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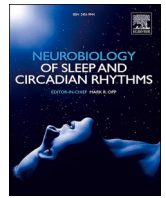
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Cardiorespiratory changes associated with micro-arousals during naps

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ABSTRACT

The autonomic nervous system (ANS) and the central nervous system (CNS) interplay during sleep, particularly during phasic events such as micro-arousals, has been the subject of several studies. The underlying mechanisms of such relationship which remain unclear, specifically during daytime sleep, were partly investigated in this study. Napping polysomnography was performed on two occasions at least one week apart in 15 healthy subjects. The following cardiorespiratory variables were extracted from the recordings: tachogram, pulse transit time (PTT), pulse wave amplitude, respiratory cycle amplitude, and frequency. Two experts first detected micro-arousal events, then, cardiorespiratory variables were averaged by 30-s epochs over 2 min centered on the onset of the micro-arousals. We found that in the 30 s preceding the arousal events as detected on the electroencephalogram (EEG) recordings, there was a decrease in tachogram, pulse wave amplitude, and PTT values while the respiratory amplitude increased. These changes were more prominent in stage N2 and N3 sleep than in stage N1. The present findings provide new insights into the autonomic changes during the pre-arousal period in daytime naps, as all the variables investigated suggest a sympathetic physiological origin for the changes.

1. Introduction

Hemodynamic and respiratory variations during sleep are governed by autonomic changes such as decreased heart rate and respiratory frequency (Bristow et al., 1969; Douglas et al., 1982; Trinder et al., 2001). The co-occurrence of such cardiorespiratory changes and modifications of the central nervous system (CNS) activity during sleep, might result from an interplay between the CNS and the autonomic nervous system (ANS). While the underlying mechanisms of this relationship remain unclear, some authors support that it could be explained by the spatial closeness between sleep regulatory systems and ANS components which regulates most of the body's internal processes (de Zambotti et al., 2018).

Recent studies have attempted to shed light on the physiological correlates of this ANS and CNS relationship by focusing on cardiovascular changes during sleep and particularly during phasic electroencephalogram (EEG) events such as micro-arousals (de Zambotti et al., 2018). It is all the more relevant to look at the ANS and CNS relationship from the angle of micro-arousals as it has been shown that phasic EEG events, closely related to a temporary lightning of sleep depth, would help to effectively address the dynamism of sleep processes (Ferini-Strambi et al., 1997, 2000). Micro-arousal events have been associated

with a biphasic cardiac activity enabling an increased heart rate followed by a slowing down to sleep values (Bonnet & Arand, 1997; de Zambotti et al., 2016; Gosselin et al., 2002; Sforza et al., 2000, 2016). Authors have attributed this change to increased sympathetic activation or decreased parasympathetic activity that would favor arousal from sleep (Bonnet and Arand, 1997; Sforza et al., 2000). Interestingly, previous studies in both animals (Quattrochi et al., 2000) and humans (Bonnet and Arand, 1997; Sforza et al., 2000, 2016) have further indicated that these cardiac activities would precede the arousal manifestation in the EEG recordings. These latter studies reported that the cardiac acceleration during the biphasic response began a few heartbeats before the micro-arousals, persisted some seconds after, and was then followed by bradycardia.

Furthermore, some important aspects of this autonomic dynamics around micro-arousals remain unexplored. Indeed, the pre-arousal modification of cardiac activity has been analyzed mostly during a few heartbeats before the micro-arousal events, with the most extended pre-event period being 20 s (Quattrochi et al., 2000; Sforza et al., 2016; de Zambotti et al., 2018). Hence, one can expect that expanding this pre-event period further than 20 s, could give new insights into ANS and CNS relationship. Furthermore, only the heart rate and the heart rate variability have been extensively used to reflect autonomic activation

