Defining, Detecting and Assessment of Microstructures in Different Stages of Sleep Apnea Transients Using ECG and EEG Features in CSA and OSA Patients

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Article

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Abstract

The sleep recordings of 32 patients with obstructive sleep apnea (OSA) and central sleep apnea (CSA) were analyzed with signal processing and statistical methods. The aim of the present study was to analyze electrocardiogram (ECG) and electroencephalogram (EEG) signals, along with other polysomnography (PSG) outcomes, according to sleep stages, sleep apnea types, and apnea/hypopnea index, and to demonstrate their association with EEG microstructures that cannot be detected visually. Patients were classified into groups according to the apnea/hypopnea index (AHI) and, results were classified according to types of apnea, and the apneas that were detected during all sleep stages (N1-N2-N3 and REM). ECG and EEG signals were analyzed with time-frequency methods. Analysis was carried out during epoch at apnea (intra-apnea), epoch before apnea (pre-apnea), and epoch after apnea (post-apnea). The findings of the present study are presented as different tables in the Results and Discussion sections, and were discussed in the Conclusion section.

1. Introduction

Sleep related respiratory disorders are known to be important factors in human health which lead to various cardiovascular [1], neurological [2] and endocrinological diseases [3, 4]. In general terms, sleep apnea is defined as a decrease in blood oxygen saturation levels or in electroencephalogram (EEG) arousals following partial/full respiratory arrest and, has three different types [5, 6]. Obstructive sleep apnea (OSA) is the condition in which there is no air flow in the mouth and the nose despite attempts to breathe whereas the absence of air flow in the same areas without an attempt to breathe is defined as central sleep apnea (CSA). The last type is the respiratory pathology that starts off as CSA, but then progresses to OSA is referred to as mixed sleep apnea (MSA) [7, 8].

The relation between ECG parameters and sleep related disorders have been an interest among researchers. There are studies on the detection of RR interval and heart rate variability (HRV) signal, its association with sleep apnea, and determination of sleep stages in the literature [9–15]. A previous study reported that normalized theta power showed a decreasing trend in apnea/hypopnea. This condition is associated with AHI [16]. Similarly, sleep and wakefulness states were investigated using power density analysis. Oximetric signals and EEG analysis were used to diagnose OSA (91% sensitivity, 83.3% specificity and 88.5% accuracy) [17]. In another study a micro association between wave width and total power was detected by FFT (Fast Fourier Transform)-power spectral analysis method [18].

A common investigation in sleep apnea studies is the detection of arousal to demonstrate the association between different PSG parameters and respiration, cardiac activities, and arousals [19]. It has been proposed that the use of adaptive time-frequency signal processing can help detect micro and macrostructures in sleep EEG [20]. Moreover, use of multiple EEG measurements may detect transients in N2 and N3 stages [21]. Furthermore, EEG spectral analysis in only REM and wakefulness stages was reported to have a correlation between EEG wakefulness and oxygen saturation [22]. In [23], correlations for neurobehavioural performance after 24 h of extended wakefulness in untreated OSA have been investigated by EEG microstructures. Biomarkers for OSA have been tried for neurobehavioural functioning in adults [24]. Again, rapid and nonrapid eye movements during the sleep have been associated to apnea hypopnea index and nocturnal hypoxemina in men [25]. A study to evaluate the relation between the severity of obstructive sleep apnea and the ECG heart rate microstructure during sleep has been given in [26]. To compare microstructural features of sleep in young and middle-aged adults with differing severities of obstructive sleep apnea syndrome (OSAS), and to investigate the relationship between sleep microstructural fragmentation and cognitive impairment, as well as daytime sleepiness, in these patients is examined and a conclusion as phase A3 index is a sensitive indicator of sleep fragmentation in OSAS is presented in [27]. Examination of brain oscillatory features related to respiratory arousals in moderate and severe OSA is realized in [28]. EEG signals obtained during, five seconds before and after the occurrence of each arousal were analyzed, then it was concluded in [28] that the dynamic range of sensorimotor cortical activity during respiratory arousals is sleep stage specific, dependent on the frequency of respiratory events and uncoupled from autonomic activation. To classify sleep stages using dual-channel unipolar electroencephalogram (EEG), chin electromyogram (EMG), and dual-channel electrooculgram (EOG) signals automatically, a machine learning based approach is proposed in [29]. Proposed model in [29] developed to classify sleep stages for both good sleepers as well as patients suffering from sleep disorders. Using an optimum orthogonal filter bank, sub-bands are obtained by decomposing 30 s epochs of signals, so high classification accuracy was obtained in [29].

According to the literature, several studies have been carried out in REM and non-REM stages, different time points, and frequencies to determine the microstructures that are formed in sleep EEG during sleep apnea. In most of these studies, EEG microstructures and ECG parameters have not been analyzed together at points of sleep transitions. In this study, the apnea transition points during all sleep stages (N1, N2, N3 and REM) are analyzed with respect to apnea types, sleep stages and AHI. In each stage, during a pre-apnea, intra-apnea, and post-apnea periods, EEG spectral analysis-based microstructures were not only evaluated by signal processing techniques, but also examined by using statistical analyses. Microstructures are defined as cortical behavior patterns that are invisible in short-term signal analyzes but can be revealed by statistical analyzes in apnea transition states. In addition, time and frequency features from the ECG signal were compared to EEG features. The main contribution of this study is analyzing sleep related microstructures from EEG together with ECG features by examining the 30 seconds epochs during intra-apnea, pre-apnea and post-apnea, in order to accelerate the initiation of the treatment process by defining the important parameters of the disease and to improve the life quality of the patient.

The rest of the paper is organized as follows: In Section 2, materials and methods including datasets used in this study, signal processing methods are described in detail. In Section 3 experimental results and discussions are given. Finally, in Section 4, some concluding remarks are presented.

2. Materials And Methods

2.1 Data Sets

A PSG is an instrument that allows synchronous recording of various physiological activity including EEG, ECG and the parameters including oronasal airflow (thermistor), respiratory effort, and oxygen saturation [30, 31]. Apnea-hypopnea index (AHI), one of the most prominent outputs of PSG, measures the apnea and hypopnea count within one hour of the sleep period.

