

Autonomic pain responses during sleep: a study of heart rate variability

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Abstract

The autonomic nervous system (ANS) reacts to nociceptive stimulation during sleep, but whether this reaction is contingent to cortical arousal, and whether one of the autonomic arms (sympathetic/parasympathetic) predominates over the other remains unknown. We assessed ANS reactivity to nociceptive stimulation during all sleep stages through heart rate variability, and correlated the results with the presence of cortical arousal measured in concomitant 32-channel EEG. Fourteen healthy volunteers underwent whole-night polysomnography during which nociceptive laser stimuli were applied over the hand. RR intervals (RR) and spectral analysis by wavelet transform were performed to assess parasympathetic (HF^{wv}) and sympathetic (LF^{wv} and LF^{wv}/HF^{wv} ratio) reactivity. During all sleep stages, RR significantly decreased in reaction to nociceptive stimulations, reaching a level similar to that of wakefulness, at the 3rd beat post-stimulus and returning to baseline after 7 beats. This RR decrease was associated with an increase in sympathetic LF^{wv} and LF^{wv}/HF^{wv} ratio without any parasympathetic HF^{wv} change. Albeit RR decrease existed even in the absence of arousals, it was significantly higher when an arousal followed the noxious stimulus. These results suggest that the sympathetic-dependent cardiac activation induced by nociceptive stimuli is modulated by a sleep dependent phenomenon related to cortical activation and not by sleep itself, since it reaches a same intensity whatever the state of vigilance.

1. Introduction

Pain is known to disrupt sleep in clinical (Moldofsky, 2001; Onen et al. 2005) and experimental conditions (Bastuji et al. 2008; Bentley et al. 2003; Lavigne et al. 2004; Lavigne et al. 2000). In healthy subjects, nociceptive stimuli delivered during sleep have been reported to induce cortical arousals in 27 to 48% of the cases, according to various factors such as sleep depth and the nature of nociceptive stimuli (Bastuji et al. 2008; Lavigne et al. 2004).

Arousal events are characterized by abrupt changes in central nervous system activity that produce electroencephalographic (EEG) activation and concomitant changes of physiologic parameters under autonomic control, such as RR intervals (RR) (Bonnet and Arand, 1997), blood pressure (BP) (Carrington and Trinder, 2008), ventilation (Trinder et al., 2001b) and systemic vascular resistance (Chaicharn et al., 2008). Previous reports point to a tight relationship between the cortical reaction and the cardiac activation: in cases of spontaneous cortical arousal (Bonnet and Arand, 1997; Gosselin et al., 2002), periodic leg movements (Lavoie et al., 2004; Sforza et al., 2002) or external sensory stimulations (Catcheside et al., 2002; Goff et al., 2008; Morgan et al., 1996), the RR decrease was significantly related to the magnitude of arousal reactions (Sforza et al., 2000; Sforza et al., 2002). Furthermore, it has been suggested that the involvement of the autonomic nervous system (ANS) in cardiac activation could differ with sleep stages, i.e. sympathetic reactivity and parasympathetic withdrawal in sleep stage 2 but sympathetic reactivity only in paradoxical (REM) sleep (Bonnet and Arand 1997).

Changes in RR were also described in response to nociceptive heat thermal stimulations (thermode) applied during nocturnal sleep (Lavigne et al., 2001), suggesting that the ANS remains reactive to painful stimuli during all sleep stages without sizeable difference of reactivity between them. However, whether nociceptive-related cardiac activation is contingent to cortical arousal remains unclear, as well as the exact participation of both sympathetic and parasympathetic systems in this cardiac activation. These issues are of interest when considering possible autonomic dysfunction in patients with chronic pain conditions and sleep disorders.

Accordingly, in the present study we assessed the autonomic reactivity to nociceptive stimuli during all-night sleep and its relationship to both cortical EEG reactivity and sleep stages. We hypothesised that 1) nociceptive stimulation should predominantly induce a sympathetic dependent cardiac reactivity, 2) this cardiac activation should be of higher intensity when stimuli give rise to cortical arousals and 3) should be associated with parasympathetic withdrawal in sleep stage 2.

