

Progressive aging does not alter the interaction between autonomic cardiac activity and delta EEG power

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Abstract

Objective: We tested the hypothesis that the reductions of the changes in the respective influence of the cardiac sympathetic and vagal activity control and delta EEG activity with aging alter the interactions between the heart rate variability (HRV) and the delta sleep EEG power band.

Methods: A polysomnography was performed on 16 healthy young men and 19 healthy middle-aged men across the first 3 NREM–REM cycles. Spectral analysis was applied to electrocardiogram and electroencephalogram recordings. High Frequency (HF_{nu}) of HRV as well as the maximum of cross-spectrum, coherency, gain and phase shifts between HF_{nu} and delta sleep EEG power band were compared between both groups.

Results: Young men experienced more deep sleep than middle-aged men ($P < 0.001$). In middle-aged subjects, HF_{nu} was lower than the HF_{nu} of their younger counterparts ($P < 0.001$), but they showed similar increases during NREM sleep and similar decreases during REM sleep as the young subjects. Cross-spectrum values, coherency, gain and phase shifts between HF_{nu} and delta were identical between the two groups. Modifications in HF_{nu} show parallel changes and precede changes in delta EEG band by a similar leads of 11 ± 6 min in young men and 9 ± 7 min in middle-aged men ($P = 0.23$).

Conclusions: Reduced changes in the respective influence of the cardiac sympathetic and vagal activity and delta EEG activity with progressive aging do not alter the relationship and phase difference between changes in the relative predominant cardiac vagal activity and delta power in middle-aged men.

Significance: Interaction between the cardiac sympathetic and vagal activity with delta EEG activity is maintained in middle-aged men.
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Keywords: Sleep; RR interval; Delta power band; Cardiac autonomic control; Young and middle-aged men; Time delay

1. Introduction

Heart rate in man is under sympathetic and vagal control. Changes in cardiac autonomic drive can be assessed by the spectral analysis of heart rate variability (HRV). Low frequency (LF) oscillations are a marker of sympathetic predominance and increase during REM sleep (Berlad et al.,

1993; Bonnet and Arand, 1997; Vanoli et al., 1995; Zemaityte et al., 1986). Faster oscillations at the breathing frequency, also called High Frequency (HF) oscillations, are a marker of vagal activity and predominate during NREM sleep (Berlad et al., 1993; Bonnet and Arand, 1997; Vanoli et al., 1995; Zemaityte et al., 1986). Several authors have studied these fluctuations in young and old men across 24 h (Jensen-Urstad et al., 1997; Yeragani et al., 1997) or across the sleep stages (Brandenberger et al., 2003; Crasset et al., 2001). They concluded that there was a relative increase in

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sympathetic activity with aging (Brandenberger et al., 2003; Crasset et al., 2001).

Sleep is also characterized by 5 spectral power bands: delta, theta, alpha, sigma and beta. These are a continuous measure of sleep quality and correspond to the various sleep stages (Aeschbach and Borbely, 1993). Several authors have studied the interaction between cardiac vagal components and sleep EEG power bands in young men (Ako et al., 2003; Brandenberger et al., 2001; Jurysta et al., 2003; Yang et al., 2002). In a previous study (Jurysta et al., 2003), we showed that HF oscillations of HRV fluctuated during the night and that this fluctuation correlated with each EEG power band. Moreover, the HF oscillations in HRV parallel changes the delta power band oscillations more than any other sleep EEG frequency band. We also described a method which allows for the estimation of the phase shift between oscillations of HRV HF power and oscillations in the EEG delta power with an improved time resolution. We showed that, in normal healthy young men, the vagal influence of changes in autonomic cardiac activity increase 12 ± 5 min before delta waves occur in the EEG.

The aim of this study was to further test the hypothesis that reductions in the cardiac vagal influence (Bonnemeier et al., 2003; Crasset et al., 2001; de Meersman, 1993) and delta wave sleep (Dijk et al., 1989; Landolt et al., 1996; Tan et al., 2000) with aging alter the coherency, gain and/or the phase shift between oscillations in the relative cardiac vagal activity and delta power band.

2. Methods

A complete description of the methods (recordings, data analysis, coherence analysis) was detailed in a previous report (Jurysta et al., 2003).