PSG data of 32 male patients (aged 42 ± 9 (mean ± std. dev.)) were obtained from Diskapi Yildirim Beyazit Education and Research Hospital (Ankara, Turkiye) Thoracic Diseases Department Sleep Disorders Diagnosis and Treatment Center. Data was recorded on a Compumedics E Series™ (Sydney, Australia) instrument and scored with ProFusion 3™ software. All night EEG recordings were scored by a certified sleep technician according to the rules defined in [32]. Patients in each group (i.e., 16 OSA and 16 CSA) were divided into subgroups according to AHI as follows: AHI < 5 (n = 4), 5 < AHI < 15 (n = 4), 15 < AHI < 30 (n = 4), and AHI > 30 (n = 4). The mean body-mass index of the patients (BMI) was 30 ± 7 kg/m^2 and there was no existing difference in demographic features between the OSA and CSA groups. EEG data were recorded according to 10–20 standard electrode positioning rules from central (C4), frontal (F4) and occipital (O2) regions. For the ECG data acquisition, 3-lead placement was used. In addition to ECG and EEG, oronasal air flow was recorded with a thermistor. Thoracoabdominal activity was measured using piezoelectric belts, a digital microphone, and a pulse oximeter. PSG sampling frequency was set to 256 Hz for ECG and EEG. A 50 Hz Notch filter was used for PSG inputs. PSG signal analysis realized via MATLAB. ECG and EEG signals were divided into 30 sec epochs and then epochs during apnea were labeled as intra-apnea, epochs 30 sec before intra-apnea were labeled as pre-apnea period, and epochs 30 sec after intra-apnea were labeled as post-apnea.

The data required for this study were not collected from the patients as a study-specific data, the dataset was created as a result of retrospectively examining the data (taken with the 64-channel Compumedics™ brand E-Series Polysomnography device) of the patients admitted to the clinic with the complaint of sleep apnea. All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by Dr. Sadık Ardıç, clinical chief of Ankara Dışkapı Training and Research Hospital sleep disorders center. In addition, the patients signed a voluntary informed consent form stating that these records would be used in engineering studies. The data of the patients who signed this consent form were used in our study.

2.2 ECG Signal Processing

The morphological structure of ECG signal can change with respect to heart rate and blood oxygen saturation. Moreover, sleep apnea, one of the causes of oxygen desaturation, is considered to affect this structure [33]. The pulse transit time (PTT), the delay of blood flow from the aortic valve to the periphery [34], is a parameter which can be determined with synchronous recordings of pulse oximeter, PSG and ECG. PTT is a measure of R wave delay in the ECG and is a solid indicator of airway resistance which causes sleep fragmentation [35]. The model developed to detect the HRV power spectral density is shown in Fig. 1. According to this model, pre-signal processing was performed, the R wave was detected by template matching, and then the Teager Energy (TE) operator was used to magnify rapid changes. Next, the HRV was constructed using a threshold comparison process in the time domain. Later, power spectral analysis was applied to analyze sympathetic/parasympathetic activity changes in the frequency domain.

2.2.1 Frequency Domain HRV Analysis

The analysis starts with applying a moving average filter (MAF) to the ECG signal in order to smooth the signal [36]. MAF is given in Eq. 1;

$$y = \sum_{m=0}^{M-1} x(n-m)$$

1

A correlation-based algorithm was used to detect R waves. The signal was correlated with a template selected from the ECG signal [37], where *f*(*x*) represents the signal; *temp*(*x*) represents the template, $\bar{f}$ is the average value of the signalf, and σ_f represents the standard deviation. The sample template chosen for correlation is plotted in Fig. 2. The cross correlation (CC) of *f*(*x*) and *temp*(x) was calculated as given in Eq. 2;

$$CrossCorrelation = \frac{1}{n}\sum_{x}\frac{(f(x)-\bar{f})(temp(x)-\bar{temp})}{\sigma_f \sigma_{temp}}$$

2

TE operator is a derivative-based operator that is commonly used for discrete and continuous time signals which reveals the rapid changes within the signal [38]. The TE operator in discrete time is shown in Eq. 3.

$$\psi(n) = x^2(n) - x(n+1)x(n-1)$$

3

After TE output, a threshold comparison of the signal was made [37, 38]. The average of a certain window on the signal was calculated, and 30% of this calculated value was set as the threshold. As the last step of the model, the Yule Walker method, a parametric AR model (Eq. 4), was used for the frequency domain analysis of HRV [39–41]. The power spectral density of the HRV is presented in Fig. 3.

$$S(f) = \frac{1}{f_s}\frac{\varepsilon_p}{\left|1+\sum_{k=1}^{p} a_p(k)e^{-2\pi jkf/f_s}\right|^2} \quad (4)$$

2.2.2 Time Domain Hjorth Parameters Analysis

Form factor (FF) was used by Hjorth [42, 43] in 1970s for non-stationary signal forms include three basic parameters. Activity, is the variance of signal (i.e., σ_x^2). Mobility, (M_x) is the square root of the ratio of variance of the first derivative of the signal to the signal variance. Mobility can be calculated as given in Eq. 5. Last parameter complexity (FF) is the ratio of the variation between the first derivative and the original signal (Eq. 6) [44, 45].

$$M_x = \left(\frac{{\sigma_x'}^2}{\sigma_{x^2}} \right)^{1/2}$$

5

$$FF = \frac{M_x'}{M_x} = \frac{\sigma_x''/\sigma_x'}{\sigma_x'/\sigma_x}$$

6

2.3 EEG Signal Analysis

The EEG signal has a magnitude between 10 µV-100 µV, and variable frequency width between 1 Hz-100 Hz. The EEG signal is the sum of delta wave (< 4Hz), theta wave (4-8Hz), alpha wave (8–13 Hz) and beta wave (13-30Hz) rhythms [46]. Some of these features are used in sleep scoring and detection of sleep related disorders. Commonly, changes in cortical activity during sleep is detected by EEG spectral analysis [47]. In particular, sleep apnea/hypopnea affects the spectral content of the EEG. There are various methods for the spectral analysis of EEG signals [48]. Among these methods are periodogram [49, 50], Welch [49], and multitaper methods (non-parametric methods) [48]; covariance and modified covariance methods, Burg [51] and Yule-Walker [50] methods (parametric methods); and eigenvector (EV) and multiple signal classification methods (subspace methods). The power of the analog signal (y) is given in Eq. 7;

$$y = \int R_{yy}(f)\, df$$

7

$R_{yy}(f)$; $r_{yy}(t)$ are the discrete Fourier transform (DFT) of the autocorrelation function. The autoregressive (all poles) AR model is presented in Eq. 8, in which x[n] represents the weighted sum of w[n] inputs.

