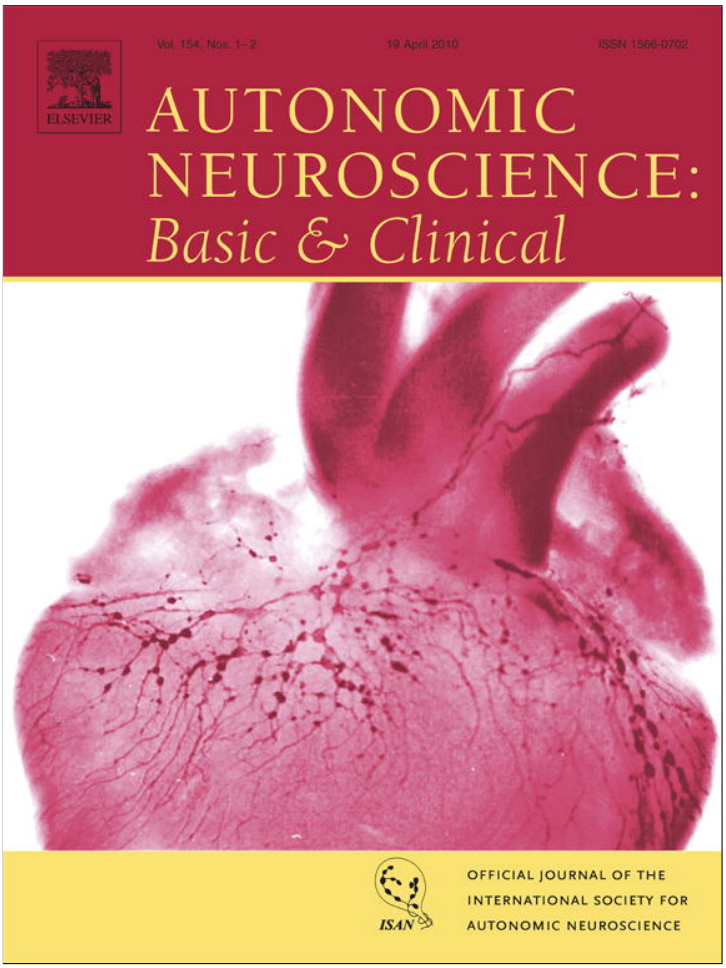

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Nonlinear analysis of heart rate variability within independent frequency components during the sleep–wake cycle

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ABSTRACT

Heart rate variability (HRV) is a complex signal that results from the contribution of different sources of oscillation related to the autonomic nervous system activity. Although linear analysis of HRV has been applied to sleep studies, the nonlinear dynamics of HRV underlying frequency components during sleep is less known. We conducted a study to evaluate nonlinear HRV within independent frequency components in wake status, slow-wave sleep (SWS, stages III or IV of non-rapid eye movement sleep), and rapid-eye-movement sleep (REM). The sample included 10 healthy adults. Polysomnography was performed to detect sleep stages. HRV was studied globally during each phase and then very low frequency (VLF), low frequency (LF) and high frequency (HF) components were separated by means of the wavelet transform algorithm. HRV nonlinear dynamics was estimated with sample entropy (SampEn). A higher SampEn was found when analyzing global variability (Wake: 1.53 ± 0.28, SWS: 1.76 ± 0.32, REM: 1.45 ± 0.19, $p = 0.005$) and VLF variability (Wake: 0.13 ± 0.03, SWS: 0.19 ± 0.03, REM: 0.14 ± 0.03, $p < 0.001$) at SWS. REM was similar to wake status regarding nonlinear HRV. We propose nonlinear HRV is a useful index of the autonomic activity that characterizes the different sleep–wake cycle stages.

1. Introduction

The relatively constant heart rate generated by the sinus node is modulated by several factors that result in a complex heart rate signal. Its high frequency (HF) component (0.15–0.4 Hz) is related to respiratory sinus arrhythmia and mediated solely by parasympathetic activity, whereas the low frequency (LF) component (0.04–0.15 Hz) is related to baroreflex control and depends upon sympathetic and parasympathetic mechanisms. A very low frequency (VLF) component (<0.04 Hz) of an uncertain origin is also found and has been attributed to thermoregulatory fluctuations in vasomotor tone as well as to humoral factors such as the renin–angiotensin system (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Stauss, 2003). In addition, heart rate variability (HRV) shows fractal scaling and nonlinear properties derived from the complex interaction of the autonomic tone and its central organization as well as from exteroceptive and interoceptive influences (Benarroch, 1993; Seely and Macklem, 2004). The nonlinear dynamics of HRV has been characterized in various forms, including short-term fractal exponent alpha (alpha-s), and sample entropy (SampEn) (Iyengar et al., 1996; Richman and Moorman, 2000).

