ORIGINAL ARTICLE

Investigation of Heartbeat Evoked Potential (HEP) Response During Different Stages of Sleep in Sleep Disorders

Babak Seddighi, Maryam Mohebbi *

Department of Biomedical Engineering, Faculty of Electrical Engineering, K.N. Toosi University of Technology, Tehran, Iran

*Corresponding Author: Maryam Mohebbi
Email: m.mohebbi@kntu.ac.ir

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Abstract

Purpose: Interoceptions are a combination of sensation, integration, and interpretation of internal bodily signals. Interoceptions are bidirectionally related to the human being mental and physiological health, and well-being. Sleep and different interoceptive modalities are proven to share common relations.

Heartbeat Evoked Potential (HEP) is known as a robust readout to interoceptive processes. In this study, we focused on the relation between HEP modulations and sleep-related disorders.

Materials and Methods: We investigated four different sleep-related disorders, including insomnia, rapid eye movement behavior disorder, periodic limb movements and nocturnal frontal lobe epilepsy, and provided HEP signals of multiple Electroencephalogram (EEG) channels over the right hemisphere to compare these disorders with the control group. Here, we investigated and compared the results of 35 subjects, including seven subjects for the control group and seven subjects for each of above-mentioned sleep disorders.

Results: By comparing HEP responses of the control group with sleep-related patients' groups, statistically significant HEP differences were detected over right hemisphere EEG channels, including FP2, F4, C4, P4, and O2 channels. These significant differences were also observed over the grand average HEP amplitude activity of channels over the right hemisphere in the sleep-related disorders as well.

Conclusion: Our results between the control group and groups of patients suffering from sleep-related disorders demonstrated that during different stages of sleep, HEPs show significant differences over multiple right hemisphere EEG channels. Interestingly, by comparing different sleep disorders with each other, we observed that each of these HEP differences' patterns over specific channels and during certain sleep stages bear considerable resemblances to each other.

Keywords: Cardiac Cycle; Heartbeat Evoked Potential; Interoception; Sleep Disorder.

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1. Introduction

Interoceptions are defined as conscious and unconscious sensations, interpretations, and integrations of internal bodily stimuli, including hunger, thirst, temperature, pain, and visceral sensations [1]. Interoceptive sensation processes are divided into multiple modality categories, including thermoception, nociception, visceral sensation, and other subjective bodily feelings [2]. Sleep and these interoceptive modalities are bidirectionally related to each other [3]. Furthermore, developing our understanding and knowledge of these relationships would help us through management and treatment procedures for sleep and mental disorders. For instance, defense mechanisms occurrence during sleep (e.g., shivering, sweating, coughing, swallowing, and hypercapnic and hypoxic responses), typically lead to arousals that disrupt sleep homeostasis [4, 5] and suppression of these defense responses is a critical component in preventing awakenings and improving sleep quality. Interoceptive sensitivity improvement is believed to prevent arousal and consequently help to protect sleep homeostasis [6].

Poor sleep quality and mental health states are shown to have bidirectional and distinct impacts on each other [7]. On the other hand, poor sleep causes deficits in cognitive (e.g., decision-making and memory function) and emotional-related cortical processing (e.g., stress) [8, 9]. Furthermore, these deficits in cognitive and attentional processes would lead to deficits in interoceptive performance as well. For instance, in the case of poor sleep quality, patients suffering from depression and anxiety are shown to have poor interoceptive accuracy, too [7].

Interoceptions and bodily signals play important roles in emotional processes [10]. On the other hand, stressful emotive stimuli cause arousal and consequently delay sleep onset [3]. Hence, cortical processes of interoception can be an important measure to investigate arousal corresponding to emotional events and affective states [11, 12].

Different studies have proven that cardiac cycle-related approaches, including Heartbeat Evoked Potential (HEP) signals are robust readouts of cortical signals responsible for interoceptions [13]. These signals are time-locked to individuals' heartbeats. Prior studies have shown that HEP amplitude differences are most prominent in the right hemisphere [14, 15] and are associated with each individual's accuracy in heartbeat detections [16]. These amplitude modulations are reported during sleep, resting state, and under external stimuli [14, 17, 18].

Previous studies have demonstrated that emotional arousal, including stress and other negative emotions, may increase HEP amplitude [19]. On the contrary, HEP amplitude is decreased in cases of reduced bodily awareness or lack of empathy, including depression [17], autism [20], and alexithymia [21]. It should be noted that negative emotions (e.g., fear and anger) typically activate the right hemisphere neural networks [22] and specifically engage the insula, amygdala, and anterior cingulate cortex [14].

Studies on HEP signals have revealed that interoceptive processes and their cortical neural activities are still present during different stages of sleep, and with regard to the sleep stage, their amplitude is comparatively attenuated in comparison with wakefulness [23, 24]. Lechinger *et al.* (2015) proved that HEP positivity declines from light sleep stages to deep sleep [23]. On the other hand, HEP signal modulations are proven to increase more during the Rapid Eye Movement (REM) stage rather than Non-Rapid Eye Movement (NREM) stages of sleep [14, 23]. These neural behaviors and inconsistent interoceptive control are believed to originate in response to the emotional and dreaming nature of the REM stage [14, 23].

Sleep and its different stages are known to be free of exteroceptive stimuli and might provide a much better environment for HEP signal assessments rather than wakefulness. On the other hand, prior to this article, merely, few authors considered scrutinizing HEP signal modulations in cases of sleep disorders during sleep [14, 23, 25]. Furthermore, to boost our knowledge and have a better understanding of the relationship between sleep and HEP responses, we need to study different sleep disorders during different stages of sleep and compare these results with each other. These further studies would help us enhance our knowledge about sleep disorders and their relationship with different mental health issues as their common sequelae.