We choose time-frequency analysis of cardiac signals based on wavelet transforms since this method is well adapted to ANS reactivity studies on short periods of data with non-stationary signals (Ducla-Soares et al., 2007; Pichot et al., 1999; Wiklund et al., 1997), and allows to accurately assess the involvement of each autonomic arm (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Pagani et al., 1984; Pagani et al., 1992).

2. Methods

2.1. Participants

Fourteen healthy volunteers were included in this study (4 women and 10 men; mean age: 32.8 ± 7.3 (SD) years). All the subjects were free from any known cardiac abnormalities, neurological or psychiatric disease, insomnia or chronic pain, and none of them was on any psychotropic medication. All subjects scored less than five in each subclass of a general health questionnaire (GHQ-28, (Goldberg and Hillier, 1979), French translation: W. Bettchart and M. Bolognini), indicating absence of significant state anxiety or depression. The study was approved by local Ethics Committee (CCPPRB Léon Bérard-Lyon), supported by the French National Agency for Medical Research (INSERM) and performed under informed consent according to the Declaration of Helsinki.

2.2. Laser stimulation

Nociceptive radiant heat stimuli were delivered with a Nd:YAP laser (Neodinium: Yttrium Aluminium Perovskite; Stimul 1340 El.En®; wavelength 1.34 μm ; pulse duration 5 ms). The laser beam was transmitted from the generator to the stimulating probe via an optical fibre of 10 m length (550 μm diameter with SMA-905 connector), which passed through a wall hole from the recording to the sleeping rooms. Stimulus intensity was determined for each participant two days before the sleep experimental session, and controlled before starting the sleep session. Stimuli of graded energy density were delivered, with random 10 to 20 s inter-stimulus intervals, on the dorsum of the left or right hands and nociceptive thresholds were obtained using a Likert-type scale, ranging from 0 (no sensation) to 10 (unbearable pain), where level 4 was defined as “pricking, moderately painful”. Stimulus energy estimated at or slightly above 4 was used for experimental session and was kept constant during the whole night (see (Bastuji et al., 2008) for more details). Energy densities were set between 50 and 79 mJ/mm^2 . These figures were within the normal values in our laboratory (Perchet et al., 2008), and in accordance with published experimental data using Nd:YAP lasers (Leandri et al., 2006; Truini et al., 2007).

2.3. Experimental protocol

The protocol took place in an acoustically and electrically shielded room of the laboratory. To increase sleep pressure, all subjects were deprived to 2-3 hours of sleep the night preceding the experimental session. Estimation of laser stimulus intensity and recording of laser evoked potentials (LEPs) during wakefulness were performed in a quiet room, contiguous to the sleeping area, with the subject seated in an armchair. Then, subjects lay down on a comfortable bed in an isolated laboratory room. A minimum of 20 minutes of sleep was allowed from the first EEG signs of sleep onset to the first laser stimulus. Identification of the different sleep stages (Stage 2 -S2-, Slow Wave Sleep -SWS- and Paradoxical (REM) sleep -PS) was done on-line by an expert in sleep studies (HB). This allowed us to stimulate in each sleep stage and to immediately discontinue the sequence if one stimulus awakened the sleeper. A second investigator (VL) entered iteratively the room to deliver laser pulses. Both the sleeping subject and the investigator wore eye protections; the investigator also wore headphones that allowed hearing a sound that announced the laser pulse. If any stimulus awoke the sleeper, the sequence was immediately discontinued. Stimuli were delivered with a mean of 30 s. inter-stimulus intervals during sleep. Subjects were awakened at 7:00 am and a final recording run was done during wakefulness.

