Profiling Objective Sleep Quality in a Healthy Taiwanese Sample: Using a Novel Electrocardiogram-based Cardiopulmonary Coupling Analysis

Albert. C. Yang, M.D.[1,2,3], Chen-Jee Hong, M.D.[2,4,5], Chung-Hsun Kuo, B.S.[4], Tai-Jui Chen, M.D.[6], Cheng-Hung Yang, M.D.[2,5], Cheng Li, M.D.[1], Shih-Jen Tsai, M.D.[2,5]

Objectives: Sleep affects the regulation of circulatory and respiratory function. The factors of age and gender are also known to have a significant impact on the cardiac physiology. We investigated the impact of the factors of age and gender on sleep-related cardiovascular and respiratory dynamics with a novel, validated cardiopulmonary coupling analysis based solely on the electrocardiogram (ECG) signal. **Methods:** We recruited 155 healthy subjects (41 males and 114 females, aged 37.6 ± 13.0 years, range being 19-67 years) to participate in this study. We evaluated their mood and sleep with self-reported questionnaires - the Beck Depression Inventory, the Pittsburgh Sleep Quality Index, and the Epworth Sleepiness Scales. Physiologic sleep measures were quantified by analysis of continuous ECG recordings using the cardiopulmonary coupling analysis. Three sleep states were determined, namely stable, unstable, and rapid eye movement (REM)/wake state, by measuring the degree of association between autonomic and respiratory drives during sleep. **Results:** The key findings in this study included: (A) Compared to subjects under age 40, subjects over age 40 showed to have significantly decreased very-low-frequency coupling, an index of REM/wake state. (B) Compared to female subjects, male subjects revealed to have lower high-frequency-coupling, an index of stable sleep, and higher low-frequency-coupling, an index of unstable sleep. And (C) ECG-based sleep characteristics were not fount to be correlated with self-reported questionnaires in this healthy adult sample. **Conclusions:** Our study results showed that aging and gender as factors had significant effects on cardiopulmonary coupling dynamics during sleep. This study also provided a profile of the physiological sleep characteristics of a healthy Taiwanese sample. We suggest that further research may enhance the use of this relatively simple ECG-based method to give a cost-efficient way to objectively evaluate sleep quality.

Key words: sleep stability, electrocardiogram, cardiopulmonary coupling analysis

(*Taiwanese Journal of Psychiatry* [Taipei] 2010; 24: 201-9)

[1] Chu-Tung Veterans Hospital, Hsin-Chu County, Taiwan [2] Division of Psychiatry, School of Medicine, National Yang-Ming University, Taipei, Taiwan [3] Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan [4] Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan [5] Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan [6] I-Shou University and E-Da Hospital, Kaohsiung, Taiwan

Received: February 1, 2010; revised: February 26, 2010; accepted: May 6, 2010

Address correspondence to: Dr. Albert C. Yang, Chu-Tung Veterans Hospital No.81, Jhongfong Road, Sec. 1, Chu-Tung Township, Hsin-Chu County 31064,Taiwan

Introduction

Currently, assessing sleep quality is largely based on self-reported sleep diaries or questionnaires which reflect only general, perceived sleep quality, and lack biological information on sleep architecture [1]. Polysomnography can be used to assess sleep objectively, but the setting of polysomnographic study needs expensive and encumbering resources that often cannot meet the timely demands of sleep examination of daily clinical practice. Moreover, conventional sleep staging is based on arbitrary criteria of identifying morphological markers in electroencephalographic (EEG) signals [2], which are found to be poorly correlated with subjective sleep measures [3-5]. Benzodiazepines are also found to suppress the "deep" sleep (i.e., decreased delta power or slow wave activity in EEG signals), but still to improve sleep continuity and subjective sleep quality [6]. These limitations may reduce the value of the polysomnographic study as an effective measure to evaluate sleep quality in clinical practice. Enhanced quantitative assessments of sleep quality, especially if measurable in a simple and inexpensive manner, could have substantial clinical use.

An alternative approach to quantifying sleep quality is based on a particular EEG morphology named cyclic alternating patterns (CAP) [7-9], which is defined by a phasic EEG activity being associated with microarousals during sleep. Thus, CAP is suggested to be a marker for sleep instability [7]. Patients with insomnia are found to have altered EEG-CAP but not altered EEG delta power [5, 10]. CAP is also found to be more closely correlated with perceived sleep quality than slow wave sleep [5], suggesting that CAP is a more sensitive marker for sleep quality than slow wave activity.