Concerning sleep, the changes in HRV have been used as a tool to explore the sympathovagal balance continuously during this process (Otzenberger et al., 1998). Slow-wave sleep (SWS, stages III or IV of non-rapid eye movement sleep) is characterized by decreased linear LF-HRV with a relative predominance of linear HF-HRV as compared to the waking state (Busek et al., 2005). Rapid Eye Movements (REM) sleep is characterized by a HRV pattern with increased linear variability as compared to SWS and wakefulness (Busek et al., 2005). There is a paucity of studies of nonlinear HRV during sleep, but available evidence suggests that nonlinear HRV is significantly higher during SWS as compared to REM sleep (Bunde et al., 2000; Togo and Yamamoto, 2001). There is increasing evidence that certain HRV measures are particularly accurate in their description of nonlinear short time HRV, including alpha-s and SampEn indexes (Seely and Macklem, 2004; Peña et al., 2009) but there are no publications employing these measures to the characterization of sleep phases. Indeed, nonlinear HRV within specific frequency components may

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help to explain the physiologic mechanisms underlying those phases (Vigo et al., 2005).

In contrast to traditional time- and frequency-domain HRV analyses (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), which quantify either RR variability along time or frequency power, the Discrete Wavelet Transform permits the assessment of frequency power changes along time (Pichot et al., 1999), giving optimal resolution both in time and in frequency domains and, thus, allowing the reconstruction of the original signal from independent frequency components (Quian and Garcia, 2003; Vigo et al., 2005). Once the reconstructed signal is obtained, nonlinear HRV can be assessed within a specific frequency band (Thurner et al., 1998; Vigo et al., 2005). This method would thus be particularly suitable for accurate description of autonomic phenomena during different phases of the sleep–wake cycle.

In the present study we tested the hypothesis that wake, REM and SWS are characterized by specific features of HRV nonlinear dynamics. In this context, we applied the analysis of individual HRV components as described above, testing whether this tool permits a characterization of peripheral autonomic control that distinguishes between phases of the sleep–wake cycle.

2. Materials and methods

2.1. Subjects

Twelve healthy males between 21 and 32 years old, who gave their written informed consent as approved by the local board, participated in this study. Exclusion criteria were the presence of chronic medical conditions warranting treatment, a lifetime diagnosis of depression, anxiety or psychosis, the presence of known sleep disturbances as reported by the participant, an Epworth Sleepiness Scale >10 points, or the presence of a respiratory disturbance index of more than five events per hour.

2.2. Recording procedure and polysomnography (PSG) analysis

We continuously monitored electroencephalogram (EEG, seven derivations), electrooculogram (EOG), electrocardiogram (ECG, one derivation), electromyogram of calf, arm, and chin muscles, blood oxygen saturation, abdominal and thoracic pletismography, air flow, and microphone (Akonic Neurotrace, Akonic SA, Buenos Aires, Argentina). On the day of the study, participants arrived at 22.00 h. Lights were off between 00.00 h and 06.00 h. Sleep architecture was determined in each subject according to Rechtschaffen and Kales criteria as assessed by two experienced sleep medicine specialists (JD and ER).

2.3. Heart rate variability (HRV) analysis

A) Epochs: We analyzed 5-min epochs of waking state, stage III or IV of non-REM sleep, and REM sleep. These epochs corresponded to a 5-min waking period before lights were off and the first complete 5-min period of each sleep stage that was free of micro-awakenings or respiratory disturbances. RR intervals resulting from sinus beats were used for the analysis. We visually identified and manually tagged premature and lost beats in the original file of RR intervals. These abnormal beats were replaced by RR intervals resulting from linear interpolation. Only series with less than 5% of abnormal beats were accepted (Pikkujamsa et al., 1999). Once the linear trend was eliminated the time series was used for non spectral HRV analysis (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). For detrended fluctuation analysis and sample entropy calculation mean value was also subtracted (Iyengar et al., 1996; Richman and Moorman, 2000). Finally, the signal was evenly sampled with a frequency of 2.4 Hz by means of a spline interpolation algorithm for Fourier transform and, in addition, zero padded to the next higher power of two for wavelet transform (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Pichot et al., 1999).