$$x[n] = a_1 x[n-1] + \cdots + a_p x[n-p] + w[n]$$

= $\sum_{i=1}^{p} a_i x[n-i] + w[n]$ (8)

In the first-degree AR process (Eq. 9):

$$x[n] = a_1 x[n-1] + w[n]$$

9

and,

$r_{xx}(0) = a_1 r_{xx}(1) + a_2 r_{xx}(2) + \cdots + a_p r_{xx}(p) + \sigma_{x,k}^2$ = 0 (10)

is divided to $\mathrm{r_{xx}}(0)$ to calculate normalized CC coefficient $\rho(\mathrm{k})$ (Eq. 10, 11).

$$\rho(k) = a_1 \rho(k-1) + a_2 \rho(k-2) + \cdots + a_p \rho(k-p)$$

$$k > 0$$

11

$\rho(\mathrm{k})$ ı s spectrum yields to Yule-Walker method in Eq. 4. Solution incline to autoregressive parameters [15, 37, 46]. The Yule-Walker parametric method was preferred as it allows windowing which was used to analyze EEG data during pre_apnea, intra_apnea, and post_apnea periods with very small frames (n = 64, %50 overlap). The signal that was analyzed as a single epoch had sampling frequency of 256Hz, and 64 samples in each window. Each epoch that made a transition to apnea was analyzed individually for all 32 patients.

2.4 Statistical Processing

The differences in the results of EEG analysis between the CEA and OSA groups were assessed using the Student's t-test or the Mann-Whitney U-Test according to the parametric test assumptions. To assess the differences between three or more groups "one-way ANOVA" was used when parametric test assumptions were met; and the Kruskal Wallis test was used when these assumptions were not met. To evaluate the significant results between three or more groups, the adjusted Bonferroni method was used. To determine the association between two dependent variables, the paired-comparison t-test was used when parametric test assumptions were met, and the Wilcoxon test was used when these assumptions were not met. P values < 0.05 were considered as statistically significant.

3. Results And Discussion

In this study, PSG data from patients with OSA (n = 16) and CSA (n = 16) were evaluated. Patients in the OSA and CSA groups were divided into equal subgroups according to the AHI score (n = 4). The classification and signal analysis method are presented in Fig. 4.

OSA and CSA patients that were classified according to AHI groups were examined for each stage of apnea transition. The sub-band spectrum of EEG signals was analyzed on the basis of epoch during pre, intra, and post_apnea periods to determine invisible microstructures. The epoch at the time of apnea transition was taken as a reference, and PTT, HRV, and FF analyses were carried out on ECG, and the presence of significant changes were analyzed with the EEG spectrum. The statistical tests showed significant differences in ECG and EEG parameters between OSA and CSA groups (Table 1). Accordingly, the FF value increased from pre_apnea to post_apnea in CSA patients whereas this trend was not followed in OSA patients where the highest FF numbers were calculated in pre_apnea. Following the first raw of Table 1, CSA patients had significantly lower EEG delta activity in pre_apnea compared to OSA. Delta activity is associated with slow wave sleep and this may be suggesting that OSA patients have higher number of slow wave episodes before apnea episode compared to CSA patients. In theta and alpha sub-bands, CSA patients had higher sleep energy compared to OSA group. Even though not significant, CSA group had lower beta activity compared to OSA suggesting that the OSA patients have higher numbers of distinctive cortical activity which may be due to increased brain activity. Same trend in delta, theta, alpha and beta activities between CSA and OSA were found during apnea episodes with only significant increase in beta activity in OSA patients. This may be suggesting that the number of wakefulness episodes are higher for OSA group.

The mean PTT values for both the groups were given in Table 1, in the second raw. Pre_apnea and intra_apnea PTT values were significantly different between the OSA and CSA groups ($p < 0.001$, and $p < 0.05$, respectively). Contrary to CSA patients, PTT duration increased during apnea in the OSA group suggesting a longer duration needed for blood to distribute from aorta to periphery.

Table 1
ECG time analysis and EEG data with respect to CSA and OSA

Apnea Group		BMI	Age	Pre_Apnea FF	Intra_Apnea_FF	Post_Apnea FF	Pre_EEG_delta	Pr
CSA	Mean ± Std. Deviation	30,08	38,44	3,75	3,76	3,84	1,49E + 06	7,1
		± 4,91	± 10,5	± 1,82	± 1,90	± 1,97	± 3127656,7	± 6
	Median (Max. - Min.)	29,15	37,00	4,15	4,36	4,16	4,02E + 05	1,0
		(38,7–22,7)	(53 – 18)	(6,54 – 1,07)	(7,02 – 1,12)	(8,01–1,18)	(723436,14-30497,06)	(3 12
OSA	Mean ± Std. Deviation	29,28	46,06	2,01	1,88	1,89	2,13E + 06	3,9
		± 6,32	± 7,069	± 1,22	± 0,99	± 1,012	± 10421650,29	± 1
	Median (Max. - Min.)	28,10	45,00	1,54	1,51	1,49	2,10E + 05	7,0
		(50,20–22,20)	(65 – 36)	(5,75 – 1,22)	(5,77 – 1,23)	(5,73 – 1,25)	(59217824,07-22505,78)	(10 75
P				0,001	0,001	0,001	0,019	0,0
Apnoea Group		Pre_EEG_beta	Int_Apnea_EEG_delta	Int_Apnea_EEG_theta	Int_Apnea_EEG_alpha	Int_Apnea_EEG_beta	Pre_PTT	Ap
CSA	Mean ± Std. Deviation	2,27E + 04	3,79E + 06	7,90E + 05	4,72E + 04	2,75E + 04	475,83	32
		± 70073,6	± 7099873,8	± 1349413,5	± 126794,26	± 92366,61	± 217,52	± 7
	Median (Max. - Min.)	5,41E + 03	5,48E + 05	1,68E + 05	1,59E + 04	7,22E + 03	364,00	31
		(386394,58-1341,92)	(38251858,9-39876,1)	(7042455,55-15123,72)	(675110,109–3826,86)	(476990,37-1145,82)	(1043,5-289)	(74 28
OSA	Mean ± Std. Deviation	5,85E + 03	7,41E + 05	1,59E + 05	1,12E + 04	4,95E + 03	317,79	38
		± 8115,2	± 1879671,42	± 333025,19	± 5460,16	± 6727,66	± 43,66	± 2
	Median (Max. - Min.)	3,61E + 03	1,78E + 05	5,65E + 04	1,18E + 04	3,38E + 03	309,00	32
		(45.098,29-1.094,27)	(9743102,69-20384,17)	(1717031,19-8759,65)	(25504,22-2139,05)	(40577,23-1103,02)	(529,00-287,00)	(13 30
P		0,066	0,012	0,004	0,001	0,005	0,001	0,0

Pre_FF, intra_apnea_FF, post_FF, pre_eeg_delta, pre_eeg_theta, pre_eeg_alpha, intra_apnea_eeg_delta, intra_apnea_eeg_theta, intra_apnea_eeg_alpha, and intra_apnea_eeg_beta showed significant differences between OSA and CSA patients. PTT parameters showed significant differences during pre_PTT intra_apnea_ptt periods between OSA and CSA patients. There was no significant difference between OSA and CSA during post PTT.

