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A study of the dynamic interactions between sleep EEG and heart rate variability in healthy young men

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Abstract

Objective: We investigated the interactions between heart rate variability and sleep electroencephalogram power spectra.

Methods: Heart rate and sleep electroencephalogram signals were recorded in 8 healthy young men. Spectral analysis was applied to electrocardiogram and electroencephalogram recordings. Spectral components of RR intervals were studied across sleep stages. The cross-spectrum maximum was determined as well as coherencies, gains and phase shifts between normalized high frequency of RR intervals and all electroencephalographic frequency bands, calculated over the first 3 NREM-REM cycles.

Results: RR intervals increased from awake to NREM and decreased during REM. Normalized low frequency decreased from awake to NREM and increased during REM while normalized high frequency evolved conversely. Low to high frequency ratio developed in opposition to RR intervals. Coherencies between normalized high frequency and power spectra were high for all bands. The gain was highest for delta band. Phase shift between normalized high frequency and delta differed from zero and modifications in normalized high frequency preceded changes in delta by 41 ± 14°.

Conclusions: Our study demonstrates that: (1) all electroencephalographic power bands are linked to normalized high frequency; (2) modifications in cardiac vagal activity show predominantly parallel changes and precede changes in delta band by a phase shift corresponding to a lead of 12 ± 5 min.

Keywords: Sleep; RR interval; Spectral analysis; Delta band; Cardiac autonomic control; Time delay

1. Introduction

Numerous cardiovascular events occur during nocturnal sleep (Vanoli et al., 1995; Lavery et al., 1997; Peled et al., 1999; Crasset et al., 2001); indeed, cardiovascular control is markedly affected by nocturnal sleep (Mancia, 1993; Somers et al., 1993). Spectral analysis has been applied to the electroencephalogram (EEG) signal to define 5 spectral frequency bands (delta, theta, alpha, beta and sigma) that characterize sleep in detail (Aeschbach and Borbely, 1993), and can be applied to the RR interval (RRI, the time between two successive R waves of the QRS signal on the electrocardiogram (ECG)) also, to assess changes in cardiac autonomic control (Akselrod et al., 1981; Vanoli et al., 1995). In healthy subjects, heart rate decreases during non-rapid-eye-movement (NREM) sleep and increases during rapid-eye-movement (REM) sleep (Somers et al., 1993; Cajochen et al., 1994; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Crasset et al., 2001). In addition, in healthy humans, heart rate displays low-frequency (LF) oscillations – a marker of sympathetic predominance (Pagani et al., 1986) that increase during REM sleep (Zemaityte et al., 1986; Berlad et al., 1993; Vanoli et al., 1995; Bonnet and Arand, 1997) – and faster oscillations of the respiratory frequency (high frequency, HF), a marker of vagal activity that predominate during

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NREM sleep (Zemaityte et al., 1986; Berlad et al., 1993; Vanoli et al., 1995; Bonnet and Arand, 1997).

Limited data are available on the dynamic interactions between sleep EEG and RRI variability (Charloux et al., 1998; Otzenberger et al., 1998; Ehrhart et al., 2000; Brandenberger et al., 2001). In particular, no information exists on which frequency band in the EEG signal is most related to the cardiac autonomic control during sleep; and little is known about the time series interactions between EEG dynamics and heart rate variability (HRV) during the night (Otzenberger et al., 1998; Ehrhart et al., 2000; Brandenberger et al., 2001).

The investigation of dynamic interactions between the spectral power bands of sleep EEGs and the HF or LF bands of HRV may contribute to a better understanding of the physiological mechanisms underlying the interactions between sleep and cardiac autonomic control.

2. Methods

2.1. Subjects

Eight young adult males aged between 18 and 23 years (mean 20.5 years) participated in the study. They were paid student volunteers, studying at the Sleep Laboratory of the ULB-Erasme Hospital. All subjects were healthy, with no current or past somatic, psychiatric, or sleep pathologies such as apnea-hypopnea syndrome, periodic legs movement syndrome, parasomnia and snoring. None had a family history of mental disorders. The participants reported a regular sleep-wake schedule and no current or past drug use, alcohol abuse, or excessive caffeine consumption.

Each subject stayed one night free of monitoring, to adjust to this sleep unit. This was followed by a night of recorded polysomnography to detect sleep pathologies as described above, and then recorded monitoring for two consecutive nights without measurements of respiratory and leg movements. Subjects were not allowed to sleep during the day, and were asked to retire around 23:00 h and allowed to wake spontaneously in the morning.

2.2. Readings

Polysomnography was recorded on the second night with a 19-channel digital polygraph (Brainnet, Medatec, Brussels, Belgium) to detect sleep pathologies as described previously. Two electrooculograms (EOG), 3 EEGs (Fz-Ax, Cz-Ax, Oz-Ax, where Ax was a mastoid reference), one submental electromyogram (EMG), and ECG activity were all recorded.

Oxyhemoglobin saturation was measured using pulse-oximetry (Biox 3740, Ohmeda, Louisville, CO). Oro-nasal airflow was detected with thermistors (Infinity, Sleepmate Technologies, Midlothian, VA). Thoracic and abdominal respiratory movements were recorded with piezoelectric sensors (Resp-EZ, Sleepmate Technologies, Midlothian, VA). Leg movements were detected with ankle piezo-electric movements strain gauges (Moving Images, Sleepmate Technologies).