B) HRV linear analysis: Time-domain (non spectral) measurement of HRV included the mean RR interval (RRm), and the standard deviation of all normal RR intervals (SDNN) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Frequency-domain (spectral) measurements of HRV were obtained by Fast Fourier Transform using a Hamming window, and included total spectral power (TA, 0–0.4 Hz, ms^2), very low frequency power (VLF, <0.04 Hz, ms^2), low frequency power (LF, 0.04–0.15 Hz, ms^2), high frequency power (HF, 0.15–0.4 Hz, ms^2), and their percentage values (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

C) Detrended fluctuation analysis and sample entropy: The scaling exponent αs, based on the "detrended fluctuation analysis", quantified the short-term fractal correlation properties of the interbeat time data (Iyengar et al., 1996). Values of α close to 0.5 are associated with white noise (no correlation between values), whereas values close to 1.5 are associated with Brownian noise (strong correlation between values). Values near 1 are characteristic of fractal like processes, associated with the dynamic behavior of time series generated by complex systems, such as the autonomic regulation of the sinus rhythm of a healthy subject. Sample entropy (SampEn) (Richman and Moorman, 2000) estimated the entropy of the RR interval time series as a measure of system complexity. Regular sequences will result in lower SampEn values whereas random behavior is associated with larger SampEn values. The methods we used herein were described in detail elsewhere (Iyengar et al., 1996; Richman and Moorman, 2000; Vigo et al., 2005).

D) Heart rate variability of independent frequency components: In order to assess heart rate variability of independent frequency spectrum components, the signal must be reconstructed from the components corresponding to the frequency of interest. By means of wavelet analysis, a mother waveform is "compressed" or "stretched" to obtain wavelets of different scales that are used along time comparing them with the original signal. For every scale level and time a correlation coefficient was obtained, representing the correspondence between the analysis wavelet and the original signal. This coefficient provides information about the moment that the RR interval is changing (time domain) and about the frequencies that are involved in these changes (frequency domain).

In this study, a five-level wavelet decomposition was employed to analyze the signal, using a Daubechies 4 wavelet function. Using this decomposition, wavelet level A5 approximately corresponds to the very low frequency band (VLF, 0–0.0375 Hz), wavelet levels D4–D5 to the low frequency band (LF, 0.0375–0.15 Hz), and wavelet levels D1–D3 to the high frequency band (HF, >0.15 Hz). Then, the coefficients corresponding to the filtered scale levels were zeroed. For example, for LF, levels A5 and D1–D3 but not levels D4–D5 were zeroed. Finally, the inverse discrete wavelet transform was applied, obtaining the time signal without the filtered frequency components (Pichot et al., 1999; Quian and Garcia, 2003). In order to describe the RR interval variability of independent frequency components along time, standard deviation (SD) and SampEn were measured within HF, LF and VLF components (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Thurner et al., 1998; Richman and Moorman, 2000; Lemire et al., 2000).

2.4. Statistical analysis

Normal distribution of data was assessed with a Kolmogorov–Smirnov test. Values were expressed as mean ± standard deviation. Continuous variables in different sleep stages were compared with a

repeated-measures analysis of variance (ANOVA) test followed by a post hoc Bonferroni test. All reported results are two-tailed and significance was assumed at an alpha = 0.05.

3. Results

Of 12 participants initially tested, results of 10 individuals are reported here, as one subject did not reach SWS and another exhibited hypopneic episodes during PSG. Mean age was 25.4 ± 3.8 years, body mass index was 24.3 ± 2.5 kg/m2 and mean Epworth Sleepiness Scale score was 5.3 ± 1.6 points. Subjects displayed a normal sleep architecture (Table 1).