2.1. Subjects

Recordings were performed on 16 young males aged between 16 and 28 (mean 21.4 ± 2.6 years; body mass index (BMI): 22.9 ± 3.2) and 19 middle-aged males aged between 36 and 54 (mean 42.9 ± 5.2 years; BMI: 24.5 ± 2.0) across 4 successive nights at the Sleep Laboratory of the Erasme Hospital-Université Libre de Bruxelles.

All subjects were healthy and did not suffer from any somatic or psychiatric pathologies. They experienced regular sleep–wake schedules and had no current or past history of drug, alcohol or caffeine abuse.

Subjects were not allowed to sleep during the day and were asked to retire at 11 pm. They awoke spontaneously in the morning.

Sleep disorders such as apnea–hypopnea syndrome, periodic leg movement syndrome, parasomnia and snoring were screened during the second night by a polysomnograph. None of the subjects suffered from primary or secondary sleep disorders. The mean sleep apnea–hypopnea

index of participants was $1.1 \pm 0.8/h$ for the young men and $2.7 \pm 3.2/h$ for middle-aged men, while the mean index for bilateral periodic leg movements was $1.6 \pm 1.9/h$ and $1.4 \pm 3.1/h$ for young and middle-aged men, respectively. Normal values for sleep apnea–hypopnea index are $<10/h$, while those for bilateral periodic leg movement index are $<5/h$.

Each subject received a detailed description and demonstration of the procedure and apparatus involved in the study before signing an informed consent form. The study protocol was approved by the local ethical committee of the Erasme University Hospital.

2.2. Recordings

Briefly, the first night of the study was free of monitoring so that the subjects were allowed to adjust to the Sleep Unit, while the polysomnography was recorded on the second night with a 19-channel digital polygraph (Brainnet, Medatec, Brussels, Belgium) to detect sleep pathologies. This was composed by two electrooculograms (EOGs), 3 electroencephalograms (EEGs) (Fz-Ax, Cz-Ax, Oz-Ax, where Ax was a mastoid reference), one submental electromyogram (EMG), an electrocardiogram (ECG), thermistors to detect the oro-nasal airflow (Infinity™, Sleepmate Technologies, Midlothian, VA), a pulse-oximetry for oxyhemoglobin saturation (Biox 3740™, OHMEDA, Louisville, CO), a microphone to record the sound of breathing (MKE™, Sennheiser, Wedemark, Germany), piezoelectric sensors (Resp-EZ™, Sleepmate Technologies, Midlothian, VA) and ankle piezoelectric movement strain gauges (Moving Images™, Sleepmate Technologies, Midlothian, VA) to measure thoracic and abdominal breathing, and leg movements, respectively.

During the 3rd and 4th nights, polysomnography was recorded by only two EOGs, 3 EEGs (Fz-Ax, Cz-Ax, Oz-Ax, where Ax is a mastoid reference), one submental electromyogram and an ECG. The other recordings were not performed in order to attenuate discomfort during sleep.

Each signal was filtered through a low-pass anti-aliasing analog filter, with a cutoff frequency of 35 Hz and was sampled at 200 Hz to be read and stored in EDF file format (Kemp et al., 1992). The stage determination, the spectrum calculation, as well as the heart rate analysis were carried out on the sampled data. The Endymion program (Dijk and Duffy, 1999; Endymion, 1993, Sleep Laboratory, Erasme Hospital) was used to score each 20 s epoch visually in agreement with standard criteria (Rechtschaffen and Kales, 1968).

2.3. Data analysis

The Fast Fourier Transform (FFT) was applied to the Cz-Ax recording to obtain the EEG power spectra. FFT was computed on each 5-s data window and the power of the delta EEG power band (0.5–3.0 Hz) was computed. These values were subsequently averaged over 20 s windows.

The EEG spectral component was expressed in normalized units. Normalized units are defined by the ratio between the power value in a specific band and the full night mean power value in this specific frequency band (Aeschbach et al., 1997; Borbely et al., 1981). The relative delta EEG power, expressed in percentage, was also determined as the ratio between delta EEG power and total EEG power across the night.