To eliminate low-frequency artifacts, drifts and offsets, time constants of 0.3 s for the EEG and 1 s for the EOG were set on the Brainnet polygraph. Before sampling, the signals were filtered through a low-pass anti-aliasing analog filter, with a cutoff frequency of 35 Hz. All channels were sampled at 200 Hz. Respiratory sound was recorded with a microphone (MKE, Sennheiser, Wedemark, Germany) inserted into a stethoscope fixed to the larynx. The sound was sampled at 2000 Hz and a rectified sound envelope was also sampled at 50 Hz. This technique allows the visual display of the sound intensity and the EEG-synchronized audio replay through headphones. The Brainnet polygraph sampled the signals and sent the resulting data to an Ethernet network, via the Netbios protocol. Data were digitized with a 12-bit analog-to-digital converter and recorded in digital format during the experiment. An acquisition program has been developed (Endymion, 1993–2002, Sleep Laboratory, Erasme Hospital) to read and store the data in the EDF file format (Kemp et al., 1992). During the 3rd and the 4th night, polysomnography was only recorded with two electrooculograms, 3 EEGs (Fz-Ax, Cz-Ax, Oz-Ax, where Ax was a mastoid reference), one submental electromyogram, and ECG activity. The other recordings were not performed in order not to disturb the sleep.

For subsequent analysis, the EEG was stored at 100 Hz, the EOG at 50 Hz and the ECG at 200 Hz. To avoid aliasing, appropriate low-pass filters were applied before sub-sampling. All subsequent analyses, such as stage determination, spectrum calculation, and heart rate analysis were carried out on the sampled data, avoiding synchronization problems between the stages and the other calculations. Using the Endymion program, each 20 s epoch was visually scored according to standard criteria (Rechtschaffen and Kales, 1968).

Fast Fourier transformation (FFT) was applied to estimate power spectra. For the present analysis, the Cz-Ax derivation was used. After a linear detrending, FFT was applied to each 5 s data window, using a rectangular window, and results were averaged every 20 s. The power of the spectrum was scaled so that the power of a 50 μV digitized sine wave was 1250 $(\mu V)^2$. The power was grouped into 5 conventional bands: delta [0.5–3.0 Hz], theta [3.0–8.0 Hz], alpha [8.0–12.0 Hz], sigma [12.0–16.0 Hz], beta [16.0–25 Hz]. The EEG spectral components were expressed in normalized units (defined as the ratio between the power value in a specific band and the full night mean power value in this specific frequency band (Borbely et al., 1981; Aeschbach et al., 1997)).

The ECG was recorded at an upsampling rate of 400 Hz, chosen for maximum precision in measurement of the RRI data. The QRS complexes were automatically

detected using an automated algorithm and the times between the occurrences of each R wave were calculated allowing computation of the RRI time series (the time differences between two successive R waves). Premature ventricular contractions and/or ectopic beats, and artifacts were automatically detected using the following criteria: RRI $<$ 350 ms or RRI $>$ 1500 ms. These 'abnormal' values were removed and the RRI times series was linearly interpolated with the surrounding values. All detected events and interpolated values were visually inspected. The RRI power spectral analysis was performed according to the recommendations of the Task Force (1996). A cubic-spline interpolation and resampling algorithm was applied to obtain a RRI time series regularly sampled at 8 Hz, and the power spectrum was computed each 20 s in a 120 s window. This 120 s window was then shifted ahead by 20 s (Fig. 1). Hence, while the analyzed windows contained 120 s of RRI, the window shifts permitted us to obtain a value for the LF and HF HRV every 20 s. This allowed us to obtain the same number of ECG and EEG spectral estimates. For each window the RRI was in turn detrended, Hanning windowed and Fast Fourier transformed. LF (0.04 Hz $< f <$ 0.15 Hz) and HF (0.15 Hz $< f <$ 0.4 Hz) spectral components were then computed. Normalized LF, $LF_{nu} = LF/(LF + HF)$, and normalized HF, $HF_{nu} = HF/(LF + HF)$, were calculated as well as the LF to HF ratio (LF/HF). For each nightlong recording, the time series of HF_{nu}, LF/HF, and EEG power in each spectral band were constructed with one value for each 20 s, corresponding to the duration of the scoring window. HRV analysis and fast Fourier transformations were performed with the software package MATLAB (The Math Works Inc., USA) and its signal processing toolbox (Matlab 6.1 with Signal Processing Toolbox 5.1). As a result, the power spectral density was computed using the spectrogram algorithm which uses either FFT or chirp-z transform on 120 s of data sampled at 8 Hz with appropriate zero padding to produce a 256 points PSD starting from 0 to 0.5 Hz.