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while studying this relationship. It is challenging to determine the physiological origins of the autonomic activation in such conditions. Therefore, studies focusing on other cardiac variables, such as those measuring directly or indirectly blood pressure or even respiratory signals, would be useful. Moreover, the majority of studies performed whole-night polysomnography (PSG), while investigating autonomic dynamics around micro-arousals, with no existing data on daytime sleep such as naps. However, it is known that nighttime and daytime sleep have distinct arousal thresholds, homeostatic, and circadian drives, and one could assume that the autonomic profile during micro-arousals would also be different in these two forms of sleep. This difference in autonomic profile could be a result of dissimilar features (e.g., total sleep time, the number of micro-arousal events and the sleep stage in which they appear, and the eventual co-occurrence of K Complexes (KC)) between daytime and nighttime sleep (Lo et al., 2014). Most importantly, autonomic profile associated with micro-arousals specifically during naps is of critical interest, as it would be a significant step forward in attempting to use ANS activity as a surrogate for EEG recordings (Radha et al., 2019). Indeed, in several environments (e.g., functional magnetic resonance imaging (fMRI)), sleep and alertness are closer to daytime than nighttime states. Given the fact that polysomnography (PSG) and EEG recordings are sometimes difficultly applicable in such environments, autonomic profile during daytime sleep would be relevant data for the automatic detection of sleep states (Radha et al., 2019).

This study aimed to investigate cardiac and respiratory changes in young and healthy adults before and after micro-arousals as noticed in the EEG recordings of naps. A various set of cardiorespiratory data will be studied as well as different features of micro-arousals (i.e., stage of sleep of the occurrence, association with a KC).

2. Material and methods

2.1. Population and experimental design

Young and healthy individuals were included in the study if their age fell between 20 and 55. The exclusion criteria were: having sleep disorders, consumption of psychotropics or other medications that could alter sleep, being dependent on alcohol or illicit drugs, and having a poor sleep quality or an irregular circadian rhythm, according to the Pittsburgh Sleep Quality Index and the Horne and Östberg questionnaires, respectively. Participants' cardiorespiratory signals were recorded during a nap, as described below. Recordings were performed on two occasions at least one week apart, in the afternoon (1–4 P.M.), in a quiet room equipped with a hospital bed and a desk. Following the installation of the recording devices, participants were instructed to take a nap which lasted for up to 30 min. Written informed consent was obtained from all participants, and the study has been approved by section *NORD OUEST III* of the national ethic committee, the Committee of Protection of Persons (CPP-IDRCB number: 2017-A02863-50). All methods were performed following the relevant guidelines and regulations.

2.2. Signals recording

All signals were recorded at a 200 Hz sampling rate.

2.2.1. Sleep

We recorded sleep using the standard PSG and international 10–20 system as recommended by the American academy of sleep medicine (AASM). Eight gold-plated electrodes (Natus®) were placed on the head to record EEG at the frontal, central, temporal and occipital areas. The EEG system used (Medatec Dream, Belgium) also allowed to record electrooculogram (EOG) by placing two electrodes around the eyes, electromyogram (EMG) with two electrodes under the chin, and the cardiorespiratory signals as described below.

2.2.2. Cardiorespiratory signals

Regarding electrocardiograms (ECG), the (–) electrode was placed under the collarbone on the right, and the (+) electrode was attached to the left anterosuperior iliac spine. We captured respiratory movements by attaching a belt to the abdomen. Finally, a photoplethysmography (PPG) sensor was placed on the left finger to measure pulse wave amplitude.

2.2.3. Events detection

Two experts scored micro-arousals and sleep stages manually according to the AASM recommendations (Berry et al., 2017). We identified micro-arousals events as follows: “Micro-arousals manifest in the EEG as an abrupt shift in the frequency, including alpha, theta, and or greater than 16 Hz which typically last for at least 3–15 s, but not including the spindle band”. We also classified micro-arousals as associated with a KC if they coincided with this latter or started within the second following it, as per AASM rules.