Table 2 summarizes the results of linear and nonlinear HRV analysis. In time-domain HRV analysis, SWS was characterized by lower heart rate while REM sleep showed greater global HRV. Frequency-domain analysis revealed a higher proportion of parasympathetic activity (HF %) during SWS, whereas during REM all components displayed higher absolute values compared to the other phases studied (Table 2). Nonlinear HRV analysis shows that SWS is associated to a higher degree of randomness in heart rate dynamics (Table 2).

Table 3 shows the results of analysis of HRV independent frequency components HF, LF, and VLF. SWS is characterized by increased randomness of VLF fluctuations as measured by SampEn, whereas REM is associated with greater amplitude of all frequency components, as assessed by SD (Table 3).

Fig. 1 shows global HRV as well as HRV of VLF, LF, and HF origin, for the waking state (top panels), SWS (middle panels), and REM (bottom panels). RR intervals are expressed in SD units to facilitate comparison between different frequencies. VLF and global nonlinear fluctuations as measured by SampEn were more frequent during SWS (Fig. 1).

4. Discussion

The main observation of the present study is that SWS is characterized by higher nonlinear HRV whereas REM is associated with increased linear HRV in all frequency components. Specifically, during SWS, HRV is characterized by high-entropy VLF and increased relative amplitude in the HF component. On the other hand, REM is indistinguishable from the wake phase regarding nonlinear HRV, but is associated with increased linear HRV globally, and in all its frequency components.

In general, these results are in agreement with previously published preliminary data in animals and humans, suggesting SWS is associated with specific changes in nonlinear HRV (Raetz et al., 1991; Bunde et al., 2000; Togo and Yamamoto, 2001). Thus, SWS was previously found to exhibit a decreased fractal correlation, possibly associated to decreased central non-reflex influences (Togo and Yamamoto, 2001), and higher beat-to-beat HRV in the setting of lower global HRV, which suggests parasympathetic predominance in this sleep stage (Raetz et al., 1991). To our knowledge, however, no previous studies have used entropy measurements, which in the present study allowed the detection of a change in global HRV and VLF-HRV.

Our finding of increased entropy during SWS in the VLF-HRV component is in line with findings of a previous study of sleep HRV by Togo et al (Togo et al., 2006). These authors found both stationary and nonstationary periodic patterns in the VLF range, which were unlikely associated with muscular and respiratory movements (Togo et al., 2006). Although the physiological mechanisms underlying VLF oscillations of HRV remain unsettled, fluctuations of thermoregulatory activity, renin–angiotensin–aldosterone system and parasympathetic outflow, have been proposed as potential factors (Taylor et al., 1998). While it is known that their activity is related to sleep cycles (Charloux et al., 1999; Yang et al., 2002; Parmeggiani, 2003), future research should investigate whether these systems have VLF nonlinear oscillations during SWS, and if they are correlated to VLF-HRV.

The random pattern in the VLF-HRV component observed during SWS may also be related to random changes in EEG (Zhuang et al., 2005). It has been described that the EEG "cyclic alternating pattern" (CAP) is associated with autonomic manifestations (Ferri et al., 2000). The CAP are phasic events associated with transient activation of EEG

Table 1
Sleep architecture.

Total recording (min)	346.0 ± 41.7
Total sleep time (min)	296.0 ± 39.5
Total wake time (min)	50.0 ± 22.8
Sleep efficiency (%)	86 ± 6.3
Sleep onset (min)	14.3 ± 7.6
REM onset (min)	95.0 ± 43.0
Stage wake (%)	9.3 ± 6.6
Stage 1 (%)	1.8 ± 1.6
Stage 2 (%)	49.0 ± 11.1
Stage 3 (%)	11.9 ± 4.4
Stage 4 (%)	10.4 ± 6.3
Stage REM (%)	17.6 ± 3.5

Values are expressed as mean ± standard deviation. REM, rapid eye movements stage.

Table 2
Heart rate variability analysis.