Recently, CAP is found to be associated with changes in the physiological dynamics of heart rate and respiration, thus opening a window to using ECG signal alone as an alternative mean to quantify sleep stability [11]. This newly developed analysis is called cardiopulmonary coupling (CPC) analysis, which has been validated to detect sleep apnea based solely on the ECG signal [11, 12]. We have shown the use of the CPC method in evaluating sleep quality in patients with major depressive disorder [13]. The results showed that depressed patients have significantly increased unstable sleep compared to healthy controls, and that this increase in unstable sleep can be partially normalized by the use of hypnotics [13].

Age and gender as factors are also known to have a significant impact on the cardiac physiology. In this study, we therefore investigated the impact of factors of age and gender on sleep-related cardiovascular and respiratory dynamics, and also established a profile of CPC-derived sleep characteristics in a healthy Taiwanese sample.

Methods

Participants and clinical assessments

We recruited 176 healthy Han Chinese volunteers at two medical centers: Taipei Veterans General Hospital (*N*=126) and Kaohsiung E-Da Hospital (*N*=50). Subjects were recruited using advertisement to hospital employees and their relatives. All subjects gave informed consent before entering the study. The study protocol was approved by the institutional review boards of both hospitals. To note, 91 subjects have been reported elsewhere as part of the healthy comparison group [13].

Each subject was carefully reviewed for a history of medical disease and psychiatric illness

as well as medication use. A psychiatrist did the clinical evaluation with a structuralized interview. Neither the enrolled subjects nor their first-degree relatives had a history of mental illness and clinically significant insomnia. Exclusion were those who had major psychiatric disorders, major cardiac arrhythmia, or major medical disease (hypertension, diabetes, and malignancy). Each enrolled subject reveived ECG monitoring and was evaluated using self-reported questionnaires, including the Beck Depression Inventory (BDI) [14], the Pittsburgh Sleep Quality Index (PSQI) [15] and the Epworth Sleepiness Scale (ESS) [16].

Of 176 subjects, 175 were successfully contacted for ambulatory ECG monitoring. Eight subjects without receiving sleep questionnaire could not enter this study. Ten subjects who were under age 10 years, were excluded from the present data analysis. Two additional subjects were excluded due to the presence of clinical depression. The final study sample consisted of 155 healthy subjects (41 males and 114 females, aged 37.6 ± 13.0 years, range being 19-67 years) with complete ECG monitoring and self-reported questionnaire evaluation.

The sleep ECG monitoring

We used Holter recordings (MyECG E3-80 Portable Recorder, Microstar Inc., Taipei, Taiwan) to collect continuous ECG data during sleep from all subjects at home. Participants were asked to maintain their usual daily activities and to avoid smoking and drinking alcoholic beverages while undergoing testing. Additional information about bed and wake times reported by the subject was used to constrain the analysis to the approximate sleep period. The ECG signals were then automatically processed and analyzed using the CPC method to generate a sleep spectrogram.

The cardiopulmonary coupling analysis

The autonomic nervous system has predictable characteristics that vary according to sleep depth and types [17, 18]. CPC analysis is derived from an estimation of the coupling of autonomic and respiratory drives, using heart rate and the respiratory modulation of QRS amplitude, respectively. This dual information can be extracted from a single channel of ECG [11]. The algorithm of CPC analysis is summarized as the following steps: (A) extraction of heart rate and respiration waveform from the ECG signal, and (B) estimation of the cross-spectral power and coherence between the ECG-derived respiration and the heart rate signals to determine sleep state. The analysis window width is 512 seconds, moving forward in 128 second increments until the entire ECG time series is analyzed. Specifically, physiologically stable sleep is associated with high-frequency coupling between heart rate and respiration at frequencies of 0.1 to 0.4 Hz. In contrast, physiologically unstable sleep is associated with low-frequency coupling between heart rate and respiration over a range of 0.01 to 0.1 Hz. The presence of *very-low-frequency coupling* between heart rate and respiration below 0.01 Hz is correlated with wake or rapid eye movement (REM) sleep [11]. Without the recording of muscle tone, we cannot distinguish REM sleep from the wake state and the detection of very-low-frequency coupling may reflect contributions from both states. The percentage of each sleep state (i.e., stable, unstable, and REM/wake state) was used as an objective measure to quantify sleep quality in this study.

