagues have shown the relationship between the PSAS and objective sleep parameters. They noted that the association existed only among psychophysiological insomniacs, not among psychiatric insomniacs.[35] Hence, the underlying psychopathology most likely biased the relationship between the PSAS and spontaneous arousals toward the null.

In conclusion, this was a cross-sectional study. We cannot make causal inference on whether subjective pre-sleep arousal results in spontaneous arousals. However, based on previous research, the effect of pre-sleep cognitive arousal may penetrate into sleep and disrupt sleep consolidation by increasing spontaneous arousals. Further studies are needed to examine our findings. First, an intervention study would help to clarify whether the severity of sleep-disorder breathing indeed modulates the relationship between pre-sleep cognitive hyperarousal and increases spontaneous arousal. Second, to more precisely estimate the magnitude of the association between pre-sleep arousal and spontaneous arousal, confounding psychopathology such as comorbid insomnia, depression, and anxiety should be directly measured and controlled. Finally, establishment of the relationship between the Somatic subscale of the PSAS and indices of autonomous nervous system arousals may help to realize the true impact of subjective pre-sleep somatic arousal on sleep consolidation and daytime impairment.

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