Table 2
Pre_HRV and post_HRV results with respect to apnea type, AHI, and sleep stage.

Apnea Group		Pre_HRV	Post_HRV
CSA	Mean ± Std. Deviation	1,94	1,89
		± 1,26	± 1,17
	Median (Max. - Min.)	1,52	1,67
		(6,26 – 0,46)	(4,97 – 0,11)
OSA	Mean ± Std. Deviation	2,19	1,85
		± 1,49	± 1,167
	Median (Max. - Min.)	1,82	1,59
		(6.07-0,45)	(5,19 – 0,33)
AHI Group		Pre_HRV	Post_HRV
AHI < 5	Mean ± Std. Deviation	1,39	1,30
		± 0,91	± 0,68
	Median (Max. - Min.)	1,22	1,06
		(4,09 – 0,45)	(2,61 – 0,33)
AHI 5–15	Mean ± Std. Deviation	2,08	1,94
		± 1,49	± 1,21
	Median (Max. - Min.)	1,55	1,63
		(6,07 – 0,54)	(5,19 – 0,69)
AHI 15–30	Mean ± Std. Deviation	2,32	1,92
		± 1,58	± 1,18
	Median (Max. - Min.)	1,75	1,67
		(6,26 – 0,49)	(4,97 – 0,11)
AHI > 30	Mean ± Std. Deviation	2,18	2,18
		± 1,16	± 1,29
	Median (Max. - Min.)	1,94	1,89
		(5,32 – 0,56)	(4,91 – 0,34)
STAGE Group		Pre_HRV	Post_HRV
N1	Mean ± Std. Deviation	2,88	2,46
		± 1,716	± 1,26
	Median (Max. - Min.)	2,55	2,40
		(6,26 – 0,79)	(4,91 – 0,68)
N2	Mean ± Std. Deviation	1,93	1,84
		± 1,25	± 1,27
	Median (Max. - Min.)	1,60	1,56
		(5,32 – 0,45)	(5,19 – 0,33)
N3	Mean ± Std. Deviation	1,36	1,60
		± 0,68	± 1,03
	Median (Max. - Min.)	1,48	1,45
		(2,36 – 0,46)	(4,35 – 0,11)
REM	Mean ± Std. Deviation	2,21	1,77
		± 1,44	± 0,97
	Median (Max. - Min.)	1,75	1,62

Apnea Group	Pre_HRV	Post_HRV
	(6,07 – 0,56)	(4,39 – 0,54)

HRV parameters (pre/post_apnea HRV i.e., pre_HRV and post_HRV) with respect to OSA, CSA and AHI classification and sleep stages are shown in Table 2. In the CSA group, the mean pre_HRV value was 1.94 ± 1.26 where as the post_apnea HRV value LF/HF power spectral ratio was 1.89 ± 1.17. In the OSA group, the mean pre_HRV value was higher (2.19 ± 1.49) compared to CSA group but both groups had decreasing trend suggesting reduced heart rate during post_apnea period in OSA patients. HRV findings with respect to AHI groups showed a decreasing trend during the post_apnea period, except the AHI > 30 (pre_HRV 2.18 ± 1.16, post_HRV 2.18 ± 1.29) group all of which showing differences in cardiac parameters through apnea types. Pre_HRV values increased with AHI severity (5 < AHI < 15 pre_HRV = 2.08 ± 1.49, 15 < AHI < 30 pre_HRV = 2.32 ± 1.58, AHI > 30 pre_HRV = 2.18 ± 1.16).

HRV changes showed differences in sleep stages. As given in Table 2, HRV decreased both in pre and post apnea as sleep deepened (N1-N3) suggesting reduced heart rate in SWS. During REM sleep, the mean pre_HRV was found 2.21 ± 1.44, and the mean post_HRV was 1.77 ± 0.97 around level of the N1 sleep stage activity indicating increased brain activity. Furthermore, when the results were analyzed through all sleep stages, the pre_HRV values showed a decreasing trend with increasing sleep depth. The same trend was present in case of post_HRV.

Delta activity and PTT parameters were classified across different AHI groups and these results were presented in Table 3. During delta sleep, delta sleep energy increased with increasing AHI severity indicating increased SWS which result in increased EEG energy in the delta frequency range. Contrary to delta energy during apnea, PTT values decreased as AHI severity increased. This was found in all apnea stages (pre, apnea and post).

There were significant changes in PTT values and delta activity of the subjects that were grouped according to AHI (Table 3). As AHI severity increases this suggest an increase in number of apnea epoisodes which would consequently stimulate central nervous system. Therefore, a significant decrease in pre-apnea PTT value would be observed as AHI severity increases. During apnea, a decrease or a local variability in PTT value could be more profound in pre-apnea region in higher AHI. This is a variable clinical consequence of patient's nervous system reflex. Similar to pre-apnea, post-apnea region PTT response show an increasing trend as AHI severity increases however the variance in changes in that period is more dramatic compared to pre-apnea region which is due to subject's exposure to higher number of apnea episodes. It can be deducted that PTT values calculated and grouped according to AHI severity show significantly different microchanges.

Significant EEG parameter in different AHI groups was found in pre-apnea delta activity. High AHI group subjects' delta energy was higher compared to those in low AHI group subjects (MAX Value: AHI > 30; Mean ± Std. Deviation 4,77E + 06 ± 8645811,23; MIN Value: AHI < 5 Mean ± Std. Deviation. 1,55E + 06 ± 3524162,57). The physiological reason behind this finding is severe AHI group's (i.e., AHI > 30) central nervous system support deeper sleep in those with lower sleep efficiency in the absence of a different stimulus.