The statistical analysis

We used Statistical Package for the Social Science version 15.0 software for Windows

(SPSS, Chicago, Illinois, USA) for statistical analyses. The differences between groups were considered significant if *p*-values were less than 0.05 (two-tailed). We compared for group differences of categorical variables with Chi-square test. With *t*-test, we compared group differences of continuous variables in demographic data, self-reported questionnaires, and CPC sleep indices between subgroups in our study sample, classified by age, gender, or subjective sleep quality.

We used general linear model (GLM) by entering the information of age and gender as covariates to detect the effect of potential age-by-gender interaction on CPC sleep indices. Partial correlation controlling for age was applied to determine the associations between CPC sleep indices and scores from self-reported questionnaires. We presented data as mean ± standard deviation (SD).

Results

The PSQI global score was 5.6 ± 3.1, the ESS score was 10.1 ± 4.5, and the BDI score was 6.7 ± 7.1 for the entire study sample. According to PSQI data, 91% (*N*=141) of subjects reported no use of hypnotics in the past month whereas the remaining 9.0% (*N*=14) of subjects reported use of hypnotics on an irregular basis (less than once a week: *N*=6, 3.9%; once or twice a week: *N*=4, 2.6%; three or more times a week: *N*=4, 2.6%). It is worthy noting that 48% of the subjects were classified as having sleep disturbance (PSQI > 5) despite the fact that no clinically significant insomnia was observed. CPC-based sleep indices for the entire study sample showed that the stable sleep index was 42.9% ± 8.4, the unstable sleep index was 32.2% ± 14.4, and the REM/wake state was 23.3% ± 9.6.

The age distribution was binomial in this study sample, with one peak at age 25 years and another peak at age 54 years. Therefore, we divided the entire study sample into two groups: under age 40 and age 40 or above (66 women and 23 men with range of 19-39 years, and 48 women and 18 men with range of 40-67 years). Table 1 shows subject characteristics and sleep data for the two age groups. Pearson's correlation analysis showed that age negatively correlated with REM/wake index (r=-0.168, p=0.037) and sleep duration (r=-0.348, p<0.001).

Table 2 lists the effect of gender as a factor on sleep characteristics. Table 3 represents the CPC-based sleep characteristics according to PSQI groups.

Since CPC-based sleep index is known to correlate with the EEG-CAP marker, which is found to be associated with perceived poor sleep quality, we expected that a CPC-based sleep index may correlate with data from self-reported questionnaires. Partial correlation analysis controlling for age was used to evaluate the association between CPC-based sleep indices and self-reported questionnaires. No significant correlation between CPC-based sleep indices and self-reported questionnaires. However, a weak but significant correlation was found between the third component of PSQI – sleep duration, and stable sleep index (r=0.221, p=021), unstable sleep index (r=-0.206, p=0.033), and measured sleep duration (r=-0.266, p=0.005).

Discussion

With a novel CPC method based solely on ECG signals, we profiled the physiological sleep characteristics of a healthy Taiwanese sample. We had three key major findings in this study: (A) Compared to subjects under age 40 years, subjects

Table 1. The effect of age as a factor on sleep characteristicss

Variable	Age < 40 years (*N*=89)	Age ≧ 40 years (*N*=66)	*t* or χ^2	*p*
Age, years	27.3 ± 4.3	51.5 ± 5.8		
Gender, female (%)	66 (74)	48 (73)	0.040	0.841
Pittsburgh Sleep Quality Index	5.6 ± 2.6	5.6 ± 3.6	-0.082	0.935
#1 Subjective sleep quality	1.3 ± 0.8	1.2 ± 0.8	0.848	0.398
#2 Sleep latency	1.0 ± 0.9	0.9 ± 0.9	0.185	0.854
#3 Sleep duration	0.7 ± 0.7	1.0 ± 0.9	-2.281	0.024*
#4 Sleep efficiency	0.4 ± 0.8	0.4 ± 0.8	-0.259	0.796
#5 Sleep disturbance	1.2 ± 0.4	1.1 ± 0.6	0.894	0.372
#6 Use of sleep medication	0.0 ± 0.1	0.4 ± 0.9	-3.703	<0.001***
#7 Daytime dysfunction	1.1 ± 0.8	0.7 ± 0.7	3.476	0.001***
Pittsburgh Sleep Quality Index Score > 5, cases (%)	45 (51)	29 (44)	0.46	0.498
Epworth Sleepiness Scale	10.9 ± 4.4	9.0 ± 4.3	2.676	0.008**
Beck Depression Inventory	7.4 ± 7.5	5.9 ± 6.7	1.125	0.263
Stable sleep index, %	40.8 ± 18.5	45.8 ± 18.0	-1.693	0.093
Unstable sleep index, %	32.6 ± 14.3	31.5 ± 14.6	0.466	0.642
REM/Wake index, %	24.8 ± 10.5	21.2 ± 7.8	2.296	0.023*
Sleep duration, hours	7.4 ± 1.4	6.4 ± 1.4	4.645	<0.001***