The other signals were extracted in European data format (EDF) and converted to be processed in MATLAB®. We used the Physionet toolbox to process the automatic detection of the cardiorespiratory events, R peak for ECG, and pulse onset and amplitude for PPG signals (Vest et al., 2018). High and low peaks in respiratory signals were detected with the findpeaks tool. All these events were individually checked and manually corrected if necessary.

The following variables were extracted:

- The tachogram, the time difference between 2 consecutive R peaks on the ECG, was used to reflect the global cardiac activity,
- Pulse wave amplitude measured by finger PPG, which is known to reflect peripheral vasoconstriction resulting from sympathetic activation (Betta et al., 2020). This biomarker was previously associated with cardiometabolic outcomes during sleep (Hirotzu et al., 2020),
- Pulse Transit Time (PTT) corresponded to the time between the electrical control of the heart (ECG R peak) and the arrival of blood at the fingertip (marked by the point of maximal slope between the pulse onset and the systolic peak on the PPG signal); this measure is a dynamic index of the actual state of the cardiovascular system, and its variation has been correlated with blood pressure (Hahnen and van Helmond, 2019),
- Amplitude of respiratory cycle and respiratory period (time difference between two consecutive peaks on the signal) was used to reflect the global respiratory activity.

2.3. Data analysis

We focused the analyses on the dynamic of cardiorespiratory signals around micro-arousal events during sleep. After a Z-score normalization for each recorded cardiorespiratory signal, they were partitioned into 2-min segments centered on the time of onset of micro-arousals. Then, we split these 2-min segments into four epochs of 30 s as the duration of a sleep scoring page (two epochs before and two epochs after the micro-arousal onset). Finally, we averaged each signal within each epoch. According to AASM rules, two micro-arousals should be separated with at least 10 s of EEG recordings of sleep (Berry et al., 2017). Given the setting of the 2-min segment used in this study, we dissociated micro-arousals more stringently by considering only events that were at least 1 min apart. This was done to limit interference between the pre and post-arousal epochs considered, allowing us to study autonomic changes associated with isolated micro-arousals.

We followed three steps in data analyses. In the first step, we compared the cardiorespiratory signals between the four epochs of 30 s regardless of the type of micro-arousals. Then we repeated the analysis considering whether micro-arousals took place in the stages N1, N2, or N3 of sleep. Given the relatively short time spent by participants in stage N3 in the present study, we analyzed micro-arousals from this stage concomitantly with events in stage N2. The last step of the analysis was

focused on micro-arousals that occurred in stages N2 and N3 and whether they were associated with a KC.

After the verification of the distribution normality by the Shapiro-Wilk test, we performed a two-way repeated-measures analysis of variance. We conducted Mauchly's test to verify the non-violation of the sphericity assumption and used the Bonferroni method for Post-hoc analyses. The statistical significance value was set at a threshold of 0.05 in IBM SPSS 24® software.

3. Results

Table 1 summarizes the characteristics of the study population, consisting of 15 individuals with a mean age of 38 years. Participants spent an average 22 min in the sleep stages. Three hundred and twenty-four micro-arousal events were scored throughout the recordings, with 63% occurring in stage N2 or N3 of sleep and the rest in stage N1. Regarding micro-arousals of stage N2 or N3, nearly two-thirds were associated with a KC.

In-depth analyses by epochs of 30 s included 198 micro-arousals. We found some cardiorespiratory modifications that occurred before the arousal manifestation in the EEG recordings. Firstly, regardless of the type of micro-arousal, the tachogram ($F_{61} = 3.03$ $p < 0.05$), the PTT ($F_{61} = 3.65$ $p < 0.05$), and the pulse wave amplitude ($F_{61} = 5.37$ $p < 0.01$) began to decrease before the micro-arousals and progressively returned to sleep levels (Fig. 1). Post-hoc analyses showed that the decreasing values before the micro-arousals were significant at 30 s before the event for each variable ($p < 0.01$ for PTT; $p < 0.05$ for tachogram and pulse wave amplitude). There was further a significant difference after the micro-arousal for PTT and pulse wave amplitude ($p < 0.05$ for both). Regarding the respiratory data, we noticed a rising amplitude ($F_{61} = 6.85$ $p < 0.001$) that returned to baseline values with here again a significant difference ($p < 0.05$) happening 30 s before the micro-arousals (Fig. 1). Secondly, we observed that the abovementioned modifications in cardiorespiratory data were more prominent in sleep stages N2 and N3 compared to N1. However, the statistical significance was reached only for the pulse wave amplitude ($F_{1,60} = 6.39$ $p < 0.05$), with a trend observed for the other variables (Fig. 1). Thirdly, regarding micro-arousals occurring in stage N2 or N3 of sleep, the presence of a KC did not influence the results.