Based on the literature reviewed above, the present study aimed to investigate HEP amplitude differences and modulations in multiple sleep-related disorders. Consequently, the HEP amplitude of four different sleep disorders, including insomnia, REM Behavior Disorder (RBD), Periodic Limb Movements (PLM), and Nocturnal

Frontal Lobe Epilepsy (NFLE) was compared with a control group to extract possible HEP responses to these disorders. Since sleep disorders are proven to modulate the HEP signal's amplitude, we expected to detect significant HEP amplitude differences while comparing different sleep disorders with the control group. We also examined whether these sleep disorders' HEP responses may correlate with the most commonly known sequelae of sleep disorders as well.

2. Materials and Methods

2.1. Participants

The dataset used in this study is the Cyclic Alternating Pattern (CAP) sleep taken from the physiobank database [26]. This study contains 35 patients and control subjects (seven subjects for each disorder and seven subjects in the control group). Healthy control subjects were not under the influence of any type of drugs that may have an impact on the Central Nervous System (CNS) and were free of any neurological disorder symptoms. Pathological recordings include waveforms of patients who had insomnia, RBD, PLM, and NFLE.

Electroencephalogram (EEG) channels were placed on the subjects' scalp, according to the international 10/20 system. Five EEG channels, including FP2, F4, C4, P4, and O2 were used in this study, and all channels were referenced to A1. Silver-chloride passive electrodes were used to acquire data. The scalp-electrode impedance was less than 5 KΩ. Signals were recorded at a 512 Hz sampling rate. Also, one ECG channel was used for R-peak detection and HEP validation procedures.

2.2. Pre-Processing

Offline data preprocessing and processing procedures and other statistical analyses were performed in the Matlab platform (Mathworks Inc.). The EEG offline preprocessing was conducted using custom scripts in the EEGLAB toolbox environment [27]. An FIR high-pass filter with a cutoff frequency of 0.3 Hz was used for the lower edges of the data, and an FIR low-pass filter with a cutoff frequency of 40 Hz was used for the upper edges. Data were then down-sampled to 256 Hz. Afterward, the data were re-referenced to average to suppress the line noise and make the total potential zero.

Since data integrity is an essential factor in HEP-related processes, using artifact rejection plugins could compromise the data integrity. Furthermore, artifacts were removed from the data by eye inspection. To ensure that the data were appropriately cleaned, ICA was used before data segmentation.

R-peak detections were performed offline and using the Pan-Tompkins algorithm [28]. Afterward, the data were segmented into 700 ms epochs with reference to R-peaks. Epochs with less than 700 ms length were excluded from further processes to avoid the undesirable electrical impact of the next heartbeat's QRS complex.

2.3. Cardiac Field Artifacts

Cardiac activity causes an electrical field to propagate throughout the body with each heartbeat. This electro-cardiac field can be measured on the body surface and scalp. Cardiac Field Artifacts (CFAs) superimpose with the brain's intrinsic electrical signals. Since cardiac cycle-related EEG signals (specifically HEP) are time-locked to heartbeats and are averaged with reference to cardiac cycles, these artifacts would leave a prominent artifactual effect on data [29, 30]. As a result, CFAs artifactual effects are stronger during more prominent electrical activities of the heart.

During the last few decades, many authors suggested different strategies to remove CFAs, including principal component analysis (PCA) [31], recording and subtracting EEG-free signals (recorded from the tip of the nose) from each channel's averaged EEG [18], CFA free zones with regard to prominent electro-cardiac activity [15,30], and Independent Component Analysis (ICA) [17]. Each of these methods left behind some CFA residue. It should be noted that no universal and agreed method has yet been defined to fully cancel CFA from cardiac cycle-related signals.

Dirlich *et al.* (1997) have illustrated that CFA artifacts are more prominent in the periods that are time-locked to ventricular depolarization (QRS complex) and repolarization (the T wave) [30]. Dirlich *et al.* (1997) and Petzschner *et al.* (2019) suggested a CFA-free zone to cancel CFA from HEP processes [15,30]. However, this method is shown to leave some minor CFA residue as well.

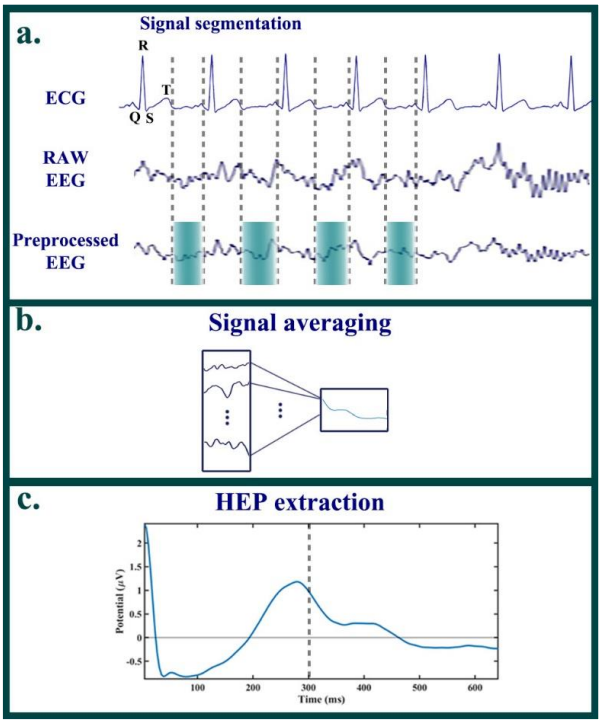

Figure 1. A paradigm of HEP signal extraction. (a) Simultaneous non-preprocessed and preprocessed EEG signals that are time-locked to ECG signal. The CFA free zone is considered after T-wave and before the commencement of the next R-peak's primary electro-cardiac field. (b) Segmented signals of each channel are averaged during different stages of sleep. (c) The schematic pattern of the final extracted HEP signal

In this study, REM and NREM sleep stages of subjects suffering from different sleep disorders were compared with normal healthy subjects. Since specific sleep stages of different groups were compared with each other, we assumed that they were experiencing similar conditions, too [15]. On the other hand, to avoid the next heartbeat QRS complex electrical effect on our processes, we segmented the EEG data into 700 ms length epochs with R peak as the onset. All trials with less than 700 ms length were removed from further processes. Finally, further processes were limited to a CFA-free zone in a Time window Of Interest (TOI) between 300 ms to 650 ms post R peak. The CFA-free zone is defined as a post T-wave zone to minimize the heart's prominent electrical activity effects on our processes. To support our theory that these approaches reduce probable CFA contamination in our processes, we examined this theory with several statistical approaches. A linear regression model was used to predict the mean of HEP from the mean ECG amplitude that is time-locked to their corresponding HEP time window. Figure 1 shows a brief and simplified paradigm of HEP signal extraction based on CFA-free zones.