Data were represented mean ± 1 standard deviation unless otherwise noted.
* Significantly different $p<0.05$ ** Significantly different $p<0.01$ *** Significantly different $p<0.001$

over age 40 years showed significantly decreased very-low-frequency coupling, an index of REM/wake state (Table 1). (B) Compared to female subjects, male subjects were found to have lower high-frequency coupling, an index of stable sleep, and higher low-frequency coupling, an index of unstable sleep (Table 2). And (C) ECG-based sleep characteristics were not correlated with self-reported questionnaires.

The effects of age on EEG sleep characteristics are well established, but the effects of age-related changes in cardiopulmonary dynamics during sleep are unclear. Our analysis complements the conventional EEG-based sleep study and demonstrates that aging was associated with a reduced very-low-frequency coupling between heart rate and respiration (Table 1). Since this very-low-frequency coupling is correlated with REM or wake state, our observation of age-related reduction in the very-low-frequency coupling is therefore in line with age-related reduction in REM sleep. But in our study we incorporated only ECG signals. Therefore, we suggest that a polysmnographic study is warranted to conform the finding. Another well-known feature of age-related change in sleep is that aging also suppresses "deep" sleep characterized by the slow wave EEG activity. Previous study results showed that the high- or low-frequency coupling between heart rate and respiration is not correlated with the slow wave EEG activity [11] .Therefore, the question of how the changes in slow wave sleep during aging could affect the cardiopulmonary dynamics, needs further research to clarify. Aging *per se* does not pro-

Table 2. The effect of gender as a factor on sleep characteristics

Variable	Male (*N*=41)	Female (*N*=114)	*t* or χ^2	*p*
Age, years	38.2 ± 13.5	37.4 ± 12.9	-0.303	0.762
Pittsburgh Sleep Quality Index	5.2 ± 3.2	5.7 ± 3.0	0.901	0.369
#1 Subjective sleep quality	1.1 ± 0.8	1.3 ± 0.8	0.921	0.358
#2 Sleep latency	0.7 ± 0.9	1.0 ± 0.9	1.882	0.062
#3 Sleep duration	0.6 ± 0.7	0.9 ± 0.8	1,670	0.097
#4 Sleep efficiency	0.2 ± 0.6	0.4 ± 0.9	1.422	0.157
#5 Sleep disturbance	1.2 ± 0.4	1.1 ± 0.5	-1.048	0.296
#6 Use of sleep medication	0.3 ± 0.8	0.1 ± 0.5	-1.588	0.114
#7 Daytime dysfunction	1.0 ± 0.9	0.9 ± 0.7	-0.871	0.385
Pittsburgh Sleep Quality Index Score > 5, cases (%)	20 (49)	53 (46)	0.060	0.806
Epworth Sleepiness Scale	11.1 ± 4.8	9.7 ± 4.3	-1.770	0.079
Beck Depression Inventory	5.2 ± 7.5	7.3 ± 6.9	1.417	0.160
Stable sleep index, %	35.3 ± 16.1	45.6 ± 18.5	3.171	0.002**
Unstable sleep index, %	40.5 ± 13.8	29.2 ± 13.4	-4.610	<0.001***
REM/Wake index, %	22.3 ± 8.7	23.6 ± 10.0	0.743	0.458
Sleep duration, hours	6.9 ± 1.2	7.0 ± 1.6	0.466	0.642

Data were represented mean ± 1 standard deviation unless otherwise noted
** Significantly different $p<0.01$ *** Significantly different $p<0.001$

Table 3. The demographic and sleep characteristics of PSQI groups

Variable	PSQI ≦ 5 (*N*=82)	PSQI > 5 (*N*=73)	*t* or χ^2	*p*
PSQI	3.3 ± 1.3	8.2 ± 2.4	-15.947	<0.001
Age, years	38.8 ± 13.0	36.3 ± 12.9	1.172	0.243
Gender, female (%)	61 (74)	53 (73)	0.060	0.806
Epworth Sleepiness Scale	9.5 ± 3.9	10.8 ± 5.0	-1.764	0.080
Beck Depression Inventory	3.7 ± 3.9	10.4 ± 8.4	-5.501	<0.001***
Stable sleep index, %	41.2 ± 16.8	44.8 ± 20.0	-1.228	0.221
Unstable sleep index, %	33.9 ± 14.7	30.2 ± 13.9	1.583	0.116
REM/Wake index, %	23.3 ± 7.7	23.3 ± 11.5	-0.004	0.997
Sleep duration, hours	6.8 ± 1.5	7.2 ± 1.4	-2.002	0.047*