2.3. Coherency analysis

From the two last nights of recording, that with no artifact was chosen. If neither night showed an artifact, one

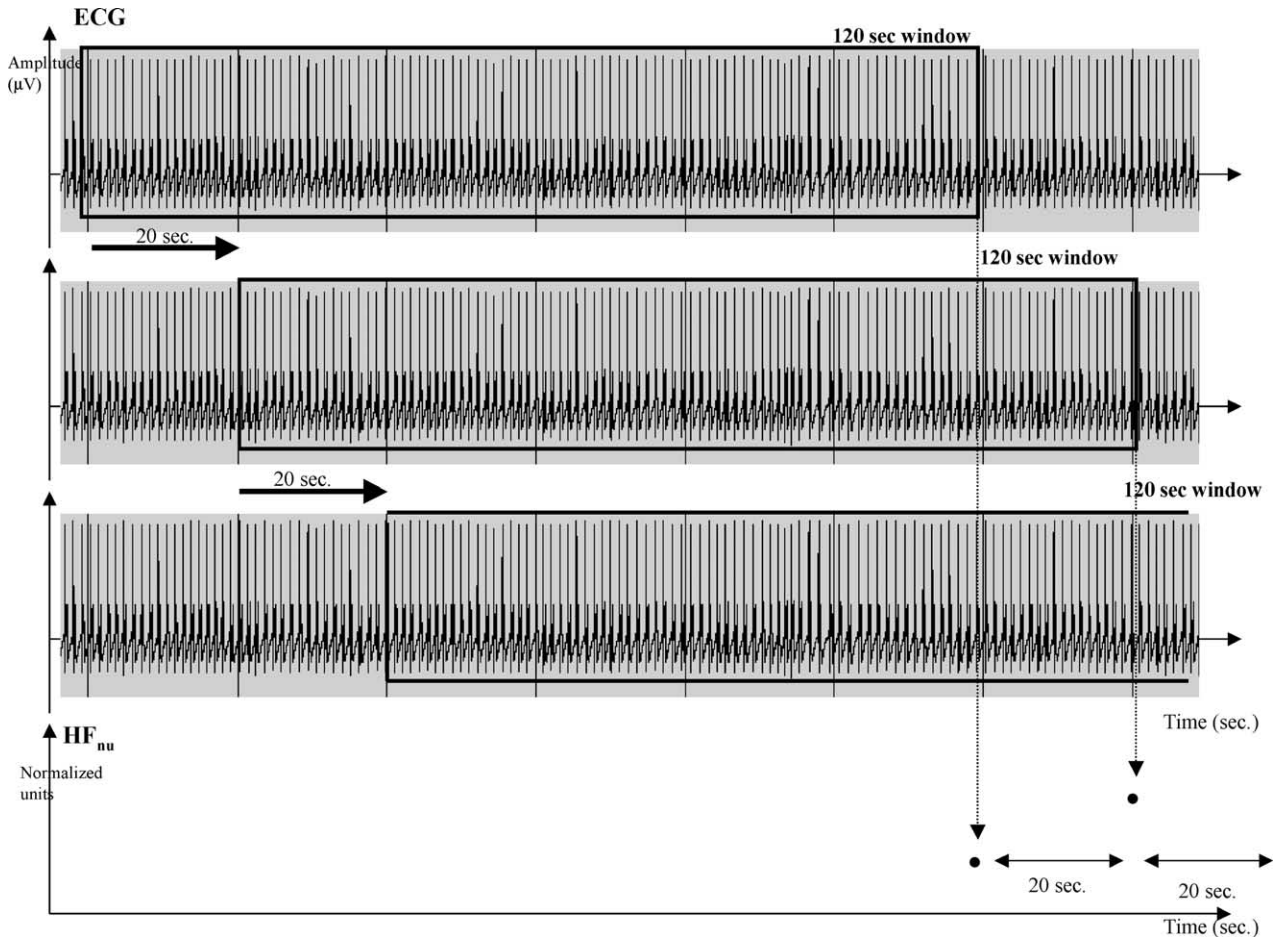

Fig. 1. The RRI power spectrum components, LF_{nu} and HF_{nu}, were computed from the ECG on a 120 s window. This 120 s window was then shifted ahead by 20 s. Each 120 s window corresponded to one spectral value for LF_{nu} and HF_{nu}. As a result, a spectral value was obtained each 20 s. On this figure, only HF_{nu} is represented.

was selected randomly. Artifacts were detected visually and by computer.

To analyze the relationship between cardiac vagal activity and the sleep EEG, a traditional coherency analysis was applied (Koopmans, 1974). This method consists of characterizing the linear relationship in the frequency domain between two continuous variables $x(f)$ and $y(f)$ (see details in Appendix A or Koopmans, 1974). In our study, the variable x was the marker of vagal activity (HF_{nu}: the normalized HF variability of RRI) and y was the normalized power density of one band of the EEG (alpha, beta, delta, sigma and theta). Bands of the EEG are tested one by one against HF_{nu}. Stationarity of the time series is required for coherency analysis (Koopmans, 1974). We therefore limited our investigation to the first 3 NREM-REM cycles, this restriction representing a compromise between the requirement for stationarity and the increase in frequency resolution in power spectra and coherency estimates.