4. Discussion

The present findings have specified some autonomic modifications arising around micro-arousals during daytime naps. These changes corresponded to an acceleration of cardiac activity (decreased tachogram), a decrease in the pulse wave amplitude and PTT, and an increase in respiratory amplitude, all occurring within 30 s before the event began. These interesting results offer new physiological insights into the relationship between ANS and CNS during micro-arousals, and could be

Table 1

Characteristics of the study population (n = 15) and nap recordings (n = 30).

Age (mean, years)	38 ± 10
Women (%)	7 (47)
Total time of sleep (mean, min)	22.43 ± 6.90
Duration in N1 Sleep	7.89 ± 2.86
Duration in N2 Sleep	10.26 ± 4.82
Duration in N3 Sleep	4.28 ± 4.81
Sleep latency (mean, min)	5.60 ± 3.37
Sleep efficiency (mean, %)	63.64 ± 17.79
Total micro-arousals events	323
Micro-arousals in stage N1 (%)	118 (37)
Micro-arousals in stage N2 and N3 (%)	205 (63)
Micro-arousals without a K Complex (%)	89 (43)
Micro-arousals with a K Complex (%)	116 (57)

Continuous variables were represented as mean ± standard error mean and categorical variables as number and percentage.

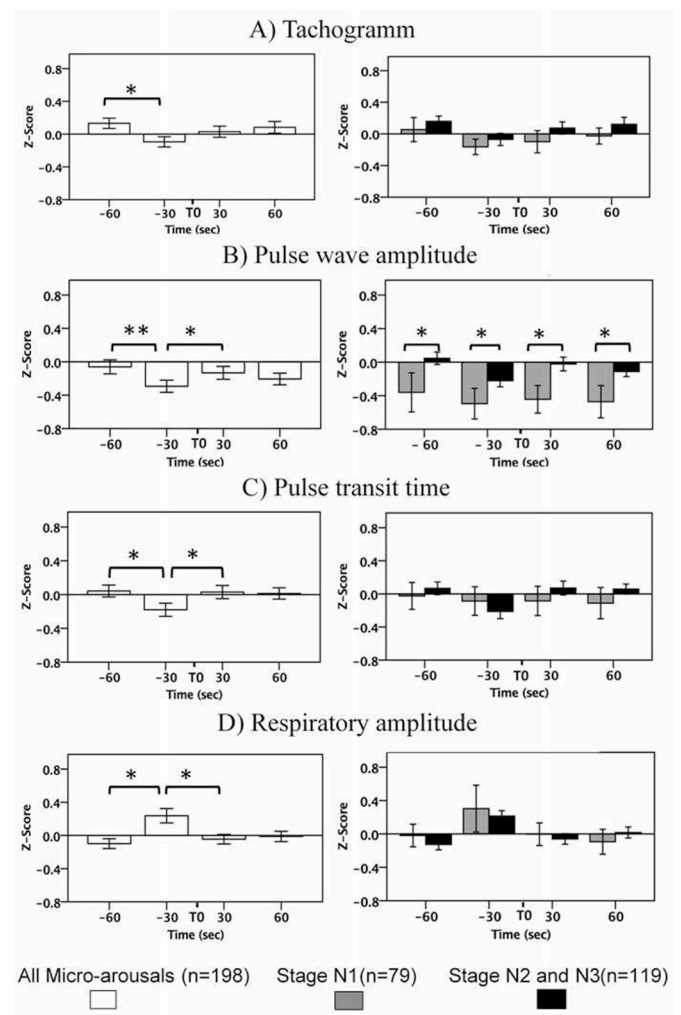


Fig. 1. Cardiorespiratory changes during micro-arousals. TO = beginning of micro-arousals events. The bars represent the mean Z-score ± Standard mean error of A) heart period, B) Pulse wave amplitude, C) Pulse transit time, and D) Respiratory amplitude. Repeated measures ANOVA followed by post-hoc analyses based on the Bonferroni method. * $p < 0.05$; ** $p < 0.01$.

of specific interest to studies attempting to use the autonomic profile as a surrogate for EEG recordings.

A new and exciting observation in the present study would be the consistency between the results obtained with different variables, all converging towards one plausible physiological explanation for the cardiorespiratory changes happening before the micro-arousals. The acceleration of cardiac activity in the pre-arousal period has been previously attributed to a decrease in parasympathetic activity or a raise in sympathetic activation (Bonnet and Arand, 1997; Sforza et al., 2000). This is partly because of the increased heart rate and associated heart rate variability reported before the micro-arousals. However, the distinction between this phenomenon's sympathetic or parasympathetic origin is hard to establish given the limited set of variables investigated in previous studies. In the present work, in