Data were represented mean ± 1 standard deviation unless otherwise noted.
Abbreviation: PSQI=Pittsburgh Sleep Quality Index
* Significantly different $p<0.05$ *** Significantly different $p<0.001$

duce unsatisfactory sleep [19]. We speculate that the absence of correlation between age and stable sleep index in our healthy sample may suggest that the measure of stable sleep (by high-frequency coupling) may be an independent indicator of "good" sleep other than conventional EEG slow wave activity.

Gender is also known to have significant effects on EEG sleep architecture, but its connection with physiological sleep characteristics is not fully understood. Males of middle and older age have more stage 1 non-REM sleep than females, while females have more slow wave sleep in stage 3 of non-REM sleep than males [20]. Changes in autonomic function during sleep are stage-related. Parasympathetic modulation is generally increased during non-REM sleep and decreased in REM or wake sates [21]. In this study, we found that compared to females, males subjects had a reduction in high-frequency coupling, and an increase in low-frequency coupling between heart rate and respiration (Table 2). Based on those findings, we suggest that males have lower parasympathetic tones during sleep than females.

Our present study did not find any association between CPC-based sleep indices and self-reported questionnaires in a healthy sample. This finding may be due to the fact that our study was based on a healthy population, in which mood and sleep were within relatively normal range. But it is worthy noting that in our previous study which is based on data from depressed patients [13], whose PSQI global scores are significantly higher than those of healthy controls, the ECG-based sleep indices are correlated with perceived sleep quality and severity of depression, particularly the REM/wake index and the degree of sleep fragmentation.

Based on our previous report and another study data, we suggest that stable sleep measured by high-frequency coupling of heart rate and respiration is associated with healthy conditions and is decreased in the disease state. These findings are similar in patients with depression [13] or sleep apnea [11]. The stable and unstable sleep indices measured basing on ECG signals reflect altered balance in autonomic functions. Reduced stable sleep in depression patients may suggest heightened sympathetic activity during sleep. The neurobiological mechanisms of the alteration in stable sleep in patients with insomnia or depression need further research. Primary autonomic control is mediated by the anterior cingulate, ventromedial prefrontal cortex, amygdala and insular cortex. Altered activity within this network is common in insomnia and depression [22-24]. These brain areas are also involved in regulating respiratory rate and rhythm, and therefore may have an impact on the result of CPC analysis.

Limitations of the study

This study had three limitations. First, the study technique could not distinguish between REM and wake states based solely on ECG signals. This limitation can be improved if muscle tone recording is integrated into the algorithm or if the actigraphy, a simple and widely accepted tool for assessing sleep/wake states, is incorporated. Second, the presence of major cardiac arrhythmias could reduce the accuracy of this method to determine sleep states. Other confounding medical/physical factors (e.g., body mass index, pulmonary or neurological diseases) might potentially affect cardiopulmonary dynamics but were not evaluated in this study sample. And third, our study did not incorporate the polysomnographic data, and the exact correlations with conventional sleep indices could not be made in this study. The spectrographic measures used in CPC analysis (i. e., low- or high-frequency coupling) are funda-

mentally different from conventional heart rate variability spectral analyses in that CPC analysis incorporates both respiration and heart rate signals and measures the degree of coupling between them.

In conclusion, the present study showed that aging and gender had significant effects on cardiopulmonary coupling dynamics. We demonstrated the applicability of this ECG-based tool to quantify objective sleep in a healthy sample. Our study result has provided a profile of physiological sleep characteristics in a healthy Taiwanese sample. We suggest that further research may enhance the use of this relatively simple ECG-based method to give a cost-efficient way to objectively evaluate sleep quality.

Clinical Implication

1. The CPC analysis described here can be used to complement traditional approaches to assess sleep quality/stability.
2. This readily reproducible ECG-based method can provide a simple, objective and cost-efficient way to evaluate and track sleep quality in clinical practice.
3. The study has provided a normal range of physiologic sleep characteristics in a healthy Taiwanese sample.