2.4. Statistical Analysis

HEP amplitude significant differences were assessed and extracted using a reliable non-parametric test named "the Monte-Carlo cluster-based permutation test" [32]. In this non-parametric test, all participants' averages of both groups (control and sleep disorders) or experiments (REM and NREM) were collected and shuffled in a single set. The resulting set was randomly divided into two new subsets with the length of primary ones, and then the test statistic on these new subsets was calculated. This last step was repeated as many times as possible (to improve the validity of the test), and the proportion of random test statistic results that had a larger value than a predefined threshold (t-value) was calculated. This resulting proportion is the p-value of this non-parametric cluster-based permutation test. If the resulting p-value was smaller than a critical statistically significant threshold ($p<0.05$), then one may conclude that the data in the two experimental conditions (paired) or groups (unpaired) are statistically different. If the number of subjects was less than enough (specifically, in cases of paired tests), the enumeration result should be used to find the permutation p-value.

To support our theories about the reliability of our methods through minimizing CFA's impact on our processing, some statistical approaches were used to compare groups and components with each other. Linear regression models with a probability threshold level of $p<0.05$ were used to explain the relationship between HEP modulations and individuals' cardiac activity. Furthermore, the mean of significant HEP amplitude differences was compared with individuals' corresponding time-locked mean ECG amplitude and heart rates. Also, a non-parametric Wilcoxon signed-rank test was provided to compare the mean of HEPs and other non-EEG data, including ECG amplitudes and heart rates.

3. Results

HEP amplitude modulations of control participants and patients were compared in different sleep stages (N2, SWS, and REM). Also, the grand average HEP amplitude activity of channels over the right hemisphere was calculated and compared during different sleep stages. A non-parametric unpaired Monte-Carlo cluster-based permutation test with a statistically significant t-value threshold ($t< 0.05$) was used to extract highly significant differences in the HEP

amplitude. Different statistical approaches were used to validate HEP amplitude detection procedures and to ensure that electro-cardiac activity and heart rates were not responsible for these statistically significant differences.

The comparison between control participants' and patients' heart rates in different sleep stages was performed using a Wilcoxon signed-rank test. Also, to ensure that HEP differences are not driven by electro-cardiac activity, the mean HEP amplitude of participants was examined with corresponding time-locked ECG amplitude using a linear regression model.

With regard to the comparison between control and different sleep disorders groups, statistically significant HEP amplitude differences were observed over different channels and during different stages of sleep. These significant differences are summarized in Table 1. A brief overview of these disorders' HEP responses demonstrates that some similarities exist between them.

Waveforms represent that psychophysiological differences exist between the HEP amplitudes' grand average of the control group and at least three disorders (Insomnia, RBD, and PLM groups). Comparing insomnia patients with the control group, the grand average in the right hemisphere demonstrated that patients suffering from insomnia experience a significantly higher HEP activity during REM (334-420 ms), SWS (346-377 ms), and N2 stages (342-420ms). In other words, the insomnia group results indicate that insomnia patients experience significantly stronger HEP amplitude during all stages of sleep. In the case of comparing RBD and the control groups, our results demonstrated that the grand average of HEPs' amplitude in the right hemisphere was significantly lower in patients suffering from RBD during REM (435-524 ms), SWS (450-501 ms), and N2 (474-497 ms) stages. Also, our results of comparing PLM and the control groups illustrate that the grand average of HEPs amplitude in the right hemisphere was significantly lower in the PLMs group during REM (470-548 ms), SWS (439-540 ms), and N2 (431-560 ms) stages (Figure 2). Note that RBD and PLM groups' HEP detected responses during different stages of sleep are considerably similar to each other as well. For a better and more transparent comparison between the control group and sleep disorders, boxplots of the grand average signal's mean HEP amplitude are provided in Figure 3.

In the case of the F4 channel, our findings indicated that people suffering from insomnia experience a significantly stronger HEP amplitude during REM (330-424 ms) and N2 stages (346-400 ms). On the other hand, the RBD group's HEP amplitude was significantly higher during REM (307-370 ms) and N2 stages (315-366 ms) and then after a deflection, HEP responses become significantly smaller than the control group during the N2 stage (450-501 ms).

Table 1. Detected statistically significant Heartbeat Evoked Potential (HEP) amplitude differences' using their Time windows Of Interest (TOI) and corresponding p-value

	REM		SWS		N2	
	TOI	***P***	**TOI**	***P***	**TOI**	***P***
Insomnia AVE	334-420	0.001	346-377	0.02	342-420	0.006
RBD AVE	435-524	0.03	450-501	0.026	474-497	0.049
PLM AVE	470-548	0.043	439-540	0.023	431-560	0.024
Insomnia F4	330-424	0.006	—	—	346-400	0.006
RBD F4	307-370	0.014	—	—	315-366	0.018
RBD F4	—	—	—	—	450-501	0.025
PLM F4	319-358	0.035	—	—	—	—
NFLE F4	334-370	0.041	—	—	323-365	0.049
NFLE F4	497-552	0.046	—	—	454-560	0.017
Insomnia C4	342-455	0.001	319-424	0.001	346-400	0.001
RBD C4	319-405	0.021	307-389	0.036	334-420	0.02
RBD C4	458-540	0.025	466-513	0.042	—	—
RBD FP2	404-432	0.029	—	—	—	—
PLM FP2	357-451	0.007	353-455	0.02	369-447	0.024
RBD P4	466-513	0.016	—	—	—	—
Insomnia O2	350-451	0.004	369-443	0.009	—	—