2.4. Electrophysiological recording

Polygraphic all-night electrophysiological recordings were performed using a Neuroscan® Scan 4.2 (Neuroscan, Charlotte, USA) amplifier and 32 Ag/AgCl electrodes mounted on an elastic cap (Quickcap®, Neuromedical supplies, Charlotte, USA) designed for the extended International 10-20 System (Nuwer et al., 1998). All EEG electrodes were referred to the nose. In addition to the EEG cap sensors, blinks and saccades were recorded with an electro-oculogram (EOG) electrode placed on the supero-lateral right canthus, and the electromyogram (EMG) was recorded using two electrodes over the mentalis muscle in the chin. One further electrode, linked to the common reference, was attached to the skin over the extensor digitorum communis in the left forearm, and was used for limb EMG and electrocardiogram (EKG). The impedance of all electrodes was kept below 5 kOhm. The electroencephalographic signal was sampled at 500 Hz, amplified 30,000 times and one-line filtered analogically (pass band (-3dB/oct 0.1-70 Hz)). Simultaneous to each laser pulse, a digital trigger was sent to the EEG recording system and stored along with EEG data, in order to determine off line the exact moment when stimuli took place. Electrophysiological data were recorded continuously between 11:00 pm and 07:00 am and were stored for off-line analysis.

2.5. Data analysis

2.5.1. Sleep analysis

Sleep stages were visually scored off-line according to Rechtschaffen and Kales criteria (Rechtschaffen and Kales, 1968) based on 30 s epochs for hypnograms. The occurrence of cortical arousal reactions was checked after each stimulus. Following the ASDA criteria (ASDA, 1992), cortical arousals were defined as bursts of wakefulness cortical activity lasting more than 3 s and less than 15 s, and were considered as stimulus-related if occurring within 15 s after stimulus onset. A full awakening was scored when the cortical reaction occurring within the 15 s after the stimulus lasted more than 15 s. Examples are presented in Figure 1.

2.5.2. RR intervals evolution analysis

Peak-to-peak analysis of EKG signal was implemented in order to detect the R wave of QRS complex in a Matlab® environment (MathWorks, Naticks, MA, USA). A first visual selection was directly performed on EKG data. All undetected QRS, ectopic beats or artefacts were corrected on EKG data or eliminated if correction was not possible; EKG data were also eliminated from analysis when other laser stimulations, artifacts or ectopic beats occurred in an interval of less than 5 heart beats before and 8 heart beats after the stimulus. Statistic comparisons were performed on the mean of 3 minimal RR between 2 and 7 heart beats post-stimulation (mean RR) compared with the mean of the 5 RR pre-stimulation.

2.5.3. Spectral analysis of RR intervals

In order to analyse RR both in time and frequency domains, wavelet analysis, applied on RR signal, was performed using the mother function *Daubechies 4*. The wavelet analysis signal allows following the time evolution of each frequency contained in the signal. Starting from this initial function *Daubechies 4*, a family of functions was built by dilatation and translocation, which constitute the so-called wavelet frame. A serial list of coefficients called *wavelet coefficients* was used, which represent the evolution of the correlation between the signal and the chosen wavelet at different levels of analysis (or different ranges of frequencies) all along the signal. The first levels (2, 4, 8) correspond to a wavelet analysis conducted with a small value of the dilatation factor applied on 2, 4 and 8 RR respectively. Thus these levels represent high-frequency variations in the signal. The last levels (16, 32, 64...) correspond to a wavelet analysis conducted with a large value of the dilatation factor applied on 16, 32 and

64 RR respectively. Consequently these levels represent low-frequency variations in the signal.

According to Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), squared *wavelet coefficients* at levels 2, 4, and 8 (high frequency: HF^{wv}) were used to assess parasympathetic reactivity. Wavelet power coefficient at levels 16 (low frequency: LF^{wv}) was used to assess sympathetic reactivity (see ref (Pichot et al., 1999; Pichot et al., 2001)). In the present study, we kept power coefficient at level 16 only in LF^{wv} , since inter stimuli intervals were too short to apply the coefficient at level 32. A LF^{wv}/HF^{wv} ratio was calculated as the ratio between the wavelet power coefficient at *levels 16* on one hand and the sum of the wavelet power coefficients at *levels 2, 4, and 8* on the other, to obtain a marker of autonomic nervous system balance. This analysis was performed on 16 RR before and after each stimulus. An example is shown in figure 2.