Table 3
EEG and PTT values according to AHI

AHI Group		Apne_EEG_delta	Pre_PTT	Apne_PTT	Post_PTT
AHI < 5	Mean ± Std. Deviation	1,55E + 06	464,94	447,67	314,98
		± 3524162,57	± 236,4	± 299,5	± 49,03
	Median (Max. - Min.)	1,46E + 05	337,50	324,00	312,00
		(13440956,26-39876,10)	(1013,50–289,00)	(1359,00-285,00)	(439,25–205,00)
AHI 5–15	Mean ± Std. Deviation	1,31E + 06	457,37	346,64	345,82
		± 2508376,44	± 218,41	± 64,96	± 124,34
	Median (Max. - Min.)	2,62E + 05	335,00	330,14	317,14
		(9920792,21-38105,75)	(1043,50–304,00)	(566,00-295,25)	(856,00-296,25)
AHI 15–30	Mean ± Std. Deviation	2,09E + 06	370,97	325,50	323,09
		± 5197918,78	± 156,58	± 37,54	± 48,94
	Median (Max. - Min.)	1,95E + 05	314,42	317,75	310,33
		(19829553,75-20384,17)	(882,00-300,00)	(484,75–300,00)	(531,00-289,00)
AHI > 30	Mean ± Std. Deviation	4,77E + 06	369,35	304,40	294,72
		± 8645811,23	± 121,6	± 12,02	± 11,49
	Median (Max. - Min.)	9,03E + 05	312,00	308,00	295,36
		(38251858,90-78926,48	(779,00-287,00)	(333,91–281,67)	(309,60–259,50)
P		0,036	0,017	0,001	0,001

Table 4
Pre/intra apnea change with sleep stages

STAGE Group		Pre_EEG_delta	Pre_EEG_theta	Pre_EEG_alpha	Pre_EEG_beta
N1	Mean ± Std. Deviation	2,81E + 06	5,93E + 05	1,79E + 04	9,13E + 03
		± 5377700,79	± 1088976,99	± 12869,97	± 6980,63
	Median (Max. - Min.)	5,44E + 05	1,48E + 05	1,45E + 04	7,40E + 03
		(17723436,14-83087,79)	(3681434,92-22217,41)	(52198,57-3146,03)	25757,21-2076,56)
N2	Mean ± Std. Deviation	2,58E + 06	5,01E + 05	3,46E + 04	2,09E + 04
		± 10733930,17	± 1830461,7	± 95930,59	± 69636,26
	Median (Max. - Min.)	3,08E + 05	8,92E + 04	1,45E + 04	5,37E + 03
		(59217824,07-47766,22)	(10131769,21-18.575,49)	(10131769,21-18575,49)(540089,88-4383,10)	(386394,58-1603,89)
N3	Mean ± Std. Deviation	1,32E + 06	3,56E + 05	4,78E + 04	2,40E + 04
		± 2066175,35	± 489455,21	± 108936,71	± 73811,3
	Median (Max. - Min.)	4,74E + 05	1,41E + 05	1,98E + 04	3,28E + 03
		(7606135,19-48604,67)	(1727842,21-21303,16)	(439541,62-8150,87)	(290586,42-2322,47)
REM	Mean ± Std. Deviation	1,98E + 05	5,87E + 04	1,03E + 04	5,64E + 03
		± 168640,19	± 46111,61	± 8479,37	± 9123,5
	Median (Max. - Min.)	1,66E + 05	4,62E + 04	7,25E + 03	2,53E + 03
		(485313,70-22505,78)	(144566,22-7562,35)	(32224,73-2104,27	(42507,80-1094,27)
P		0,005	0,003	0,002	0,014
STAGE Group		Intra_EEG_delta	Intra _EEG_theta	Intra _EEG_alpha	Intra_EEG_beta
N1	Mean ± Std. Deviation	5,97E + 06	1,16E + 06	2,00E + 04	1,06E + 04
		± 11052034,27	± 2027210,46	± 13479,5	± 6553,96
	Median (Max. - Min.)	1,10E + 06	2,76E + 05	1,68E + 04	1,05E + 04
		(38251858,90-20384,17)	(7042455,55-8759,65)	(52589,87-3595,28	(22637,27-2014,52)
N2	Mean ± Std. Deviation	1,98E + 06	4,19E + 05	3,59E + 04	2,14E + 04
		± 3920919,1	± 730204,26	± 101601,59	± 75957,93
	Median (Max. - Min.)	2,90E + 05	8,59E + 04	1,41E + 04	5,22E + 03
		(19829553,75-40678,73)	(3660725,24-16419,50)	(571567,35-5492,94)	(421586,30-1849,84)
N3	Mean ± Std. Deviation	2,71E + 06	6,40E + 05	6,56E + 04	3,75E + 04
		± 5066995,95	± 1122429,54	± 169202,18	± 121726,92
	Median (Max. - Min.)	3,03E + 05	1,09E + 05	1,57E + 04	4,55E + 03
		(15670939,42-78926,48)	(3700075,10-36044,62)	(675110,11-8890,33)	(476990,37-1803,61)
REM	Mean ± Std. Deviation	9,31E + 05	2,25E + 05	8,95E + 03	3,33E + 03
		± 2921450,83	± 537598,21	± 5564,65	± 2152,03
	Median (Max. - Min.)	1,46E + 05	4,48E + 04	7,48E + 03	2,50E + 03
		(9743.102,69-38105,75)	(1864421,25-13088,93)	(22993,79-2139,05)	(8223,86-1103,02)
P		0,031	0,012	0,001	0,001
STAGE Group		Post_EEG_delta	Post_EEG_theta	Post_EEG_alpha	Post_EEG_beta
N1	Mean ± Std. Deviation	1,00E + 06	2,39E + 05	1,30E + 04	4,99E + 03
		± 2103476,31	± 458694,51	± 6955,67	± 2980,17
	Median (Max. - Min.)	3,58E + 05	1,03E + 05	1,23E + 04	4,00E + 03