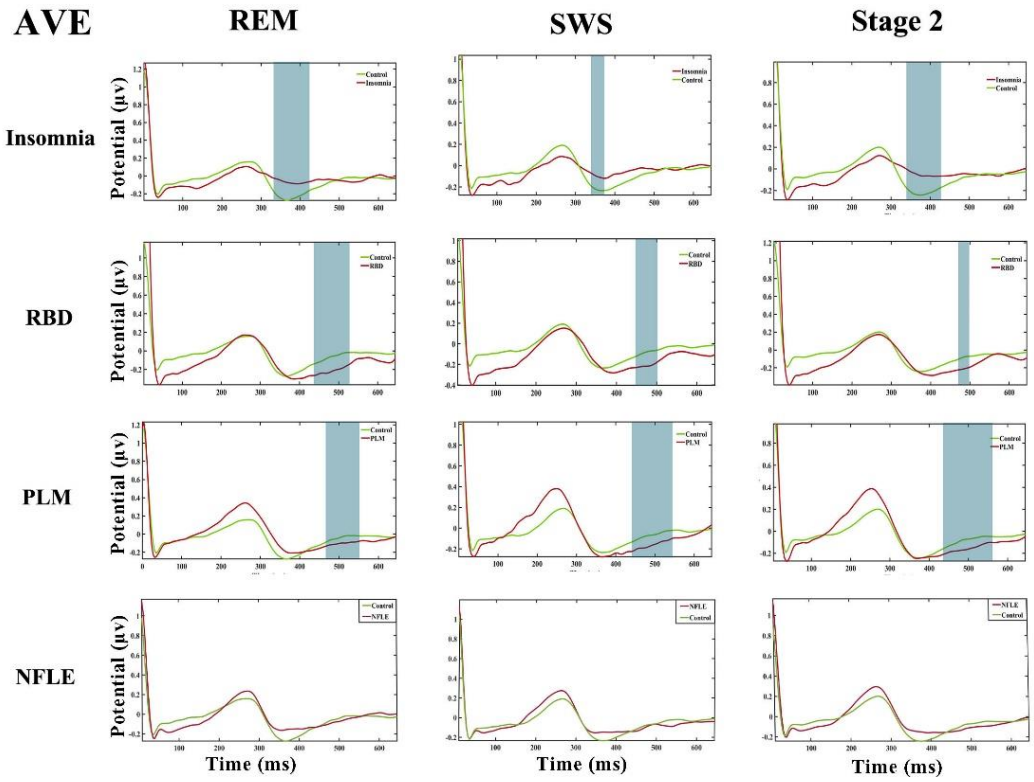

Figure 2. The comparison of HEP amplitudes' grand average in the right hemisphere channels between the control group and different disorders (Insomnia, RBD, PLM, and NFLE) during different sleep stages (REM, SWS, and N2 stages)

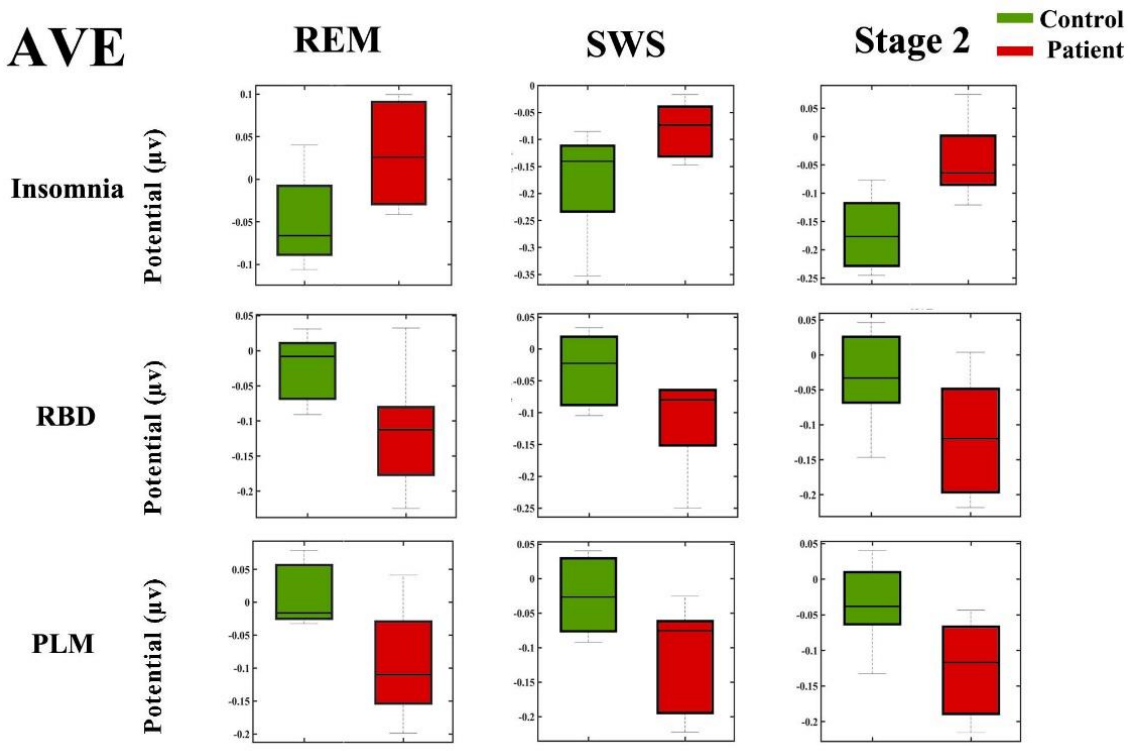

Figure 3. Boxplots for the comparison of the grand average signal's mean HEP amplitude between the control group and sleep disorders (Insomnia, RBD, and PLM groups) during different sleep stages (REM, SWS, and N2 stages)