An automated algorithm for the detection of the QRS complexes in the ECG was applied. The time differences between the R waves of two successive QRS complexes were calculated to define the RR interval (RRI) time series. Premature ventricular contraction beats and/or ectopic beats, and artifacts were automatically detected. These ‘abnormal’ values were removed and the RRI time series were linearly interpolated with the surrounding values. All detected events and interpolated values were visually inspected. The RRI power spectral analysis was performed on 120 s windows, according to the recommendations of the Task Force (1996). Shifting the 120 s windows ahead by 20 s, we obtained a value for Low Frequency (LF: $0.04 \text{ Hz} < f < 0.15 \text{ Hz}$) and High Frequency (HF: $0.15 \text{ Hz} < f < 0.4 \text{ Hz}$) HRV every 20 s. This allowed us to obtain the synchronized values of HRV and delta EEG spectral estimates. The normalized LF, $\text{LF}_{\text{nu}} = \text{LF}/(\text{LF} + \text{HF})$, and the normalized HF, $\text{HF}_{\text{nu}} = \text{HF}/(\text{LF} + \text{HF})$, were calculated as well as the LF over HF ratio (LF/HF).

HRV analysis and FFT computation 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).

2.4. Coherence analysis

For the purposes of this analysis, one artifact-free night was chosen from the last two nights. If neither night showed any artifact, one was selected randomly. Artifacts were detected by the software that was developed for data analysis and were controlled visually. Artifacts were defined by abnormal beats (as described above), and by alterations in the ECG or EEG recordings such as deviation of EEG/ECG recordings from the base-line, as an infiltration of the ECG recording in the EEG recording. Young and middle-aged subjects were compared using the first 3 NREM–REM cycles.

As described in a previous manuscript (Jurysta et al., 2003), a coherency analysis between the HF_{nu} of the RRI and the normalized delta sleep EEG power band was applied to study the relationship between the vagal influence of autonomic cardiac activity and sleep EEG.

Coherency, gain and phase shifts were calculated at the frequency ($f_{\text{NREM-REM}}$) of the main peak in the cross-spectrum between HF_{nu} and delta sleep EEG power band located below $1.1 \times 10^{-3} \text{ Hz}$. This limit corresponds to the value that 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).

Coherency is a measure in the frequency domain of the relative strength of the linear relationship between two-time series (Koopmans, 1974), the HF_{nu} of RRI and delta EEG power band. The gain can be interpreted as the regression coefficient of one process against the other process at any frequency $f_{\text{NREM-REM}}$. The phase shift at any frequency $f_{\text{NREM-REM}}$ can be expressed in time units by dividing the angular phase shift by the frequency $f_{\text{NREM-REM}}$.

2.5. Statistics

Values are expressed as mean \pm standard deviation. A *t*-test for independent sampling was performed to test differences between both groups (young vs middle-aged). Within each group, an analysis of variance for repeated measures was used to compare the characteristics of sleep stages and the spectral components of HRV. A $P < 0.05$ value was considered significant. All statistical procedures were computed using SPSS software (SPSS, 11.5, SPSS, Inc., Chicago, USA).

3. Results

3.1. Sleep characteristics

As expected (Dijk et al., 1989, 1999; Landolt et al., 1996), deep sleep duration and delta power percentage decreased with aging ($P < 0.001$, for both comparisons). The mean duration of the first 3 NREM–REM cycles was not different between the groups nor was the mean duration of light sleep, REM sleep and awake stage. The efficiency of sleep, defined as the ratio between ‘total sleep time’ and ‘time in bed’, did not show any significant differences between young and middle-aged men. The values are shown in Table 1.

Table 1
Sleep characteristics in young and middle-aged men across the first three NREM–REM cycles

Parameters	Young men	Middle-aged men	<i>P</i> value
Total mean duration (h:min)	5:17 \pm 1:08	4:43 \pm 0:42	0.085
Efficiency (%)	88.6 \pm 6.1	88.3 \pm 4.1	0.846
Light sleep duration (min)	177 \pm 42	183 \pm 33	0.298
Slow waves sleep duration (min)	65 \pm 26	27 \pm 21	0.000***
REM duration (min)	63 \pm 26	60 \pm 21	0.128
Awake duration (min)	11 \pm 5	14 \pm 8	0.853
Delta power (%)	80.8 \pm 2.6	72.0 \pm 6.7	0.000***

Deep sleep duration (expressed in minutes) and delta power (expressed in percentage) is larger in young men than middle-aged men ($P < 0.001$ for both). The other sleep characteristics do not differ between young and middle-aged men. The results are expressed as mean \pm standard deviation for the three first NREM–REM cycles. *** $P < 0.001$.