	Wake	SWS	REM	*p*
Time domain				
RRm (ms)	892 ± 120	992 ± 130 **	943 ± 145	0.006
SDNN (ms)	65 ± 22	63 ± 25	105 ± 32 *	0.002
Frequency domain				
ln TA (ms^2)	8.12 ± 0.76	8.05 ± 0.82	9.18 ± 0.66 *	0.002
ln VLF (ms^2)	7.05 ± 0.98	6.28 ± 0.89	7.99 ± 0.66 ***	0.002
ln LF (ms^2)	6.98 ± 0.89	6.99 ± 1.11	8.19 ± 0.79 *	0.001
ln HF (ms^2)	6.50 ± 0.95	7.13 ± 0.73	7.64 ± 1.11 **	0.001
VLF (%)	38.5 ± 20.9	18.7 ± 9.17 **	33.6 ± 15.2	0.012
LF (%)	35.0 ± 14.2	37.1 ± 15.2	39.5 ± 13.3	0.635
HF (%)	26.5 ± 19.0	44.2 ± 18.0 *	26.9 ± 18.3	0.007
Nonlinear analysis				
αs	1.11 ± 0.22	0.88 ± 0.22 *	1.10 ± 0.19	0.001
SampEn	1.53 ± 0.28	1.76 ± 0.32 *	1.45 ± 0.19	0.005

Values are expressed as mean ± standard deviation. *Different from both other values, **different from wake, ***different form SWS. Repeated-measures ANOVA followed by Bonferroni post hoc test. SWS, short wave sleep (stages III or IV of non-rapid eye movement sleep); REM, rapid eye movements stage; RRm, mean RR interval; SDNN, standard deviation of all normal RR intervals; TA, total area (total spectral power); VLF, very low frequency power; LF, low frequency power; HF, high frequency power; αs, short-term scaling exponent alpha; SampEn, Sample Entropy.

Table 3
Heart rate variability analysis within independent frequency components.

	Wake	SWS	REM	*p*
VLF				
SD (ms)	35.7 ± 16.4	22.8 ± 8.2	53.4 ± 15.2 *	<0.001
SampEn	0.13 ± 0.03	0.19 ± 0.03 *	0.14 ± 0.03	<0.001
LF				
SD (ms)	34.0 ± 12.7	35.0 ± 17.4	56.3 ± 17.1 *	0.001
SampEn	0.52 ± 0.03	0.52 ± 0.09	0.52 ± 0.06	0.993
HF				
SD (ms)	31.1 ± 13.0	38.1 ± 12.3	55.5 ± 31.0	0.019
SampEn	0.93 ± 0.19	0.80 ± 0.13	0.85 ± 0.13	0.115

Values are expressed as mean ± standard deviation. *Different from both others values. Repeated-measures ANOVA followed by Bonferroni post hoc test. SWS, short wave sleep (stages III or IV of non-rapid eye movement sleep); REM, rapid eye movements stage; VLF, very low frequency; LF, low frequency; HF, high frequency; SD, standard deviation of RR intervals; SampEn, Sample Entropy.