The cross-spectrum, Pxy, between x and y data is shown in Fig. 2. The frequency, $f_{NREM\text{-}REM}$, of the common oscillation present around the NREM-REM rhythm is identified as the main peak in the cross-spectrum Pxy

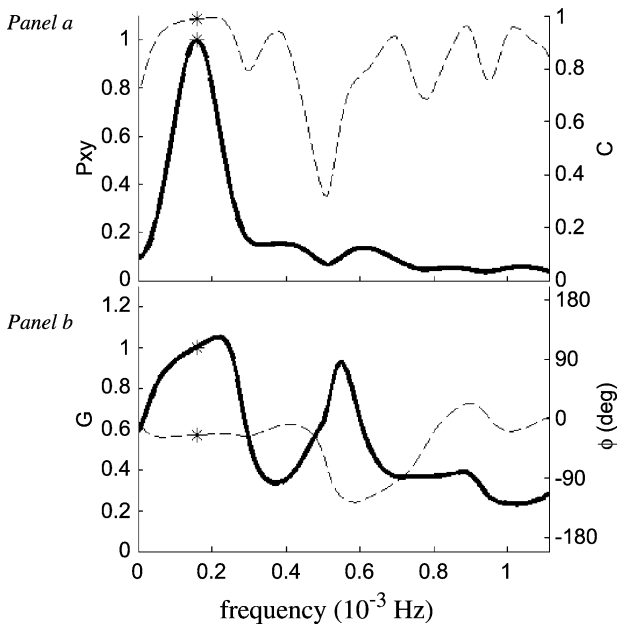

Fig. 2. Values of cross-spectrum (Pxy), coherency (C), gain (G) and phase shift (Φ) in degrees (deg) between HF_{nu} of RRI variability and normalized delta EEG band for a subject. The cross-spectrum $Pxy(f)$, which is the cross-spectral density of x and y, is the natural tool for examining the linear relationship between two times series x and y in the frequency domain. The coherency is a measure of the relative strength of the linear relationship between the two time series. The gain can be interpreted as the regression coefficient of the process y on the process x at any frequency f. The frequency corresponding to the maximum of the cross-spectrum is marked by an asterisk (*). Pxy is represented by the bold line in panel (a) while C is represented by the dashed line on the same panel. G is represented by the bold line in panel (b) while Φ is represented by the dashed line. In this figure, the variable x is the marker of vagal activity (HF_{nu}: the normalized HF variability of RRI) and y is the normalized power density of delta band of the EEG.

below 1.1×10^{-3} Hz, a limit corresponding to the value we defined for the minimum duration of one NREM-REM cycle. Indeed, 15 min is the minimum time between two successive REM epochs to define a new NREM-REM cycle (Rechtschaffen and Kales, 1968).

Fig. 2 also shows the coherency, C, between x and y. In the frequency domain, the coherency has a similar meaning to the squared correlation coefficient in the time domain, and is thus a measure of the relative strength of the linear relationship between the two time series (Koopmans, 1974). The coherency can be interpreted as the proportion of the power of one time series that can be explained by its linear regression on the other series at a given frequency f. A coherency > 0.5 means that the variance shared by both variables is greater than 50% at the frequency of interest.

The corresponding gain and phase shift were extracted for further analysis (Fig. 2). The gain can be interpreted as the regression coefficient of the process y on the process x at any frequency f. The phase shift at any frequency f can be expressed in time units by dividing the angular phase shift by the frequency f.

The gain and phase lag between oscillations in the HF_{nu} band of RRI and each frequency band of EEG were calculated only when the coherency between this data was > 0.5 (Taylor et al., 1998).

2.4. Statistics

Values are expressed as mean ± standard deviation. An analysis of variance for repeated measures was used and a $P < 0.05$ value was considered significant (Statview, Abacus). We used a Bonferroni correction to determine the significance levels of the pairwise contrasts. Comparisons were realized between NREM sleep or delta band and each of the other sleep stages or the other sleep EEG frequency bands, respectively.

Table 1
First 3 NREM-REM periods and phase shift between HF_{nu} of RRI variability and normalized delta EEG band with its corresponding time lag for each subject

Subject	First 3 NREM-REM periods (min)	Phase shift (degrees)[a]	Time lag (min)[a]
1	284	−46	−9
2	251	−23	−7
3	360	−54	−20
4	249	−34	−7
5	281	−36	−9
6	421	−64	−17
7	315	−43	−15
8	425	−27	−10
Mean	323	−41	−12
SD	71	14	5

[a] A negative value means that cardiac vagal activity precedes the occurrence of delta waves in the EEG.

3. Results

3.1. Sleep characteristics

The mean duration of NREM sleep was 357 ± 29 min (71 ± 4%) and of REM sleep was 109 ± 15 min (22 ± 3%), while the mean duration of the awake stage was 38 ± 19 min (7 ± 4%). The sleep efficiency was 86 ± 7%. These results were in line with our previously reported normal values (Linkowski et al., 1989). The mean duration of the first 3 NREM-REM cycles was 323 ± 71 min (Table 1).