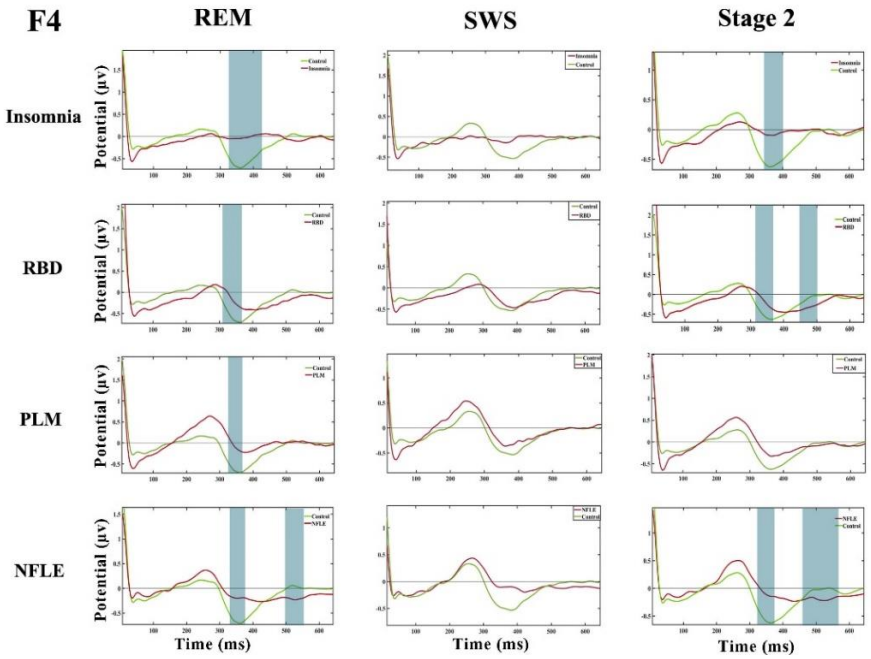

Figure 4. The comparison of the HEP amplitude differences over the F4 channel in different sleep disorders (Insomnia, RBD, PLM, and NFLE) and during different sleep stages (REM, SWS, and N2 stages). The F4 channel results indicate that all sleep disorders experience significantly higher HEP amplitude during the REM stage of sleep. Also, three sleep disorders (Insomnia, RBD, and NFLE) experience significantly higher HEP amplitude during the N2 stage of sleep

PLM group results also indicated significantly stronger HEP response during REM (319-358 ms). Finally, our results demonstrated that NFLE group first showed a significantly higher HEP amplitude during REM (334-370 ms) and N2 stages (323-365 ms), and later, after a deflection, the HEP amplitude became significantly smaller during REM (497-552) and N2 stages (454-560 ms). We should note that similar to previous results, our primary HEP results over the F4 channel and around 350 to 400 ms post R-peak in all sleep disorders showed considerably similar HEP response patterns during REM and N2 stages of sleep. Also, the second HEP amplitude shows deflection around 500 ms post R-peak in RBD and NFLE disorders during the same stages (Figure 4). Finally, in Figure 5, boxplots of the mean HEP amplitude over the F4 channel are provided for more clear comparison between the control group and sleep disorders.

Our insomnia group results over the C4 channel showed that HEP amplitude was significantly higher during REM (342-455 ms), SWS (319-424 ms), and N2 stages (322-450 ms). Also, our findings indicate that HEP of the C4 channel in RBD patients was at first significantly higher during REM (319-405 ms), SWS (307-389 ms), and N2 (334-420 ms) stages. Afterwards, after a deflection in the second detected considerable HEP difference TOI, the HEP amplitude of the C4 channel became significantly lower during REM (458- 540) and SWS (466-513) stages of sleep. Note that over the C4 channel and during different stages of sleep, HEP responses of the insomnia group occur during almost similar latency as the RBD group (Figure 6). Finally, in Figure 7, boxplots of the mean HEP amplitude over the C4 channel are provided for both insomnia and RBD groups.

In the case of the FP2 channel, HEP responses of PLM patients showed significantly lower amplitude during REM (357-451 ms), SWS (353-455 ms), and N2 (369-447 ms) stages of sleep. Also, the HEP amplitude of the FP2 channel was significantly lower in the RBD group during the REM (404-432 ms) stage (Figure 8). Note that for a better comparison between

the control group and sleep disorders (RBD and PLM), boxplots of the mean hep amplitude over the FP2 channel are illustrated in Figure 9.

Finally, significant HEP differences were detected over the O2 channel between insomnia and control groups as well. Patients who have insomnia had a significantly lower HEP amplitude during the REM (350-451 ms) and SWS (369-443 ms) stages of sleep (Figure 10).