3.2. RRI variability during sleep

Although RRI of the young men was longer than that of the middle-aged men during NREM sleep ($P < 0.01$) and REM sleep ($P < 0.05$), RRI showed the same progression between both groups across the night: RRI increased during the shift from the awake stage to NREM sleep ($P < 0.001$) and decreased during the REM sleep ($P < 0.01$) (Fig. 1a).

In middle-aged subjects HF_{nu} was lower than HF_{nu} of the young subjects across all sleep stages ($P < 0.001$) but showed the same modifications during the night: HF_{nu} increased during the NREM sleep and decreased during REM sleep and awake stage ($P < 0.001$) (Fig. 1b). Conversely, LF_{nu} was larger in the middle-aged group than in the young group ($P < 0.001$) and showed an inverse relationship to the HF_{nu} across sleep stages (Fig. 1b).

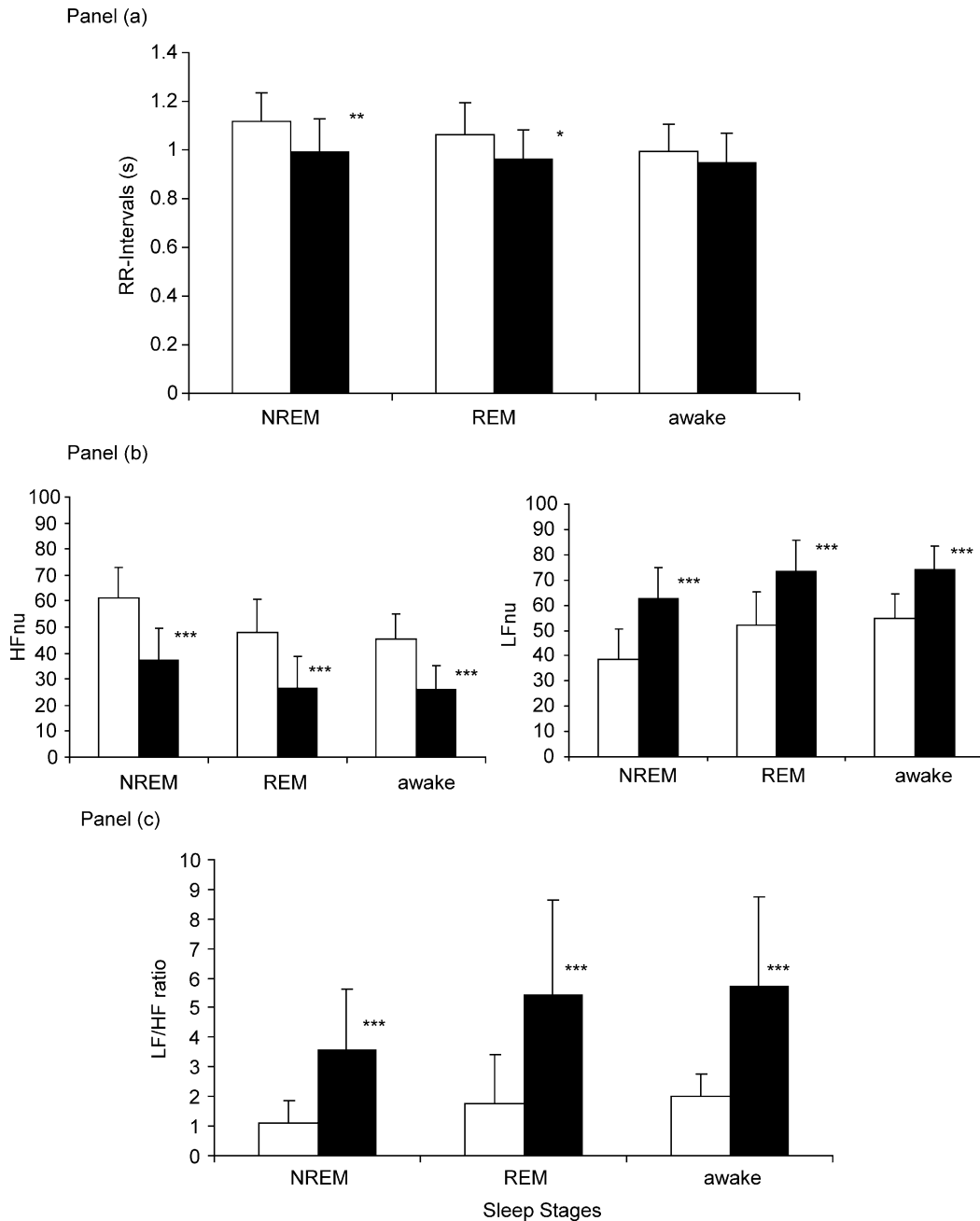


Fig. 1. (a) Variations in the duration of RR intervals (in s) across sleep stages in young and middle-aged men. (b) Evolution of High Frequency (HF) (shown on the left-hand side of this panel) and Low Frequency (LF) (on the right-hand side of this panel) of HRV across all sleep stages in young and middle-aged men. LF and HF are expressed in normalized units (nu). (c) Variations in LF/HF ratio across sleep stages in young and middle-aged males. The young men are represented by white boxes while the middle-aged men are represented by black boxes. Bars are standard deviations. NREM, non-rapid-eye-movement sleep; REM, rapid-eye-movement sleep. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 2

Mean frequency ($f_{\text{NREM-REM}}$), coherency, gain and phase shifts between HF_{nu} and delta sleep EEG band across the first three NREM–REM cycles in the young and the middle-aged subjects

Parameters	Young men	Middle-aged men	<i>P</i> value
$f_{\text{NREM-REM}}$ ($\times 10^{-4}$ Hz)	1.67 ± 0.33	1.77 ± 0.54	0.542
Coherency	0.86 ± 0.13	0.88 ± 0.13	0.698
Gain	4.37 ± 2.05	4.66 ± 1.76	0.651
Phase shift (°)	−38.79 ± 18.88	−31.21 ± 19.82	0.258
Phase shift (min)	11 ± 6	9 ± 7	0.232

$f_{\text{NREM-REM}}$, coherency, gain and phase shifts between HF_{nu} and delta sleep EEG band do not show any significant difference between young and middle-aged subjects. The results are expressed as mean ± standard deviation for the first three NREM–REM cycles.