3.2. RRI variability during sleep (Fig. 3)

RRI increased during the shift from the awake stage to NREM sleep and decreased during REM sleep, while the LF_{nu} decreased during the shift from the awake stage to NREM sleep and increased during REM sleep ($P < 0.0001$). Conversely, HF_{nu} increased during NREM

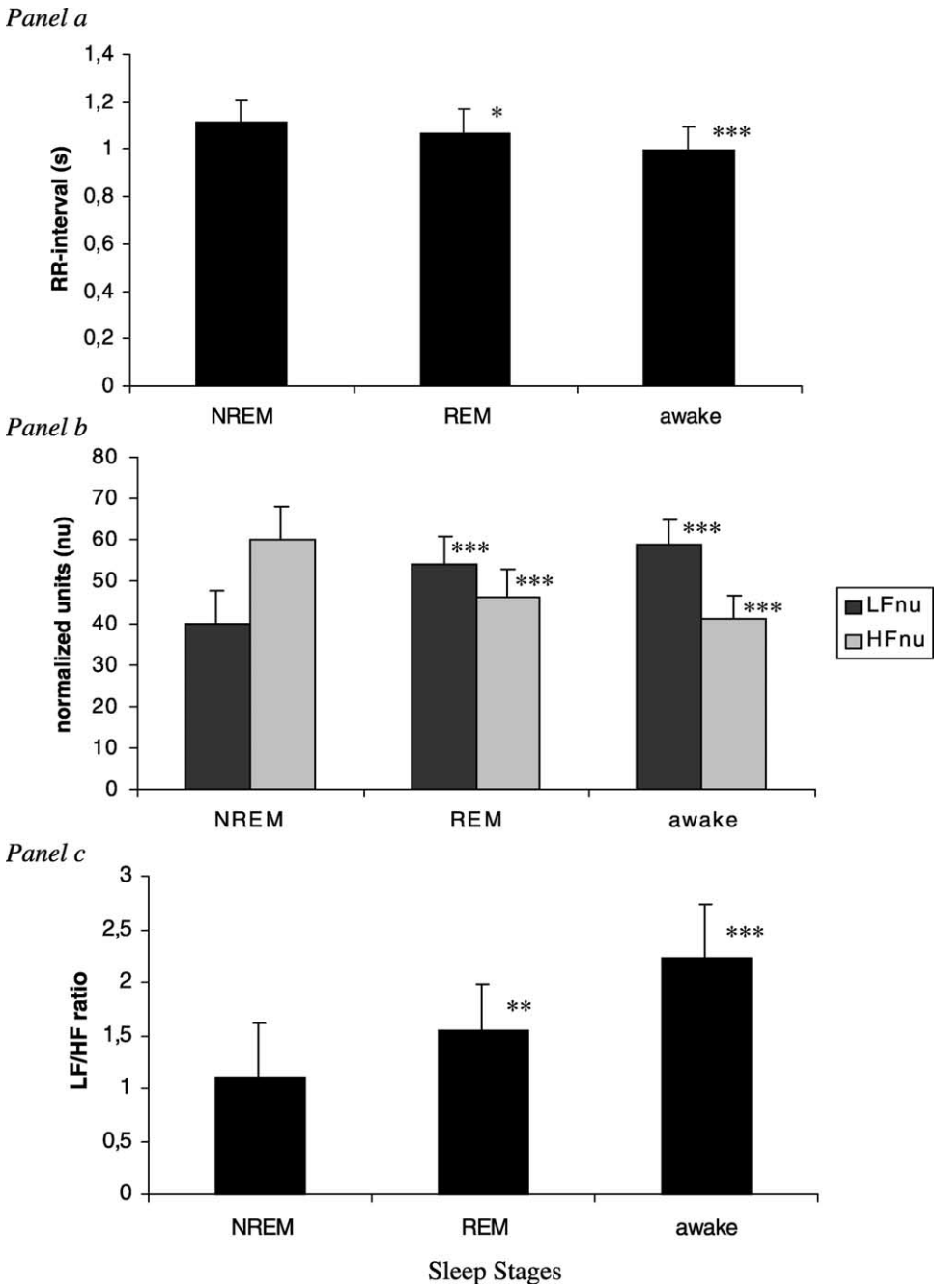

Fig. 3. (a) Variations in the duration of the RR interval (in seconds) across sleep stages. (b) Evolution of low frequency (LF) and high frequency (HF) across sleep stages. Both are expressed in normalized units (nu). (c) Variations in LF/HF ratio across sleep stages. Bars: standard deviation. NREM, non-rapid-eye-movement sleep; REM, rapid-eye-movement sleep. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