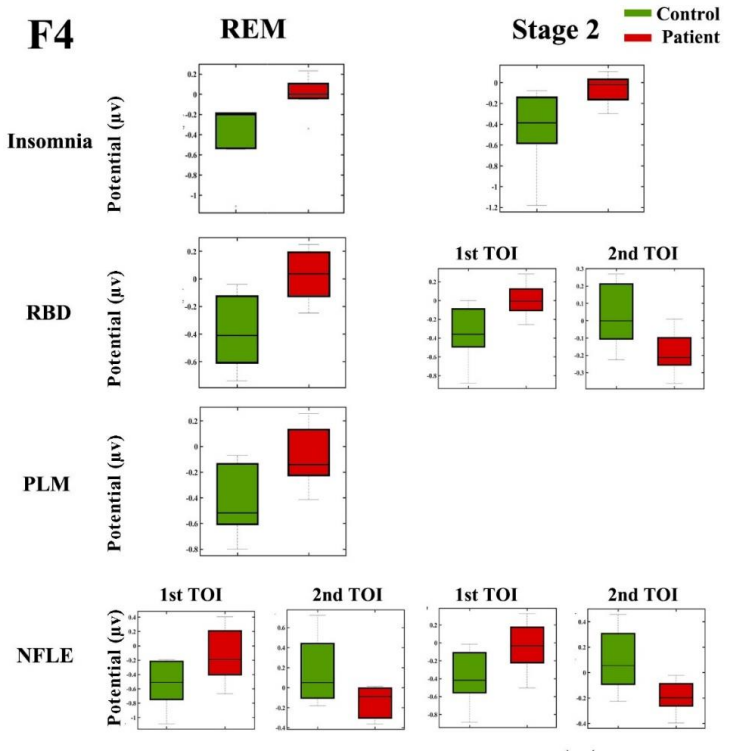

Figure 5. Boxplots for the comparison of the mean HEP amplitude over the F4 channel between the control group and sleep disorders (Insomnia, RBD, PLM, and NFLE) during different sleep stages (REM and N2 stages)

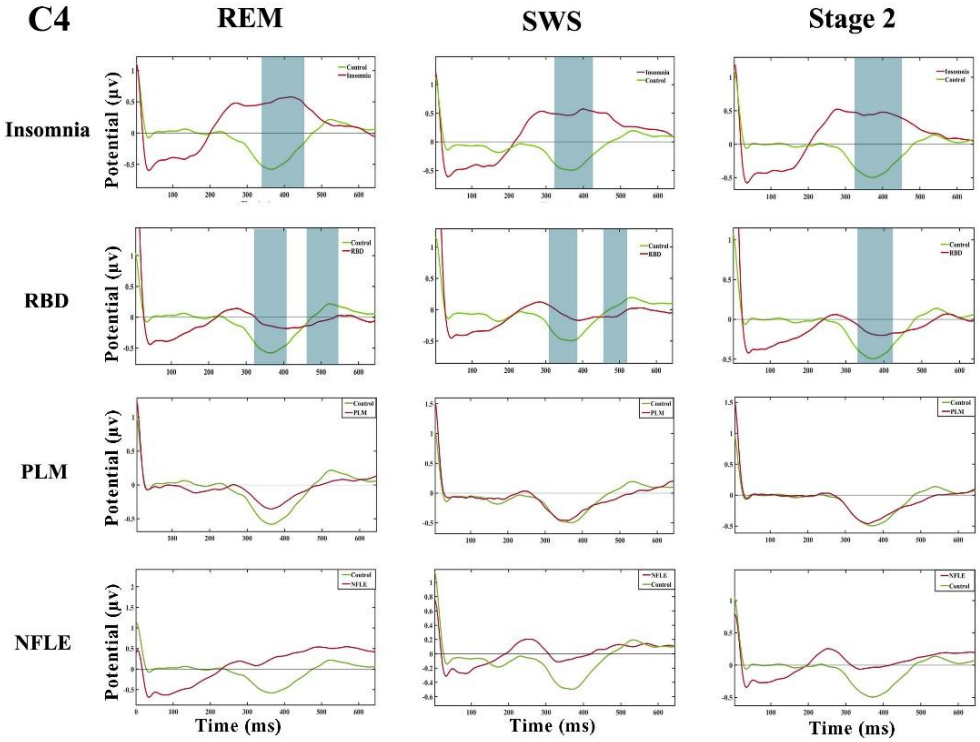

Figure 6. The comparison of HEP amplitude differences over the C4 channel in different sleep disorders (Insomnia, RBD, PLM, and NFLE) and during different sleep stages (REM, SWS, and N2 stages). Our C4 channel results indicate that both insomnia and RBD groups experience a considerably stronger HEP amplitude during all stages of sleep

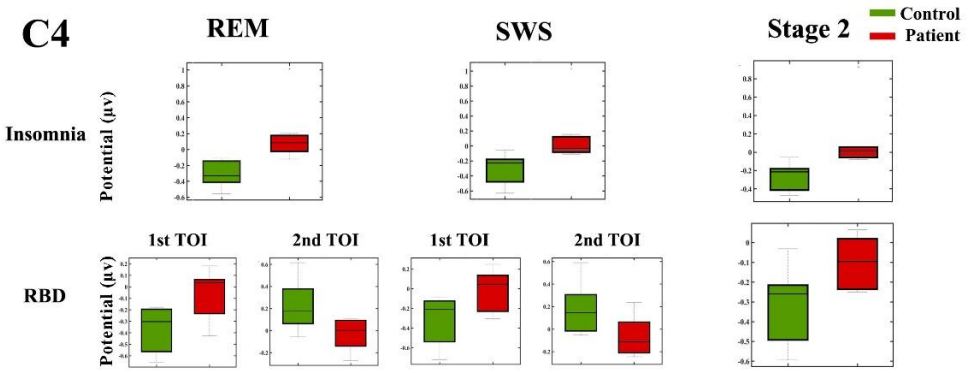

Figure 7. Boxplots for the comparison of the mean HEP amplitude over the C4 channel between the control group and sleep disorders (Insomnia and RBD) during different sleep stages (REM and N2 stages)