Although the ratio LF/HF evolved identically between the two groups, its values were larger in the middle-aged men than in the young men across all sleep stages ($P < 0.001$). The LF/HF ratio increased progressively from NREM to REM sleep and to the awake stage ($P < 0.001$) (Fig. 1c).

3.3. Coherency, gain and phase shift

All young and middle-aged subjects showed coherence between the HF_{nu} and delta EEG band larger than 0.50.

The comparisons between the young and the middle-aged groups did not demonstrate any differences for the mean frequency $f_{\text{NREM-REM}}$, coherency, gain or phase shifts between HF_{nu} and delta sleep EEG band. Results are shown in Table 2.

4. Discussion

In contrast to what was anticipated, the absence of changes in coherency, gain and phase shifts suggests that the link between changes in the respective influence of the cardiac sympathetic and vagal activity with delta EEG power band is unaffected by progressive aging.

A large number of studies have explored the interaction between the HF of HRV, a marker of cardiac vagal modulation, and sleep EEG power bands in young men (Ako et al., 2003; Brandenberger et al., 2001; Jurysta et al., 2003; Yang et al., 2002). None studied the impact of age on the relationship between cardiac vagal modulation and delta sleep EEG power band.

In our study, we measured the effects of aging on the relationship between cardiac autonomic control, which is reflected by the spectral components—LF_{nu}, and HF_{nu}—of HRV and their ratio, and delta sleep EEG power band.

We showed a decrease in changes in the vagal influence of autonomic cardiac activity and deep sleep duration with aging. Despite this decrease, our data provides the evidence that the link between the changes in the relative

predominant cardiac vagal activity—HF_{nu}—and the delta EEG power band presents stability across the age spectrum. The advance of the appearance of vagal predominance in the cardiac autonomic modulation before the appearance of delta waves, previously reported in young men (Jurysta et al., 2003), was preserved in middle-aged men.