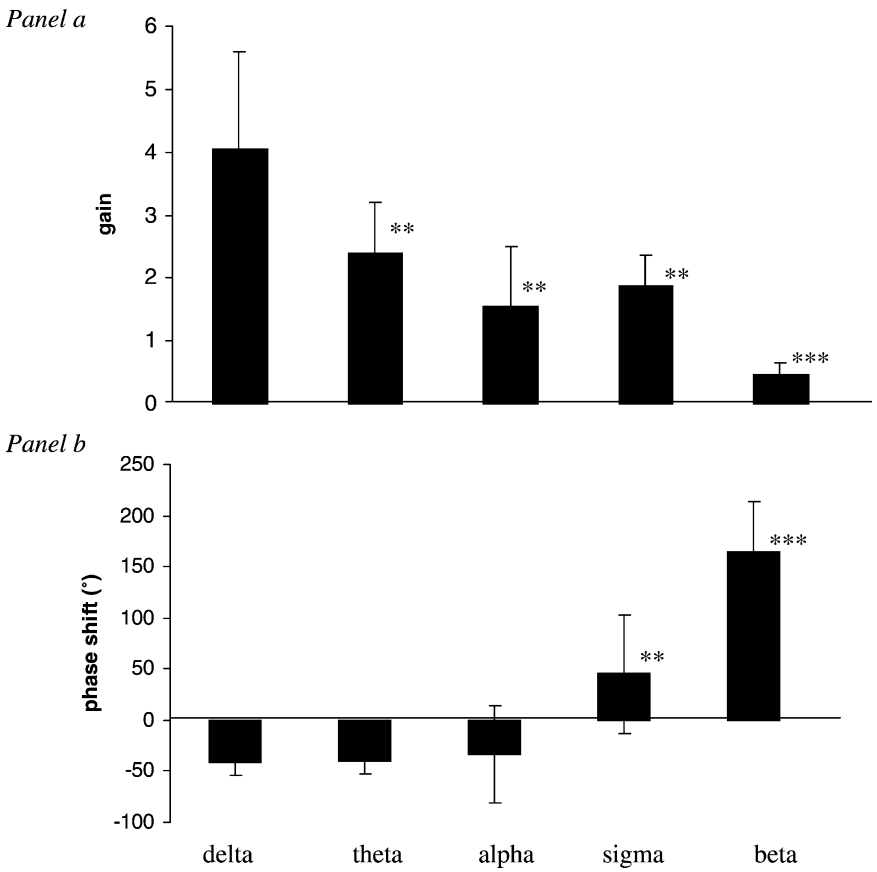

Fig. 4. Values of gains (a) and phase shifts in degrees (°) (b) between HF_{nu} of RRI and each normalized EEG power band (delta, theta, alpha, sigma, beta) across the first 3 NREM-REM cycles. Values are expressed with their standard deviation. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

sleep and decreased during REM sleep and the awake stage ($P < 0.0001$). The HF_{nu} was lower during the awake stage that during REM sleep ($P < 0.0001$). The LH/HF ratio of RRI variability peaked during the awake stage and decreased during REM sleep and NREM sleep ($P < 0.0001$).

3.3. Coherency, gain and phase shift (Fig. 4)

The range of the mean frequency, $f_{\text{NREM-REM}}$, for each EEG power band was $(1.7 \pm 0.4) \times 10^{-4}$ to $(2.1 \pm 1.2) \times 10^{-4}$ Hz ($P > 0.05$). Coherency, gain, and phase shift between HF_{nu} of RRI variability and each EEG power band were calculated at these mean frequencies.

The coherencies between each EEG power band and HF_{nu} were higher than 0.50 for all subjects. Mean coherency values between each EEG power band and HF_{nu} ranged from 0.74 ± 0.16 to 0.88 ± 0.09 with no significant differences.

The gain between the EEG power band and HF_{nu} oscillations was highest for the delta band ($P < 0.0001$), indicating that HF_{nu} oscillations of RRI variability show parallel changes to the delta power band oscillations more than to any other frequency band.

All phase shifts between EEG frequency bands and HF_{nu} fluctuations differed from zero ($P < 0.05$) except for the alpha and sigma power bands. The HF_{nu} fluctuations preceded the delta frequency oscillations in the EEG with a phase advance of $41 \pm 14°$ corresponding to a lead in shift of 12 ± 5 min (Table 1). This indicates that cardiac vagal activity increased 12 min before the occurrence of delta waves in the EEG. Such a phase advance for one of the subjects in shown in Fig. 5. Interestingly, phase shifts between beta oscillations and HF_{nu} were in phase opposition with the corresponding phase shifts between delta oscillations and HF_{nu}, this finding being logical as delta and beta bands are known to evolve out of phase (Uchida et al., 1992).

4. Discussion

Interest in the interactions between cardiac activity and sleep is growing. Indeed, a large number of cardiovascular events occur during the night (Lavery et al., 1997; Crasset et al., 2001). This study investigates the dynamic interactions between heart rate variability and EEG power