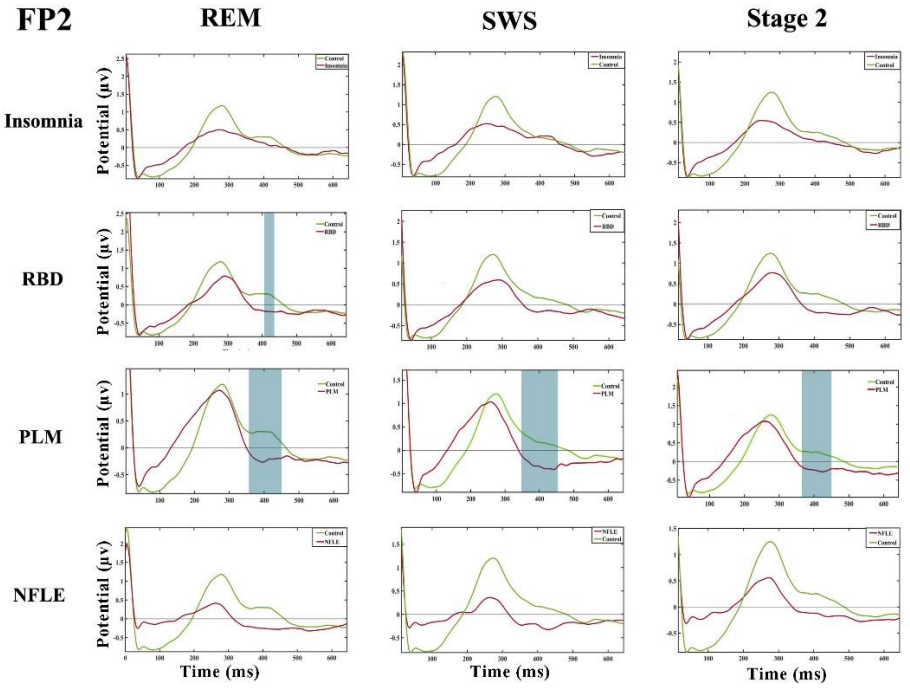

Figure 8. The comparison of HEP amplitude differences over the FP2 channel in different disorders (Insomnia, RBD, PLM, and NFLE) and during different sleep stages (REM, SWS, and N2 stages). The FP2 channel results demonstrate that the PLM group experiences a significantly lower HEP amplitude in all stages of sleep (REM, SWS, and N2 stages)

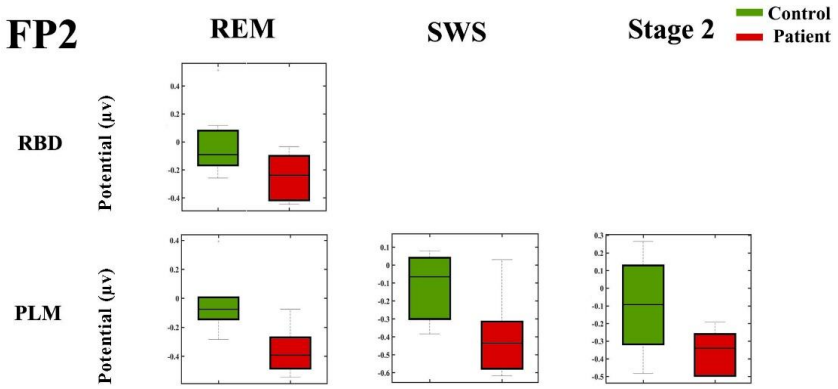

Figure 9. Boxplots for the comparison of the mean HEP amplitude over the FP2 channel between the control group and sleep disorders (RBD and PLM) during different sleep stages (REM, SWS, and N2 stages)

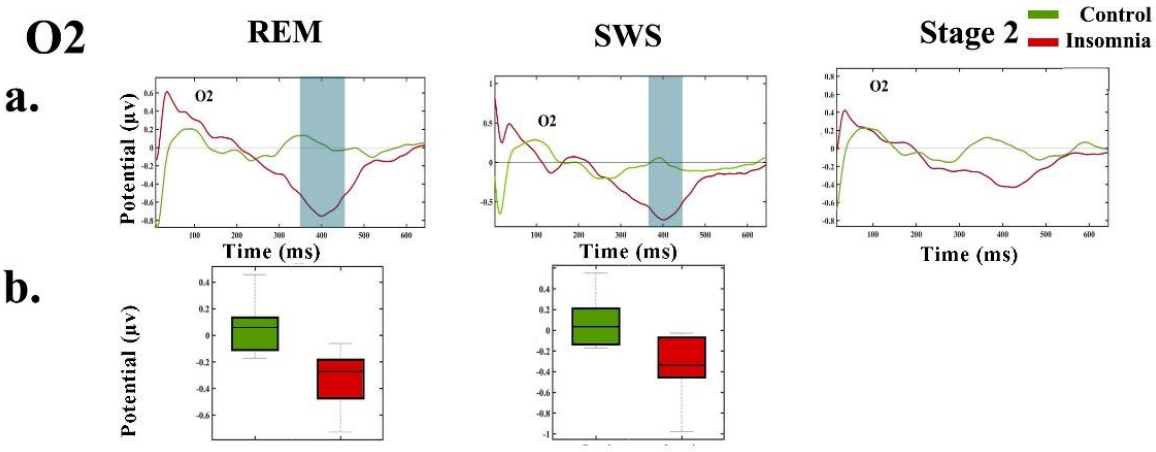

Figure 10. The comparison of HEP amplitude differences over the O2 channel and during different sleep stages (REM, SWS, and N2 stages). (a) Waveforms indicate that the insomnia group experiences a significantly lower HEP amplitude during the REM and SWS stages of sleep. (b) Boxplots are used for the comparison of the mean HEP amplitude over the O2 channel between control and insomnia groups during REM and SWS stages of sleep

4. Discussion

This study provides the assessment of HEP modulations during sleep in patients suffering from insomnia, RBD, PLM, and NFLE. Our results indicate that significant HEP amplitude differences exist between patients and control groups during different stages of sleep.

Numerous studies on HEP signals have proven that interoceptive stimulus activates multiple regions of the brain and cortical structures, including the insular cortex, somatosensory cortex, cingulate cortex, amygdala, thalamus, and parieto-occipital cortex [2, 18, 22, 33]. These HEP modulations are mainly elevated in the right hemisphere [15, 16, 34]. For instance, cardiac perceptions modulate HEP over frontal regions of the brain [31], visual perception tasks cause significant HEP changes over the parieto-occipital region [18], and finally, cognitive processes modulate HEP over right frontopolar and central regions. On the other hand, almost all sleep disorders are followed by some similar sequelae, including depression, anxiety, and cognitive impairments in which most of them share similar HEP responses to sleep disorders as well.