addition to the decreased tachogram in pre-arousal periods, the results regarding the other variables used to examine autonomic response are enlightening. Indeed, the decreased pulse wave amplitude is consistent with the pulse wave amplitude drops (PWAD), a phenomenon frequently encountered during sleep. PWAD is associated with obstructive events such as sleep apnea (Delessert et al., 2010), and it has been demonstrated that it would also be a result of sympathetic activation (Betta et al., 2020). In addition, some authors have reported that the PWAD would be associated with an

increase in EEG power density in all frequency bands (Delessert et al., 2010), an argument in favor of an arousal event following the drop. Furthermore, decreasing PTT values have been associated with the augmentation of blood pressure (Hahnen and van Helmond, 2019). Henceforth, decreased value of PTT in pre-arousal periods in this study, would comply with a sympathetic explanation of the autonomic changes. Finally, the increased respiratory amplitude in the pre-arousals period, is in line with well-documented respiratory responses during micro-arousals (Gleeson et al., 1990), and also support the sympathetic explanation.

While the autonomic response observed before the arousal in EEG recordings in the present study agrees with the few previous works (de Zambotti et al., 2018), the fact that this response would occur within 30 s before the event is new. However, it might sound odd that such a modification could happen long before the arousal event. Most of studies have focused on the changes that a micro-arousal can provoke in autonomic activity after its onset in the EEG recordings (de Zambotti et al., 2018). The few studies investigating cardiorespiratory data during pre-arousal periods have stated that autonomic modifications happened a few heartbeats before the event and continue a few seconds after (Bonnet and Arand, 1997; Gosselin et al., 2002; Sforza et al., 2000). Our results depict the same case scenario except on a larger time scale, suggesting that the autonomic pre-arousal changes would be present broadly during the 30 s preceding the event. Furthermore, the discrepancies between our findings and previous results might be attributed not only to the fact that we analyzed a more extended period before the micro-arousals, but also to differences in sleep architecture. Indeed, all the previous studies have conducted a whole-night PSG contrary to the daytime nap investigated in the present study.