2.6. Statistical analysis

Data were analysed using PASW Statistics 18 (SPSS Inc®, Chicago, USA) software. Mean RR, HF^{wv} , LF^{wv} and LF/HF^{wv} ratio values were submitted to 2 different repeated-measures analyses of variance (ANOVA), each one with 2 within factors and with Greenhouse-Geisser correction of degrees of freedom when appropriate. The first factor was time (pre- vs post-stimulation) in both ANOVA while the second factor was: (a) states of vigilance (wakefulness vs S2 vs SWS vs PS) in the first ANOVA and (b) cortical reactivity (arousal vs no reaction) in the second one. Newman-Keuls post-hoc test was performed when appropriate.

The association between cortical arousal duration and each of the three variables (mean RR, HF^{wv} , LF^{wv} and LF/HF^{wv} ratio) if significantly modified by the stimulation, were tested by simple regression analyses for continuous variables.

Differences were considered significant when $p < 0.05$ and values are expressed as mean \pm SEM.

3. Results

Three out of 14 subjects had to be excluded from analysis: two because they had very few sleep (less than 2.2 hours) and one because his EKG data were missing. Mean sleep duration for the 11 remaining subjects was 397.9 ± 60.3 (mean \pm standard deviation (SD)) minutes (table 1). From a total of 909 laser stimuli delivered, 881 were included in analysis and 28 excluded because of too short inter stimulus intervals for RR analysis or of uncorrected artefacts and ectopic beats. For the whole group, 80.1 ± 30.6 stimulations per subject were selected, of which 20.1 ± 20.2 were in wakefulness, 29.5 ± 9.3 in S2, 21.3 ± 14.3 in PS and 9.3 ± 10.3 in SWS (table 1). Due to technical problems (see RR intervals evolution analysis in Methods), sleep stages or wakefulness data were missing in some subjects. Then, statistical analysis was performed on 8 subjects for the comparison between states of vigilance and on 11 subjects for the comparison between cortical arousal and absence of cortical arousal.

3.1. RR intervals and wavelet analysis across states of vigilance

3.1.1. RR intervals analysis

Mean RR varied significantly as a function of time ($F(3,7) = 27.78$; $p = 0.001$), whereas there was no significant effect of states of vigilance ($F(3,7) = 1.29$ $p = 0.303$) but an interaction ($F(3,7) = 4.62$; $p = 0.024$). RR was significantly decreased after the stimuli as compared to pre-stimuli periods and basal level of RR was lower during wakefulness in comparison with basal level of RR during sleep stages (see figure 3A).

3.1.2. Wavelet analysis

LF^{WV} was modified significantly as a function of time ($F(3,7) = 19.95$; $p = 0.003$) and states of vigilance ($F(3,7) = 4.74$; $p = 0.033$) with an interaction between them ($F(3,7) = 4.49$; $p = 0.040$). LF^{WV} was significantly increased after the stimuli as compared to pre-stimuli periods. Post-hoc tests showed lower level during wakefulness than those during stage 2 ($Q = 4.56$; $p = 0.020$) and paradoxical sleep ($Q = 4.42$; $p = 0.014$) but not during slow wave sleep ($Q = 1.98$; $p = 0.180$). No difference appeared between sleep stages (stage 2 vs slow wave sleep: $Q = 1.82$, $p=0.083$; stage 2 vs paradoxical sleep: $Q = 0.096$, $p=0.930$; paradoxical sleep vs slow wave sleep: $Q = 1.73$, $p=0.099$). These results were illustrated in figures 3B.

HF^{WV} was not significantly modified as a function of states of vigilance ($F(3,7) = 2.50$; $p = 0.142$), nor of time ($F(3,7) = 0.37$; $p = 0.564$) and there was no interaction ($F(3,7) = 1.10$; $p = 0.361$) (see figure 3C).