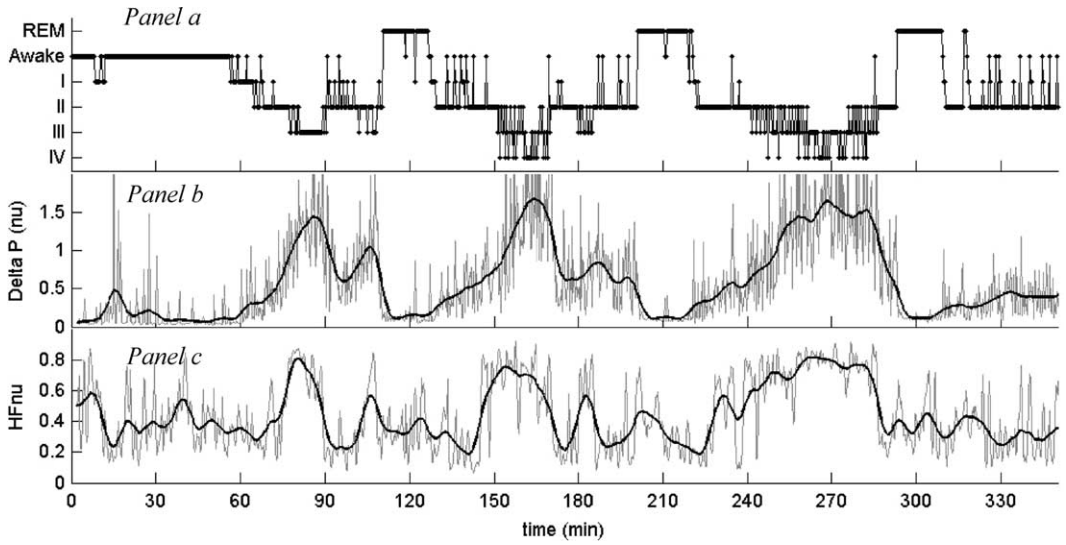

Fig. 5. Delta EEG power (Delta P) in normalized units (nu) (b) and normalized high frequency (HF_{nu}) of the RRI (c) across sleep stages (a). Visual inspection of the readings reveals that HF_{nu} fluctuations precede the delta frequency oscillations. For this subject, the phase advance between cardiac vagal activity and the occurrence of delta waves in the EEG is of 23° corresponding to a lead in shift of 7 min. Sleep stages are visualized on the hypnogram. REM, rapid-eye-movement sleep; I, stage I; II, stage II; III, stage III; IV, stage IV of sleep.

spectrum across the first 3 NREM-REM cycles of nocturnal sleep in healthy young men.

Heart rate changes during sleep have also been studied in order to determine if this could provide a new basis for sleep staging. The majority of these studies show that heart rate decreases during NREM sleep and increases during the subsequent REM sleep. These changes have not always been significant (Cajochen et al., 1994; Burgess et al., 2001). Heart rate also decreases across successive NREM-REM cycles but these changes did not reach the level of statistical significance during successive NREM episodes (Cajochen et al., 1994).

Several authors studied in details the changes in heart rate across all sleep stages (Somers et al., 1993; Vaughn et al., 1995; Pivik et al., 1996) and during the REM-NREM transitions (Cajochen et al., 1994; Burgess et al., 2001). These studies compared heart rate during awake, stage 2, slow-waves (stages 3 and 4) and REM sleep. These publications have shown a significant decrease in heart rate from REM sleep, to stage 2 sleep, to slow-waves sleep (Pivik et al., 1996). Further results demonstrated that heart rate decreased from awake to slow-waves and REM sleep to stage 2 (Vaughn et al., 1995). Heart rate also decreased from wakefulness and REM sleep to stage 4 (Somers et al., 1993). Heart rate increased rapidly over the NREM-REM transition periods and decreased more gradually at the REM-NREM transition periods. Heart rate increased several minutes before REM sleep and continues to rise into the REM sleep (Cajochen et al., 1994; Burgess et al., 2001). These observations reveal a tight link between changes in sleep stages and heart rate. They also provide a strong rationale for our study on the interactions between cardiac autonomic control and EEG variability during sleep.

We demonstrate, in agreement with others (Somers et al., 1993; Cajochen et al., 1994; Crasset et al., 2001), that RRI increase during NREM sleep and decrease during REM sleep and the awake stage in healthy young men. We confirm also previous studies showing that these changes are mediated by a reduction in the cardiac sympatho-vagal balance during NREM sleep (Vanoli et al., 1995) and by a rise in the sympatho-vagal balance during REM sleep (Berlad et al., 1993; Bonnet and Arand, 1997).

Previous research on the coupling between EEG and cardiac autonomic activity has focused mainly on the interactions between sleep delta and alpha activity and cardiac control (Ehrhart et al., 2000), while our study extended this analysis to all conventional EEG frequency bands.

To standardize studies on HRV, the Task Force (1996) recommends using 5 min windows and 500 Hz ECG. However, for short term HRV calculation, the Task Force also propose window durations of 2–5 min, and propose an optimal range of 250–500 Hz for ECG sampling. It is also mentioned that precise RRI determination can be achieved when one uses appropriate numerical methods of ECG signal with a sampling frequency of at least 100 Hz. Therefore, we believe that our sampling frequency of 200 Hz and appropriate numerical method for upsampling the ECG strictly follows the recommendations of the Task Force. Moreover, other studies have also used ECG frequencies less than 500 Hz and window durations of less than 5 min (Migeotte et al., 2003).

Other investigations on the interaction between EEG and HRV have used cross-correlation techniques to assess the link between fluctuations in EEG and cardiac autonomic control (Otzenberger et al., 1997, 1998; Charloux et al., 1998; Ehrhart et al., 2000; Brandenberger et al., 2001).

We used a slightly different method, i.e. a coherency analysis, to determine if a specific EEG frequency band varied largely with RRI variability. With this technique, we were able to demonstrate that all EEG bands disclose a high level of coherency with the HF_{nu} fluctuations in RRI. Our study, therefore, reveals that EEG spectral bands other than delta and alpha are also closely linked to changes in cardiac autonomic activity.

Our analysis allowed us to determine the gain between changes in RRI variability and EEG power bands. The gain describes in a linear manner the magnitude of changes in a specific EEG frequency band associated with modifications in HF_{nu} variability of RRI. We demonstrate that the gain was larger for the delta band than for all other bands. Thus, modifications in cardiac autonomic regulation are mostly associated with changes in the delta EEG band.