STAGE	Group	Pre_EEG_delta	Pre_EEG_theta	Pre_EEG_alpha	Pre_EEG_beta
		(7.564.130,19-15.887,08)	(1.667.053,27-5.557,88)	(31.216,08-2.882,79)	(10.165,19-1.880,59)
N2	Mean ± Std. Deviation	1,36E + 06	2,99E + 05	3,10E + 04	1,88E + 04
		± 3071919,5	± 593599,095	± 95578,96	± 70964,72
	Median (Max. - Min.)	3,72E + 05	9,83E + 04	1,16E + 04	3,63E + 03
		(14.519.599,08-44.163,94)	(2.827.699,75-22.628,38)	(535.636,89-4.699,55)	(391.734,24-1.949,89)
N3	Mean ± Std. Deviation	1,01E + 06	2,68E + 05	5,81E + 04	3,49E + 04
		± 1554141,7	± 383514,1	± 162905,49	± 111054,21
	Median (Max. - Min.)	2,37E + 05	7,26E + 04	1,68E + 04	4,16E + 03
		(4.788.226,95-70.228,39)	(1.191.909,49-22.715,83)	(646.603,62-6.696,59)	(435.602,58-2.148,89)
REM	Mean ± Std. Deviation	5,41E + 05	1,28E + 05	1,17E + 04	7,56E + 03
		± 1312100,47	± 262474,41	± 9817,93	± 14175,61
	Median (Max. - Min.)	1,50E + 05	4,45E + 04	8,51E + 03	3,09E + 03
		(6.007.984,18-23.722,61)	(1.209.202,23-7.943,19)	(45.448,55-2.087,29)	(66.109,70-1.261,65)
P		0,06	0,08	0,045	0,06

The EEG activity during sleep stages are presented in Table 4 as analyzed in different apnea states. Significant differences in pre_apnea EEG sub-bands and intra_apnea with respect to sleep stages were found with the Bonferroni ($p < 0.05$) analyses. These results show direct changes in brain activity in different sleep stages. Due to increased distinct spectral features of these sleep stages, results mirror what would have been expected in the spectral EEG analysis. On the other hand, sleep energy post_apnea shows significantly increased alpha activity during N3 stage and increased levels of beta activity. The first suggest an unusual increase in the N3 stage which is highly correlated with delta activity. The latter might suggest sleep fragmentation due to increased number of wakefulness episodes following apnea.

When different sleep states were considered (Table 4) delta activity was higher in N1 and N2 stages than in N3 and REM sleep. This might be due to suppression of inclination to deep sleep. A similar trend can be observed in theta activity that is higher in N1 and N2 stages compared to in N3 and REM sleep, which is consistent with homeostatic sleep cycles. During pre-apnea, increased brain activity biomarkers alpha and beta activities, more spesicificaly alpha activitywas increased in NREM sleep transitions (i.e., N1, N2 and N3). However, the ratio of theta and beta activity in total activity decreased (Table 4). This could be a result of increased synchronization of neurons to prepare brain to wakefulness by raising activation. In REM sleep an adverse effect on alpha and beta activity was observed. Both of these activities started to decrease, after a certain level of awareness was reached, to incline to sleep again.

Nevertheless, when apnea periods were scrutinized, statistical changes in EEG measurements could be observed. Brain responded to apnea and more specifically delta activity decreased as per pre-apnea period in N1-REM stages. In REM sleep delta activity was found to be much higher in intra-apnea than pre-apnea period (i.e., 9,31E + 05 ± 2921450,83 and 1,98E + 05 ± 168640,19 consecutively). This might be indicating a microstructure within the EEG that was originated to support a complete wakefulness if needed during apnea. A similar variation could also be seen in theta activity.

Moreoever, activities that are highly associated with sleep transitioning and wakefulness (i.e., alpha and beta) were elevated in N1, N2 and N3 compared to REM stage. This is an expected result as brain's impulse is to wake the patient up during apnea. Consequently, delta and theta activities were more pronounced as microstructures in brain response that were reflected in the EEG.

4. Conclusion

The classification based on OSA and CSA provided a sharp contrast. The pre_apnea and intra_apnea analyses of sleep energy between CSA and OSA patients showed significant differences across all brain activity bands. In the CSA group, all EEG sub-band activities increased during the post_apnea to intra_apnea transition. On the other hand, these activities decreased in OSA patients. The FF value increased during the pre_apnea to intra_apnea transition in the CSA group, but decreased in the OSA group. The duration of PTT decreased in the pre to intra apnea transition in the CSA group, and increased in the OSA group (Table 5).

Table 5. Increasing/decreasing trend in the CSA/OSA group

Pre/Intra Apnea Transient	Delta	Theta	Alpha	Beta	FF	PTT
CSA	↑	↑	↑	↑	↑	↓
OSA	↓	↓	↓	↓	↓	↑

The apnea process is less resistant in CSA patients. Patients make a transition to apnea without visual symptoms. Sleep continues in its regular course but a variability in heart morphology appeared during CSA. This progress indicates the presence of rapid variables in ECG. PTT showed dramatic increases in the pre_apnea period. During apnea, regulation is ensured with decreasing duration (pre_p_{ptt} $p < 0.001$, intra_p_{ptt} $p < 0.005$). Cardiac alterations were observed simultaneously with ongoing changes in brain activity. During OSA, there was a decreasing trend in all activities. The apnea process is more mechanical in OSA. In particular, HRV alteration and the increase in PTT duration during apnea emphasize cardiac findings in determining apnea. When the delta activity and PTT parameters were classified across different AHI groups (Table 3) it was found that sleep energy increased with the increasing in AHI severity which may be a consequence of increased SWS which would result in increased EEG energy in the delta frequency range. Unlike the PTT results presented in Table 1 for the CSA and OSA groups, PTT has a more definitive decreasing trend across AHI. Therefore, AH index might be a better scale for classification when the effects of the disease on cardiac parameters are investigated.

Delta, theta, alpha and beta activities were direct indicators of energy and frequency features of the signal and a result of integrative analysis. FF based analyses on the other hand are derivative based. Moreover, PTT is a spatial analysis. The conclusive results obtained from CSA and OSA patients showed discriminating trends. This shows central nervous system's response to apnea in order to ensure homeostasis. Furthermore, direct indicators of over-looked microstructures and clinical parameters to e used as attributors in sleep research.

Table 6 shows the post_apnea / pre_apnea change trend. Here, the results contain different findings contrary to the observations. There was an increasing trend in all EEG sub-bands during N1 superficial sleep, and the quantitative results are presented in Table 4. During the N2 stage, there was a decrease in the delta and theta band energies. During N3 – SWS sleep, all EEG sub band energies increased. These results are consonant with the literature as it may be showing the increased synchronization of the neurons as sleep deepens which result in increased EEG levels in these sub-bands [52–54]. However, there was a decrease in alpha and beta energies during the REM stage where prominent activity is theta and alpha [30].