LF^{WV}/HF^{WV} ratio was modified significantly as a function of time ($F(3,7) = 15.61$; $p = 0.006$) but not states of vigilance ($F(3,7) = 2.60$; $p = 0.097$) without interaction between them ($F(3,7) = 0.24$; $p = 0.782$). LF^{WV}/HF^{WV} was significantly increased after the stimuli as compared to pre-stimuli periods (see figure 3D). ~~These results were illustrated in figures 3B, 3C and 3D.~~

3.2. RR intervals and wavelet changes according to cortical arousal

3.2.1. RR intervals analysis

Mean RR was significantly modified as a function of time ($F(1,10) = 59.39$; $p < 0.001$) and cortical reactivity ($F(1,10) = 30.80$; $p < 0.001$), with an interaction ($F(1,10) = 8.20$; $p = 0.017$). RR was significantly decreased after the stimuli as compared to pre-stimuli periods and RR ~~response was lower in~~ decreased more with cortical arousal in comparison with no cortical reaction (figure 4A).

3.2.2. Wavelet analysis

LF^{WV} did not vary significantly with cortical reactivity ($F(1,10) = 1.26$; $p = 0.288$) whereas there was a significant effect of time ($F(1,10) = 8.656$; $p = 0.015$) without an interaction ($F(1,10) = 2.44$; $p = 0.149$). LF^{WV} was significantly increased after the stimuli as compared to pre-stimuli periods. These results were illustrated in figures 4B.

HF^{WV} was not significantly modified as function of cortical arousal ($F(1,10) = 3.58$; $p = 0.088$), of time ($F(1,10) = 3.54$; $p = 0.089$) and there was no interaction ($F(1,10) = 1.03$; $p = 0.334$) (see figure 4C).

LF^{WV}/HF^{WV} ratio did not vary significantly with cortical reactivity ($F(1,10) = 3.38$; $p = 0.096$) whereas there was a significant effect of time ($F(1,10) = 16.18$; $p = 0.002$) without an interaction ($F(1,10) = 4.53$; $p = 0.059$). ~~These results were illustrated in figures 4B, 4C, 4D.~~ LF^{WV}/HF^{WV} was significantly increased after the stimuli as compared to pre-stimuli periods (see figure 4D).

3.3.4. Associations between duration of cortical arousal and autonomic indexes

Simple regression analyses showed no significant association between the duration of cortical arousal, and mean RR ($t = 0.28$, $p = 0.779$ and $r < 0.01$), LF^{WV} ($t = -1.07$, $p = 0.28$ and $r = 0.01$) nor LF^{WV}/HF^{WV} ratio ($t = 0.54$, $p = 0.593$ and $r < 0.01$).

4. Discussion

Nociceptive stimulation induced a sympathetic-dependent cardiac activation, which was not modulated by sleep stages, but varied contingently with cortical reactivity. Indeed, cardiac reactivity was found to be higher when nociceptive stimuli produced cortical arousals, even though preserved in absence of subsequent arousals.

4.1. Cardiac autonomic activation according to the states of vigilance.

Comparing pre and post stimulus mean heart rate values, Lavigne et al. (2001) have also reported a cardiac activation in reaction to nociceptive stimulations during all sleep stages without any significant difference between them. The present study confirms that autonomic reactivity, well known during wakefulness (Moltner et al., 1990; Paine et al., 2009), is preserved during all sleep stages. Furthermore, the present study was able to characterise the temporal course of pain-related cardiac activation, which begins within the two seconds following the stimulation, reaches its maximum at about five seconds and lasts up to 10 seconds after the stimulation (see figure 3A). Nevertheless, it is interesting to notice that the level reached was indeed the same in sleep and wakefulness since the sleep basal level of cardiac activity is known to be lower than that of wakefulness (Baharav et al., 1995; Bonnet and Arand, 1997; Trinder et al., 2001a; Vanoli et al., 1995; Vaughn et al., 1995; Versace et al., 2003). Thus, this suggests that, whatever the basal state of autonomic system, which depends on the states of vigilance, nociceptive stimulations give rise to a the same level of activation whatever the states of vigilance, probably related to the intensity of the stimulation.