The Brandenberger and Otzenberger groups assessed a delay of 1–2 or 5 min between changes in the HF of HRV and EEG delta activity, but with a limited accuracy ranging from 1 to 5 min, respectively (Otzenberger et al., 1997; Brandenberger et al., 2001). The present investigation allowed us to assess these delays with a time resolution of just 20 s and to show that changes in cardiac vagal activity precede changes in delta EEG power by a phase shift of $41 \pm 14°$ corresponding to 12 ± 5 min. Therefore, our results clearly reject the hypothesis of a null phase shift or a null minute advance. Our findings are also different from reports where changes in cardiac autonomic control are preceded by 5 ± 5 min changes in delta EEG variability (Brandenberger et al., 2001). The different delay in our study could be due to the improved time resolution.

With regard to the presentation of average results for our group of subjects, angle phase shift is preferred to time lag, as illustrated below. Indeed, NREM-REM cycles show large inter-subject differences (Table 1). Therefore, computing a time advance by dividing the relative phase advance by its corresponding frequency introduces a supplementary source of inter-subject variability in the calculation of the group average. For each subject, the phase shift is computed and the corresponding time delay is then derived by using the corresponding individual $f_{NREM\text{-}REM}$ frequency. The group average phase shift (in degrees) and time lag (in seconds) are then computed with relative standard deviations of 33 and 43%, respectively. Average phase shifts provide a more precise determination than time lags.

The results obtained for relative standard deviations suggest that the brain-stem directed cardiovascular control and sleep are not related to each other by a simple oscillator mechanism that would introduce a time delay between the two physiological functions. A possible way of describing the relation between cardiovascular control and sleep could be a system of two coupled oscillators (Chang et al., 2000). This system could be viewed as a brain-stem structure involved in the cardiac autonomic control with a phase coupling the brain-stem structure to the sleep regulation structures, such as the thalamus and cortex. Each of these units would be paired with a different phase lag. However, these suggestions are speculative and more study is needed to confirm or invalidate this hypothesis.

Possible limitations of our methodology and interpretation of our results may include the facts that the time series under investigation here were not stationary during the night and that their interrelationship is not purely linear. We limited our analysis to the first 3 NREM-REM cycles to reduce the possible impact of non-stationarity. Nevertheless, there was not rigorous stationarity. However, a pure linear relationship is unlikely between sleep and cardiovascular regulation mechanisms, and similar conditions to those used in this study, with a failure to meet strict stationarity requirements, are common to nearly all physiological studies on healthy humans. For example, Pagani et al. (1986), in their study to assess the relative role of vagal and sympathetic activities determining the variability in heart rate and arterial pressure, and de Boer and colleagues, in their beat-to-beat model of the cardiovascular system studying the spontaneous short-term variability in arterial blood pressure and heart rate (de Boer et al., 1987), used transfer function analysis in a very similar way to us, without satisfying a strict linear relationship or stationarity.

HRV is not only under autonomic control but is also influenced by changes in the breathing pattern (van de Borne et al., 2001), not assessed in the present study. Respiration is more irregular during REM sleep and this mechanism favors a reduction in the HF variability of RRI. However, we have observed that changes in the breathing pattern during sleep contribute only modestly to the nocturnal changes in RRI variability (van de Borne et al., 1995). Thus, it is unlikely that reduction in the HF variability of RRI due to irregular respiration interfered importantly with our measure of HF_{nu}.

In conclusion, our study reveals the new findings that all EEG spectral bands are closely linked to cardiac autonomic activity. Moreover, among the EEG bands, the delta power band suffers the largest variations in response to the HF_{nu} of RRI variability, reflecting the vagal cardiac autonomic regulation. Finally, a physiological regulatory sequence is indicated by the observation that changes in cardiac autonomic activity precede changes in the EEG power bands during sleep.

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Appendix A

The cross-spectrum $Pxy(f)$ is the natural tool for examining the linear relationship between two times series x and y in the frequency domain. More precisely when expressing y (the output, here the EEG delta band) as a linear filtered version of x (the input, here the *HFnu*), the linear filter whose transfer function $H(f)$ is given by

$$H(f) = P_{xy}(f)/P_{xx}(f) \tag{1}$$

with $Pxx(f)$ the x autospectrum, minimizes the mean squared error resulting from this linear description. The corresponding gain $G(f)$ and phase shift $\Phi(f)$ are given by

$$G(f) = |H(f)| \tag{2}$$

$$\Phi(f) = \tan^{-1}\left(H_{\mathrm{I}}(f)/H_{\mathrm{R}}(f)\right) \tag{3}$$

where $|H(f)|$, $H_{\mathrm{I}}(f)$ and $H_{\mathrm{R}}(f)$ denote the modulus, the imaginary and real part of $H(f)$, respectively.

The coherency $C(f)$ defined as

$$C(f) = \left|P_{xy}(f)\right|^2 \Big/ P_{xx}(f)P_{yy}(f) \tag{4}$$

measures the reliability of the transfer function estimate and thus the reliability of the linearity of the x-y relation.

The closer $C(f)$ is to 1, the more closely the two processes x and y at frequency f are linearly related. $C(f) = 0$ indicates total linear independence of the two signals.

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