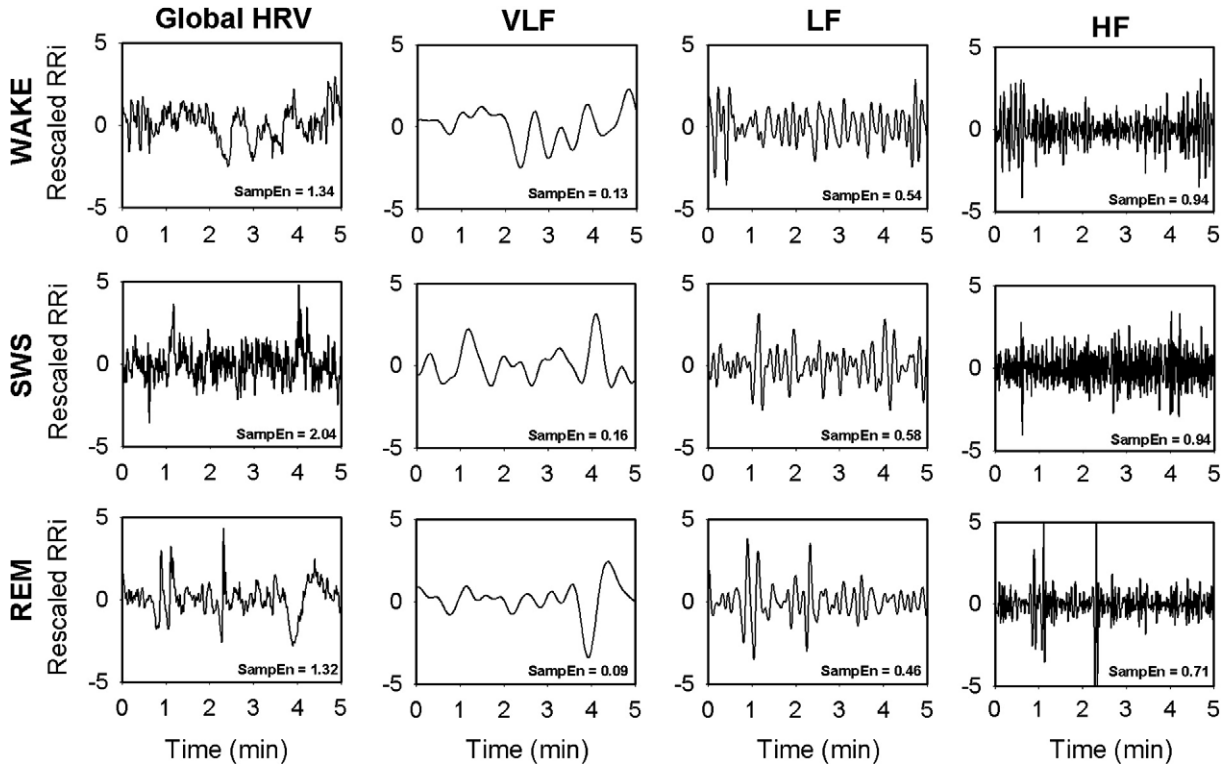

Fig. 1. Global heart rate variability and independent frequency components variability across the sleep–wake cycle. Panels show 5 min records of RR interval duration (RRi) which were rescaled as standard deviation units centered around a mean of zero, to account for differences in the mean and amplitude of heart rate fluctuations. Global HRV time series seems to be more irregular at SWS stage. SWS, short wave sleep (stages III or IV of non-rapid eye movement sleep); REM, rapid eye movements stage; RRi, RR interval duration; VLF, very low frequency; LF, low frequency; HF, high frequency; SampEn, Sample Entropy.

(phase A) that periodically interrupt the tonic type theta/delta non-rapid eye movement sleep (phase B). In stage IV these oscillations have a frequency of 0.05 Hz. The complementary condition (non CAP) is a background EEG rhythm with isolated phasic events randomly distributed (Terzano and Parrino, 2000).

Regarding REM sleep, our findings are similar to those of previous studies in which this phase seems characterized by a global increase of linear HRV (Busek et al., 2005) and similar nonlinear HRV indexes than those of wakefulness (Bunde et al., 2000). This could be explained by an activation of central structures as high as in wakefulness (Hobson and Pace-Schott, 2002) but with open-loop operations of central origin that impair the homeostasis of physiologic functions (Parmeggiani, 2005).

The analysis of linear HRV within independent frequency components during REM sleep showed that linear changes were significant for all frequency components, but especially for VLF and LF. This result was attributed to an activation of both branches of the autonomic nervous system, with a sympathovagal shift to a prevailing sympathetic activity, conditioned by several mechanisms such as an activation of orexinergic hypothalamic neurons or limbic structures, both with effects over structures of the central autonomic network (Benarroch, 1993; Busek et al., 2005).

Taken together, the results described herein are in agreement with the hypothesis, put forward by other groups (Recordati and Bellini, 2004; Kiyono et al., 2005; Katayose et al., 2009) that nonlinear HRV fluctuations could be related to the stability and energy expenditure of the sleep wake cycle stages. Active wakefulness and REM are high energy expenditure (Katayose et al., 2009), unstable states, where heart rate is controlled continually to converge to values that naturally tend to abandon (Recordati and Bellini, 2004), resulting in a decreased nonlinear HRV (Kiyono et al., 2005). At the opposite end, SWS is a low energy expenditure (Katayose et al., 2009), stable state, where heart rate naturally tends to adopt the values that characterize the state (Recordati and Bellini, 2004), with decreased central influences over heart rate (Togo and Yamamoto, 2001) that determine an increased nonlinear HRV (Kiyono et al., 2005). While this hypothesis requires elaboration, the observed results contribute to further characterize the autonomic pattern associated to sleep–wake cycle.

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