This autonomic cardiac reactivity to nociceptive stimuli was mainly due to an increase in sympathetic activation which was the same in all sleep stages. Conversely, in the present study there was no pain-induced modification of parasympathetic activity, as assessed by HF^{WV} . While sympathetic activation has been documented to a wide variety of sensory stimuli, the participation of parasympathetic system in the response during sleep remains controversial. It was absent in response to pain stimuli in our study (see figure 3C) and to periodic leg movements (Sforza et al., 2005), but present with auditory stimuli (Blasi et al., 2003) or spontaneous arousals in a previous study (Bonnet and Arand, 1997). These discrepancies could be explained by the different kinds of stimulation used, but more probably arise from different methodological approaches. Since parasympathetic activation has slower dynamics than sympathetic arousal, it could have been hidden in our study because of too short inter-

stimuli intervals precluding its full expression (Sforza et al., 2000). Thus, stimuli of different origins induce a cardiac reflex activation implying essentially sympathetic activity, and with a parasympathetic involvement which seems to be less clear and possibly dependent on stimulus parameters.

4.2. Sleep autonomic reaction to nociception and the hierarchy of arousal.

Cardiac ANS reactivity was present even in absence of cortical arousal; but it was significantly greater when the nociceptive stimuli were followed by an arousal (see figure 4). However, as autonomic and cortical responses seem to occur simultaneously, about one second after the stimulus (see figure 4 and (Bastuji et al., 2008)), there is no evidence, in these studies, to suggest that one lead the other.

A recent study in our laboratory has shown that, although nociceptive stimuli were processed by the sleeping cerebral cortex even in absence of arousal (Bastuji et al., 2008), a cognitive component peaking around 500 ms post-stimulus, was enclosed within the laser evoked potential (LEP) when the stimulations gave rise to subsequent cortical arousals. This result suggests another level of modulation of nociceptive information leading to behavioural reaction and transient interruption of sleep. Thus, the hierarchy in arousal reaction during sleep, previously proposed (Halasz et al., 2004; Sforza et al., 2000), may consist of a first level response with sympathetic dependent cardiac and nociceptive somatosensory cortex activations, and a second one, more sophisticated including a cognitive process of the stimulation, a higher sympathetic activation associated with a cortical arousal.

The mechanisms underlying both autonomic and cortical responses followed by arousals are probably complex and interrelated. First, it has been shown that the autonomic nervous system activity influences the amplitude of LEPs (Edwards et al., 2008). Second, both somatosensory cortical (Bastuji et al., 2008) and cardiac autonomic responses (Bonnet and Arand, 1997; Sforza et al., 1999; Sforza et al., 2000) are known to occur before the “classical” EEG arousal response. Therefore, as nociceptive stimuli are supposed to induce in parallel two cortical activations, one by the nociceptive somatosensory pathway and the other by the vegetative one, we cannot exclude that both activations determined the EEG cortical arousal.

From this point of view, cortical arousal could be considered as the response to a somatosensory-visceral summation when a certain threshold is reached. At that time, when this level is reached, sympathetic cardiac activation seems to have no more influence in the

intensity of cortical activation, since no association was found between the duration of cortical reactivity and RR intervals decrease in the present study.

However, the question remains why repetitive stimulations of same physical intensity should induce different levels of reactivity during sleep. An extrinsic factor, such as variation in stimulus intensity, cannot be excluded. Although stimulus intensity was supposed to be constant along the experiment, there may have been minor variations of energy received by the hand due to slight position change of the laser pointer or small thermal skin changes during the night. It is also likely that spontaneous changes in the internal system's state during sleep do influence the effect of a same stimulation applied at periods of different reactivity.