The front-runner nature of cardiorespiratory changes associated with micro-arousals raises an interesting question on the timing of the activation of the brain regulatory systems throughout the events. One could argue that the activation of subcortical structures would occur first leading to autonomic activation, and subsequently, cortical activation would elicit the micro-arousal as identifiable in the EEG recordings. This hypothesis of a progressive activation of brain areas during micro-arousals would favor the existence of different types of micro-arousals depending on the threshold of the arousing stimulus and the subsequent activated regions. Some authors even support that in some cases, there could be only a subcortical activation, also referred to as subcortical arousal as opposed to cortical arousal (Sforza et al., 2000). Interestingly, in line with this observation, abrupt and transient autonomic activations, associated with increased sympathetic activity and peripheral vasoconstriction, have been shown to occur also in the absence of visually identifiable cortical EEG arousals (Bartels et al., 2016; Catchside et al., 2002; Grote, 2003; Johnson et al., 1967). Moreover, one could assume that the autonomic response before the actual arousal in the EEG recordings, would be a setting up of the body to induct a waking state in line with a previously described role of micro-arousals which is to preserve the possibility to wake up in case of any biological danger (Halász, 1998). Henceforth, it is essential to better apprehend such diversity in micro-arousals events based on associated autonomic profiles, especially in studies attempting to substitute EEG with cardiorespiratory data.

The difference between the autonomic response across sleep stages is noteworthy. The more prominent cardiac activity, mainly decreased pulse wave amplitude, during stages N2 and N3 of sleep, than in stage N1, could be explained by sleep physiology. Indeed, it is known that sleep depth is associated with gradually reduced sympathetic activity and increased parasympathetic activation (Bristow et al., 1969; Douglas et al., 1982; Trinder et al., 2001). The sympathetic pressure is thus lesser in the deepest sleep stages (N2 and N3) than in light sleep (N1). Assuming that the physiological origins of the autonomic response associated with micro-arousals would be sympathetic, the low pressure of this system in the deepest sleep stages could explained the more prominent response in stage N2 and N3 than in N1. Furthermore,

whether the micro-arousals were associated with a KC, in N2 or N3 sleep, does not influence the autonomic response, suggesting that all micro-arousals in deep sleep would share the same autonomic profile. This strengthens the hypothesis of sleep depth having a major influence on ANS modification during micro-arousals.

One major limitation of this study could be the preference to analyze averaged data during epochs of 30 s, instead of a continuous temporal investigation during pre and post-arousal periods. The principal motivation for choosing the duration of 30 s is its use in clinical practice to score sleep stages. Interestingly, when smaller duration (epochs of 10 and 15 s) were chosen, we still observed the same autonomic modifications in the total period of 30 s preceding arousal events. In addition, data collected during the investigation of 30 s epochs is more suitable to attempt to substitute EEG with cardiorespiratory data, as loads of existing data on sleep have been conducted using this duration. Finally, despite the small sample size used in the present study, one can rely on the strong consistency of the results while using a various set of variables. Future research should test such variables continuously to determine the precise temporality of the autonomic changes around naps while benefiting from larger sample size. In addition, some other direct measures of the sympathetic activity (e.g., blood pressure) would be useful in testing the hypothesis of the physiological origins.

The present paper has investigated the relationships between autonomic and cortical events throughout micro-arousals during daytime naps. The findings favor an anteriority of subcortical changes, associated with increased sympathetic activation, in regards to cortical activation identifiable in the EEG recordings. These findings confirm the previously described role of micro-arousals which is to hold an eventuality of waking up as the autonomic response would prepare the body to induct a waking state.

This body preparation can be seen as a “fight or flight” situation where waking up would be to cope with a potential danger (Thayer et al., 2012), thus strengthening the likeliness of its sympathetic origin.

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Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CRedit authorship contribution statement

Elpidio Attoh-Mensah: Conceptualization, Investigation, Visualization, Validation, Formal analysis, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Ivan Igor-Gaez:** Writing – review & editing, Visualization, Data curation, Software. **Lydie Vincent:** Investigation, Writing – review & editing. **Nicolas Bessot:** Resources, Writing – review & editing. **Clément Nathou:** Validation, Visualization, Writing – review & editing. **Olivier Etard:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ATTOH-MENSAH Elpidio reports financial support was provided by European Regional Development fund. IGOR GAEZ Ivan reports financial support was provided by European Regional Development Fund.

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