Apnea transition change trends in EEG bands were tabulated in Table 6. There were increments in sub-band energies in N1 and N3 stages whereas in N2, delta and theta activities were decreasing in intra_apnea. This could be seen as a proof that the nervous system intervenes in deep sleep transition which can be particularly dangerous during apnea periods. Apnea periods are rare in REM stages due to activated brain states. However, during apnea periods contrary to general clinical observation, there were increasing trends in alpha and beta activity whereas in delta and theta this trend was in opposite direction. A physiological response to apnea is formed but the brain reacts in order to sustain sleep cycle and consistency.

Table 5. Increasing/decreasing trend in the CSA/OSA group

Pre/Intra Apnea Transient	Delta	Theta	Alpha	Beta	FF	PTT
CSA	↑	↑	↑	↑	↑	↓
OSA	↓	↓	↓	↓	↓	↑

The relative change of increasing/decreasing trends is presented in Table 7. During the N1 stage, the highest increase was observed in delta and theta energies. The decrease in delta and theta energies during N2 stage is not so sharp. During apnea in the N3 stage, delta activity significantly increased as expected where slow wave activity is prominent. There was also an increase in theta activity as the stage after N3 is either REM or N2 indicating transitions between sleep states. The increases in delta and theta activities were considerably high during REM stage. A blunt decrease was observed in alpha and beta energies.

Table 7
Intra_apnea / pre_apnea transition rate of change

Intra / Pre Apnea Transient Ratio	Delta	Theta	Alpha	Beta
N1	2,12	1,96	1,11	1,16
N2	0,77	0,84	1,04	1,03
N3	2,05	1,80	1,37	1,56
REM	4,72	2,83	0,87	0,59

Rate of change in increasing/decreasing trends were given in Table 7 to draw a better picture. Decay in delta and theta activity during N2 stage is lower than the rise in those energy sub-bands in N1 and N3 stages. Decline in delta and theta activity (Table 4) during NREM sleep shows brain's activity change towards wakefulness. Nevertheless, the increase in the same energy sub-bands in N1 and N3 in intra-apnea supply the fact that microstructures were generated to support sleep cycle without affecting homeostatic balance.

Similarly, delta and theta activity increased in REM sleep during intra/pre apnea regions. This is an ingenious reaction of the central nervous system. Even though a physiological response is formed, brain suppresses alpha and beta activity to interrupt sleep process. This effect is highly related to patient's apnea severity as well as physiological parameters but overall, sleep maintaining trend is kept despite apnea.

Dingli et al. [16] investigated the apnea/hypopnea process in 10 second windows. The authors determined an increase in activity in alpha, beta, and delta bands in REM and non-REM stages, including apnea/hypopnea, and a decrease in theta band. According to our current findings, when a single epoch was analyzed with < 1s windows, alpha and beta energies decreased by 23% and 41%, respectively. However, there was a transformation to a higher alpha energy in the post_apnea period (1.17E + 04 ± 9817.93) compared to the pre_apnea period. Beta energy was 7.56E + 03 ± 14175.61. The intra/pre burst in delta energy (Table 7) (5.41E + 05 ± 1312100.47) returned to its initial level during the post_apnea period.

The situation was the same for theta energy. The burst in intra_apnea period was regulated during the post_apnea period (1.28E + 05 ± 262474.41). In conclusion, there are sudden dramatic changes in the REM stage during apnea. The transition to apnea during the REM stage had a clinically longer duration compared to other stages. This, in return, may indicate instantaneous microstructures changes, which are not observed in the cortical activity in fact it is reflected in alpha and beta energies. The situation is also variable in the N2 stage (Tables 4 and 7). The decreasing trends in delta sleep during pre and intra periods continued in the post period as well (1.36E + 06 ± 3071919.5). The decreasing trend in theta energy (2.99E + 05 ± 593599.095) continued. The increase in alpha energy with the onset of apnea decreased below its initial level during the post_apnea period (3.10E + 04 ± 95578.96). It displayed alpha energy behavior in the beta band. N2 is at a critical position among all stages of sleep. It is a transition band with SWS, and sub cortical activities can show considerable variability [54]. The current results indicate that N2, similar to the REM region, showed a different reaction to the apnea process. Alpha and beta energy levels that formed during apnea were regulated during the post period. Clinical studies also suggest that the apnea transition during N2 is shorter. The N1 level is the beginning of the superficial sleep, and pre_apnea and intra_apnea increase in the delta energy decreased below its initial level (1.01E + 06 ± 1554141.7). The N3 stage showed an increased trend in pre_apnea to intra apnea transient equilibrium. During the post_apnea period, the delta energy decreased below its intra_apnea value, but it was the most predominant type in the whole energy scale (1.01E + 06 ± 1554141.7).

In conclusion, the heart and brain exert different behaviors during apnea, depending on the apnea type (Tables 1 and 5). There was no significant difference in cardiac results with respect to sleep stages ($p > 0.005$). EEG behavior is significantly different with respect to sleep stages. Despite various studies, an analysis of the epoch apnea process (apnea event) showed differences in instantaneous EEG behavior.

During superficial sleep transition (N1) and deep sleep (N3) stages; activity variability was observed in all pre, intra, and post energies. The REM region involves the most complex apnea transition. During REM sleep, alpha and beta activity and delta and theta activity was characterized differently. This could be an indicator of different cortical behavior during the REM stage. The present study can provide a different technical perspective to the analysis and statistical evaluation of EEG and ECG parameters. One of the most striking findings is the delta and theta and alpha and beta characterizations. Moreover, the trend in delta and theta activities in N2 and REM can contribute to the clinical interpretation of different microstructures in the cortical region during apnea.

Declarations

Acknowledgment

Consent for sleep apnea research studies was provided from the patients whose PSG recordings were analyzed in this study.

Author Contributions

O. K., Z. T., O. E. developed the methodology, prepared the original draft and realized formal analysis. O. K. implement the computer code and supporting algorithms. C. F. and Z. T. provided writing-review-editing and visualization. Z.T. and O. E. provided validation and supervision of the study. All authors reviewed the manuscript.

Data Availability Statement

The dataset analyzed during the current study are available in the https://zenodo.org/ repository, [https://zenodo.org/record/7822289#.ZDb3yHZByUl].