Notwithstanding these facts, different levels of reactivity have been reported to happen in reaction to sensory stimuli of constant intensity during a same sleep stage (Bonnet and Moore, 1982), suggesting that these different levels of response could also be related to intrinsic fluctuations of brain activity, actually known to occur during sleep. Paradoxical sleep has phasic and tonic periods, as well as thalamocortical coupling and uncoupling periods (Magnin et al., 2004), while fluctuations in sleep stage 2 and slow wave sleep are related to the occurrence of K complexes and spindles, cyclic alternative pattern and slow oscillations (Steriade et al., 1993). Furthermore, fluctuations in brain activity are not an exclusive phenomenon of sleep since they were recently shown to modulate somatosensory perception during wakefulness (Boly et al., 2007).

4.4. Limitations

Several limitations of this study have to be considered, the first concerning the number of subjects. Although the results were clearly significant, any generalisation is hampered by the limited sample (data obtained from only 11 of 14 subjects). From a technical point of view, our time-frequency spectral analysis of RR intervals was performed without the last power coefficients of LF^{WV} band (wavelet coefficient power at level 32) to limit overlap in wavelet power analysis (Pichot et al., 1999). This could have attenuated the LF^{WV} increase on statistical grounds. In spite of this, the LF^{WV} analysis was highly significant, consistent with the RR changes and with others results obtained from spectral analysis of RR after spontaneous arousals (Bonnet and Arand, 1997), periodic leg movements (Sforza et al., 2005), or auditory stimuli (Blasi et al., 2003).

4.5. Clinical implications

In chronic pain condition (Mahowald et al., 1989) when iterative cardiac autonomic response is associated with sleep fragmentation, it may entail a persistent high sympathetic-cardiac activity during sleep (Martinez-Lavin et al., 1998) and participate to ANS dysfunction as recently suggested in fibromyalgic patients (Sarzi-Puttini et al., 2006). Wavelet analysis could be applied to chronic pain patients and may bring information on sympathetic-cardiac activity during sleep in several chronic pain syndromes (Thomas et al. 2010). However, an autonomic dysfunction related to sleep fragmentation remains to be demonstrated in chronic pain syndromes with further studies.

In conclusion, the present study suggests that the sympathetically-driven cardiac activation in reaction to somatosensory nociceptive stimulations is preserved during all sleep stages and that a higher cardiac autonomic reactivity is concomitant to cortical arousal. This autonomic reactivity might be considered as the first mechanism that allows potential behavioural response and could take part in occurrence of cortical arousals. Its involvement in persistent autonomic and cardiovascular alterations in chronic pain conditions remains to be ascertained in future investigations.

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Table 1

Characteristic and sleep parameters of 11 remaining healthy volunteers (mean \pm standard deviation (SD)).

	Mean	SD	Range
Age	32.8	7.3	[18-47]
Total sleep time (min)	397.9	60.3	[272-507]
GHQ-28 Score	2.8	0.5	[2.3-3.5]
Number of analysed stimulations during per subject:			
Wakefulness	20.1	20.2	[0-66]
Stage 2	29.5	9.3	[5-60]
Paradoxical sleep	21.3	14.3	[4-40]
Slow wave sleep	9.3	10.3	[0-33]
Total number	80.1	30.6	[44-143]
Percentage of arousal after stimulation per subject in:			
Stage 2	28.8	17.1	[2.4-61.1]
Paradoxical sleep	21.3	27.0	[0-100]
Slow wave sleep	14.2	19.1	[0-50]

GHQ-28, general health Golberg and Hillier questionnaire.