Different studies have reported a loss of parasympathetic activity and a relative increase in sympathetic activity in older men across the day (Jensen-Urstad et al., 1997; Molgaard et al., 1994; Yeragani et al., 1997) and the night (Brandenberger et al., 2003; Crasset et al., 2001; Jensen-Urstad et al., 1997; Molgaard et al., 1994; Yeragani et al., 1997). These studies limited their attention to certain parts of NREM–REM cycles (Brandenberger et al., 2003; Crasset et al., 2001) or to complete nights without any distinction between sleep stages (Molgaard et al., 1994; Yeragani et al., 1997). These studies assessed changes between sleep periods and modifications in the cardiac sympathico-vagal balance, but they never directly assessed the interactions between cardiac autonomic control and the EEG spectral components of sleep.

Despite this fact, it was observed in middle-aged men that the delta power (Table 1) as well as the relative vagal predominance in cardiac autonomic activity (Fig. 1) decrease across the night, while the gain between HF_{nu} and delta sleep EEG power does not change with aging (Table 2). This may be explained by an equal relative decrease of both variables with aging.

The exact contribution of modifications in the cardiac sympathetic and vagal activities to variations in RRI during sleep is still debated (Yang et al., 2002, 2003; Zemaityte et al., 1984). We decided therefore to assess interactions between EEG fluctuations and the normalized HF variability of RRI, since this latter parameter reflects the respective influence of the cardiac sympathetic and vagal activity during sleep (Crasset et al., 2001). Interactions between changes in EEG and absolute LF or HF components of RRI were not assessed, since these parameters are primarily affected by modifications in either sympathetic or vagal activity, respectively (Grossman et al., 2004; Guzzetti et al., 2002; Malliani et al., 1994a,b).

Several authors have implicated breathing in falling HF_{nu} during the night (Brandenberger et al., 2003; Van de Borne et al., 1995). In our study, breathing was not measured because all subjects had an index of sleep apnea–hypopnea $< 10/h$.

We had previously observed that changes in breathing patterns during sleep contribute only modestly to nocturnal changes in RRI variability (Van de Borne et al., 1995). Moreover, sleep breathing patterns change across all sleep stages (Brandenberger et al., 2003; Crasset et al., 2001; Van de Borne et al., 1995). During NREM sleep, the mechanical effects of changes in the breathing pattern favor the increase in HF oscillations of the RRI (Crasset et al., 2001). More recently, the study of Monti and his group demonstrated that the spectral components of HRV were not

modified by changes of the breathing pattern across the night in subjects with an index of sleep apnea–hypopnea <10/h (Monti et al., 2002). Thus, it is unlikely that differences in breathing patterns can explain our observations.

A previous study reported that the decreased HF_{nu} with aging is related to an increased number of arousals (Brandenberger et al., 2003). In our study, the relative decrease in parasympathetic activity was not due to increased awakenings (Table 1). This could be due to the fact that our subjects were younger than those of Brandenberger et al. (2003) (42 vs 65 years, respectively) and were free of sleep disturbances such as apnea, leg movements and snoring. The increased awakenings previously reported (Brandenberger et al., 2003) could be related to other concomitant physiological events that increase with aging as well, such as apnea (Ancoli-Israel, 1989; Hirshkowitz et al., 1992; Levy et al., 1996; McGinty et al., 1982) or leg movements (Ancoli-Israel, 1989; Bliwise et al., 1988; Hirshkowitz et al., 1992).

The tendency for sympathetic dominance and the predominant loss of parasympathetic activity is likely to lower the duration of slow wave sleep observed in older men (Brandenberger et al., 2003). Our observation of an important and stable relationship between HF_{nu} and delta band with progressive aging also points in this direction, even if we cannot conclude that parasympathetic activity directly influences sleep modifications. Methods other than the linear techniques used in this study (synchronization likelihood, phase synchronization, etc.) should be applied in future research.

In conclusion, our study provides evidence that the link between the relative vagal influence of autonomic cardiac activity and delta power band shows important stability across the middle-lifespan.

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