Acknowledgements

This work was supported by the National Science Council of Taiwan (NSC 95-2314-B-075-111), and Taipei Veterans General Hospital (V96C1-083, V97C1-132, V97F-005). The authors wish to thank Shan-Ing Chen, Chen-Ru Wang (Taipei Veterans General Hospital), and Zi-Hui Lin (E-Da Hospital) for their excellent technical assistance.

References

1. Buysse DJ, ncoli-Israel S, Edinger JD, Lichstein KL, Morin CM: Recommendations for a standard research assessment of insomnia. *Sleep* 2006;29: 1155-73.
2. Rechtschaffen A, Kales A: *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Los Angeles, California: UCLA Brain Information Service, 1968.
3. Armitage R, Trivedi M, Hoffmann R, Rush AJ: Relationship between objective and subjective sleep measures in depressed patients and healthy controls. *Depress Anxiety*. 1997;5:97-102.
4. Saletu B: Is the subjectively experienced quality of sleep related to objective sleep parameters? *Behav Biol* 1975;13:433-44.
5. Terzano MG, Parrino L, Spaggiari MC, Palomba V, Rossi M, Smerieri A: CAP variables and arousals as sleep electroencephalogram markers for primary insomnia. *Clin Neurophysiol* 2003;114:1715-23.
6. Achermann P, Borbely AA: Dynamics of EEG slow wave activity during physiological sleep and after administration of benzodiazepine hypnotics. *Hum Neurobiol* 1987;6:203-10.
7. Ferre A, Guilleminault C, Lopes M: Cyclic alternating pattern as a sign of brain instability during sleep. *Neurologia* 2006;21:304-11.
8. Terzano MG, Parrino L: Origin and significance of the cyclic alternating pattern (CAP). *Sleep Med Rev* 2000;4:101-23.
9. Terzano MG, Mancia D, Salati MR, Costani G, Decembrino A, Parrino L: The cyclic alternating pattern as a physiologic component of normal NREM sleep. *Sleep* 1985;8:137-45.
10. Parrino L, Milioli G, De Paolis F, Grassi A, Terzano MG: Paradoxical insomnia: the role of CAP and arousals in sleep misperception. *Sleep Med* 2009;10: 1139-45.
11. Thomas RJ, Mietus JE, Peng CK, Goldberger AL: An electrocardiogram-based technique to assess cardiopulmonary coupling during sleep. *Sleep* 2005;28: 1151-61.

12. Thomas RJ, Mietus JE, Peng CK, et al.: Differentiating obstructive from central and complex sleep apnea using an automated electrocardiogram-based method. *Sleep* 2007;30:1756-69.
13. Yang AC, Yang CH, Hong CJ, et al.: Sleep state instabilities in major depressive disorder: detection and quantification with electrocardiogram-based cardiopulmonary coupling analysis. *Psychophysiology* in press.
14. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J: An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561-71.
15. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193-213.
16. Johns MW: A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-5.
17. Dumont M, Jurysta F, Lanquart JP, Migeotte PF, van de Borne P, Linkowski P: Interdependency between heart rate variability and sleep EEG: linear/non-linear? *Clin Neurophysiol* 2004;115:2031-40.
18. Kuo TB, Shaw FZ, Lai CJ, Yang CC: Asymmetry in sympathetic and vagal activities during sleep-wake transitions. *Sleep* 2008;31:311-20.
19. Driscoll HC, Serody L, Patrick S, et al.: Sleeping well, aging well: a descriptive and cross-sectional study of sleep in "successful agers" 75 and older. *Am J Geriatr Psychiatry* 2008;16:74-82.
20. Hume KI, Van F, Watson A: A field study of age and gender differences in habitual adult sleep. *J Sleep Res* 1998;7:85-94.
21. Elsenbruch S, Harnish MJ, Orr WC: Heart rate variability during waking and sleep in healthy males and females. *Sleep* 1999;22:1067-71.
22. van Eijndhoven P, van Wingen G, van Oijen K, et al.: Amygdala volume marks the acute state in the early course of depression. *Biol Psychiatry* 2009;65:812-8.
23. Bae JN, MacFall JR, Krishnan KR, Payne ME, Steffens DC, Taylor WD: Dorsolateral prefrontal cortex and anterior cingulate cortex white matter alterations in late-life depression. *Biol Psychiatry* 2006; 60:1356-63.
24. Drevets WC, Price JL, Furey ML: Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct* 2008;213:93-118.