Figure

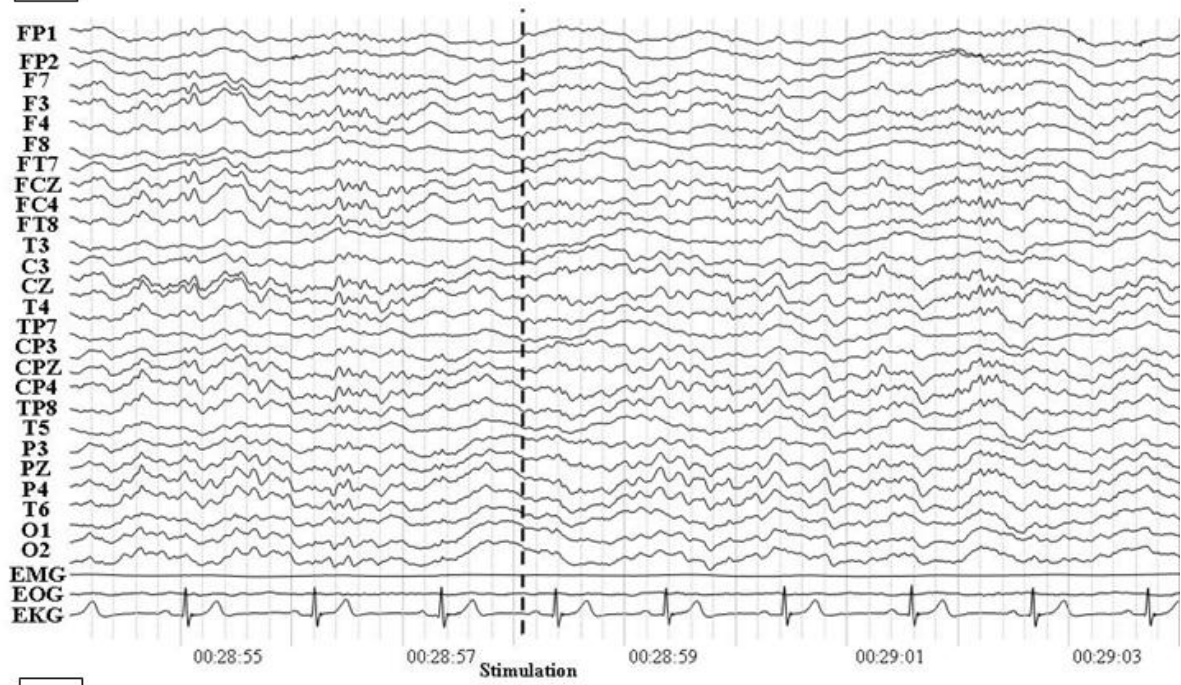
Figure 1. Examples of behavioural reactions to laser stimuli. The upper traces correspond to EEG, and the three bottom traces to EOG, chin EMG and EKG. The arrow and dotted line indicate the onset of the stimulus (5 ms duration). (A) slow wave sleep, no cortical reaction to the stimulus and (B) stage 2, cortical arousal.

Figure 2. A representative example of (A) RR intervals (RR), (B) low (LF^{wv}) and (C) high frequency (HF^{wv}) wavelet power and (D) LF^{wv}/HF^{wv} ratio before and after an isolated nociceptive stimulation in one subject during sleep stage 2. Time (s) in abscissa refer to the time of one analysed period during polysomnographic recording. Dotted line represents nociceptive stimulation.

Figure 3. Comparisons between states of vigilance: (A) RR intervals (RR), (B) low (LF^{wv}) and (C) high frequency (HF^{wv}) wavelet power and (D) LF^{wv}/HF^{wv} ratio before and after nociceptive stimulations (mean \pm SEM). * $p < 0.05$ mean RR after the stimulation in comparison to pre stimulation value. An overall effect appeared in LF^{wv} and in LF^{wv}/HF^{wv} ratio between before and after stimulation. Nociceptive-induced RR decrease was preserved in all sleep stages, and this cardiac activation was related to a sympathetic reactivity.

Figure 4. Comparisons according to cortical arousals: (A) RR intervals (RR), (B) low (LF^{wv}) and (C) high frequency (HF^{wv}) wavelet power and (D) LF^{wv}/HF^{wv} ratio before and after nociceptive stimulation during no cortical and cortical arousals (mean \pm SEM). * $p < 0.05$ mean RR during post stimulation in comparison to pre stimulations. An overall effect appeared in LF^{wv} and in LF^{wv}/HF^{wv} ratio between before and after stimulation. Nociceptive stimulation induced a sympathetic-dependent RR decrease which was higher when nociceptive stimuli produced cortical arousals.

A



B