Our results indicate that the insomnia group experience significantly higher HEP amplitude over the right hemisphere grand average HEP responses during different stages of sleep and in a considerably wide time window around 330 up to 420 ms post R-peak (Figure 2).

Interestingly, our findings indicate that the insomnia group experiences a significantly stronger HEP amplitude over the F4 channel, and during REM and N2 stages of sleep. On the other hand, prior works on the relationship between insomnia and HEP signals were mainly concentrated on closed-eyes and opened-eyes tasks and were assessed during wakefulness [35]. Prior studies' results indicated that during closed-eyes tasks, insomnia patients had experienced significantly higher HEP amplitude (376-500 ms) over frontal electrodes [35]. Latencies of our frontal and central channels are consistent with previous works on insomnia patients during wakefulness. This indicates that REM emotional arousal and heightened sensitivity impact on interoceptive signals are present during daytime wakefulness, too. Also, we have declared that HEPs are detectable during sleep and wakefulness. Furthermore, since interoception occurs outside the realm of conscious awareness, sleep may provide a better environment to investigate new aspects of these signals.

In cases of RBD and PLM groups, the grand average of the HEP's amplitude over the right hemisphere, with almost similar resemblance, was significantly lower in RBD and PLM groups during different stages of sleep and in a wide time window around 500 ms post R-peak (Figure 2). On the other hand, the C4 channel showed a deflection in the second detected HEP differences and around 500 ms post R-peak time windows. Also, it

should be noted that, however, the PLM group HEP responses over the C4 channel did not reach the significance threshold in a time window around 500 ms post R-peak, but it has shown a similar pattern to the same HEP responses' latencies of the RBD group (Figure 6). These similar patterns of HEP responses are consistent with Terhaar *et al.*'s (2012) article results in which they observed almost similar response in patients suffering from depression during wakefulness [17]. They demonstrated that patients suffering from depression have a lower HEP amplitude over the whole scalp grand average [17]. Also, the scalp topography revealed that HEP differences were slightly more pronounced around the central region of the brain [17].

Another important result around the C4 channel is derived from insomnia and RBD groups. The C4 channel showed higher HEP amplitude during REM, SWS, and N2 stages in insomnia and RBD groups and around 350 up to over 400 ms post R-peak. Note that cognitive impairments are one of the foremost common complaints in insomnia and many other similar sleep disorders patients. Prior studies have demonstrated that increased HEP amplitude over the C4 channel corresponds with cognitive impairments as well [36].

The FP2 channel HEP amplitude of the PLM group was significantly lower during the REM, SWS, and, N2 stages of sleep. Also, the HEP amplitude of the FP2 channel was significantly lower in the RBD group and during the REM stage of sleep. We should note that, however, only these four time periods of FP2 channels became statistically significant, the HEP signals of almost all disorders and in all three stages of sleep showed similar HEP response patterns.

Interestingly, we should note that almost all patients' groups had a significantly higher HEP amplitude over the F4 channel during REM and N2 stages of sleep (which are believed to share more similar attributes to wakefulness than deep sleep) and around 350 ms post R-peak. On the other hand, this statistically significant difference was not observed during the SWS stage of sleep. Note that although the HEP differences did not reach the significance threshold during the SWS stage of sleep, these prominent HEP differences were still evident during this stage, too. With regard to these HEP responses and the emotional related intrinsic structure of the REM and N2 stage of sleep [14], these changes and differences over the F4 channel are believed to be under the influence of emotional arousal.

Finally, significant HEP differences were detected over the O2 channel between insomnia and control groups as well (Figure 10). With being overly cautious about the interpretations of this result, one may conclude that this significant difference may illustrate an interaction between visual perceptions and interoceptive processes. This may be the reason behind insomnia's common visual perception deficits, which are proven to be an important sequela of this disorder as well [18, 36].

The present study investigated the possibility of HEP amplitude modulation in cases of different sleep disorders. To traverse the gap between ML development and ML deployment in clinical settings, we need to make substantial progress in boosting our knowledge about HEP amplitude responses to sleep disorders. Furthermore, since, from clinical perspectives, many different characteristics, including gender, age, and race may lead to data shifts and consequently model deteriorations, we need to extend our datasets and generate models on the basis of more universal features [37]. Different HEP characteristics, including mean HEP amplitude, peak of HEP amplitude, HEP TOI length, and HEP TOI latencies may provide important features for better sleep disorder classification and more advanced model developments. As a result, more similar studies and boosting our knowledge on the basis of the relation between different HEP characteristics and sleep disorders may lay the foundation for future progresses in the application of possible ML developments in clinical settings. Furthermore, to deploy Machine Learning (ML) systems in clinical settings and to move from model development to model deployment, we need to augment available datasets. By extending related datasets and having a better understanding of different sleep disorders, we would be able to introduce practical ML models to test HEP responses as a new possible feature for a more robust classification of sleep disorders.

5. Conclusion

We used HEP signals to investigate different sleep-related disorders, including insomnia, RBD, PLM, and NFLE. Our results have demonstrated that statistically significant HEP differences exist between the control group and patients suffering from each of the above sleep disorders over multiple right hemisphere EEG channels. Also, our results indicate that patients suffering from different sleep disorders mainly experience similar HEP

responses patterns over similar channels and with almost similar latencies.

As referred before, our HEP results bear considerable resemblances to previous studies on sleep and mental-related disorders. Furthermore, as future works, more focused studies over each of these mental issues during sleep may help to come to a universal agreement on the relationship between mental states and HEP responses and how these mental issues originate as a sequela of sleep-related disorders. In other words, HEP latencies, the length of significant difference windows, and the amplitude intensity bear important factors about each mental state, and they may help to define more precise guidelines about the relation between HEP responses and mental or sleep-related disorders.

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