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Figures

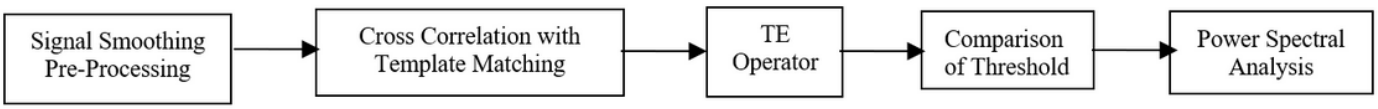

Figure 1

ECG Signal Processing Steps

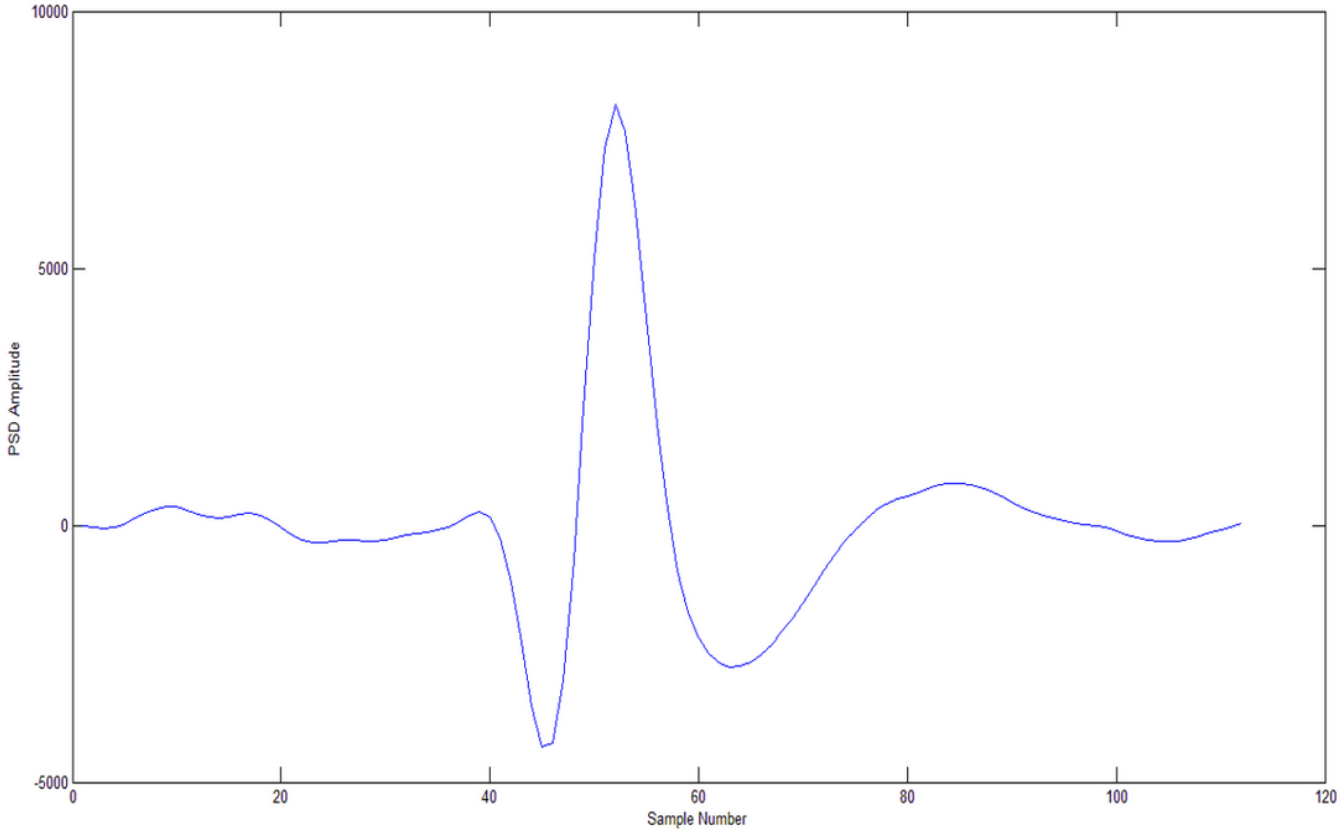

Figure 2

Template for Cross correlation

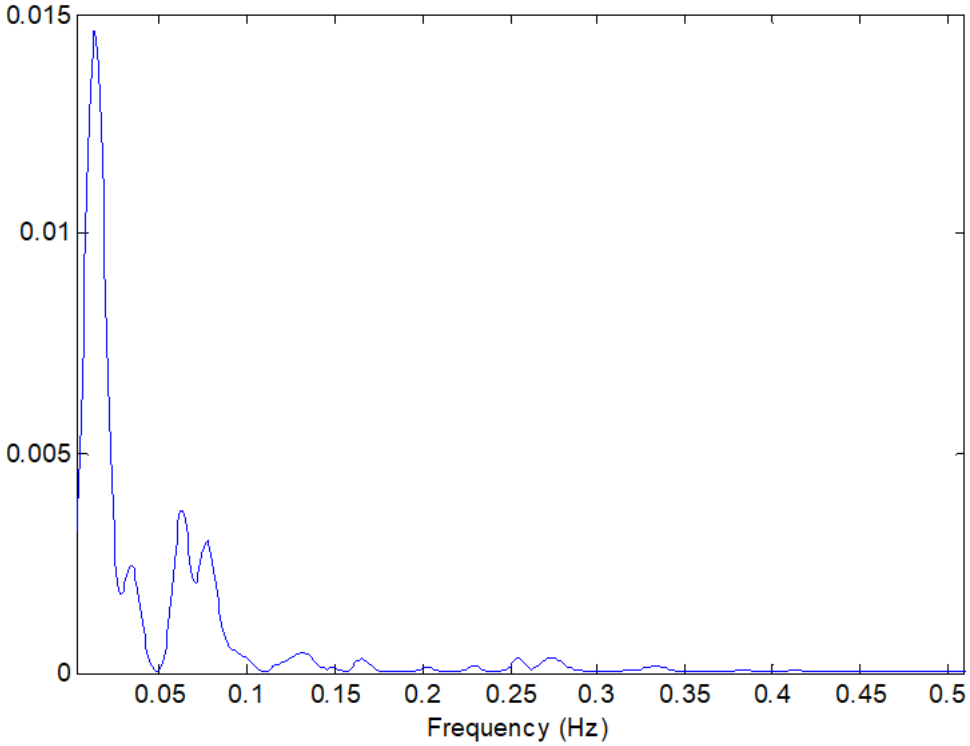

Figure 3

HRV Frequency Spectrum VLF<0.04Hz, LF between 0.04Hz – 0.15Hz, HF between 0.15Hz – 0.4Hz

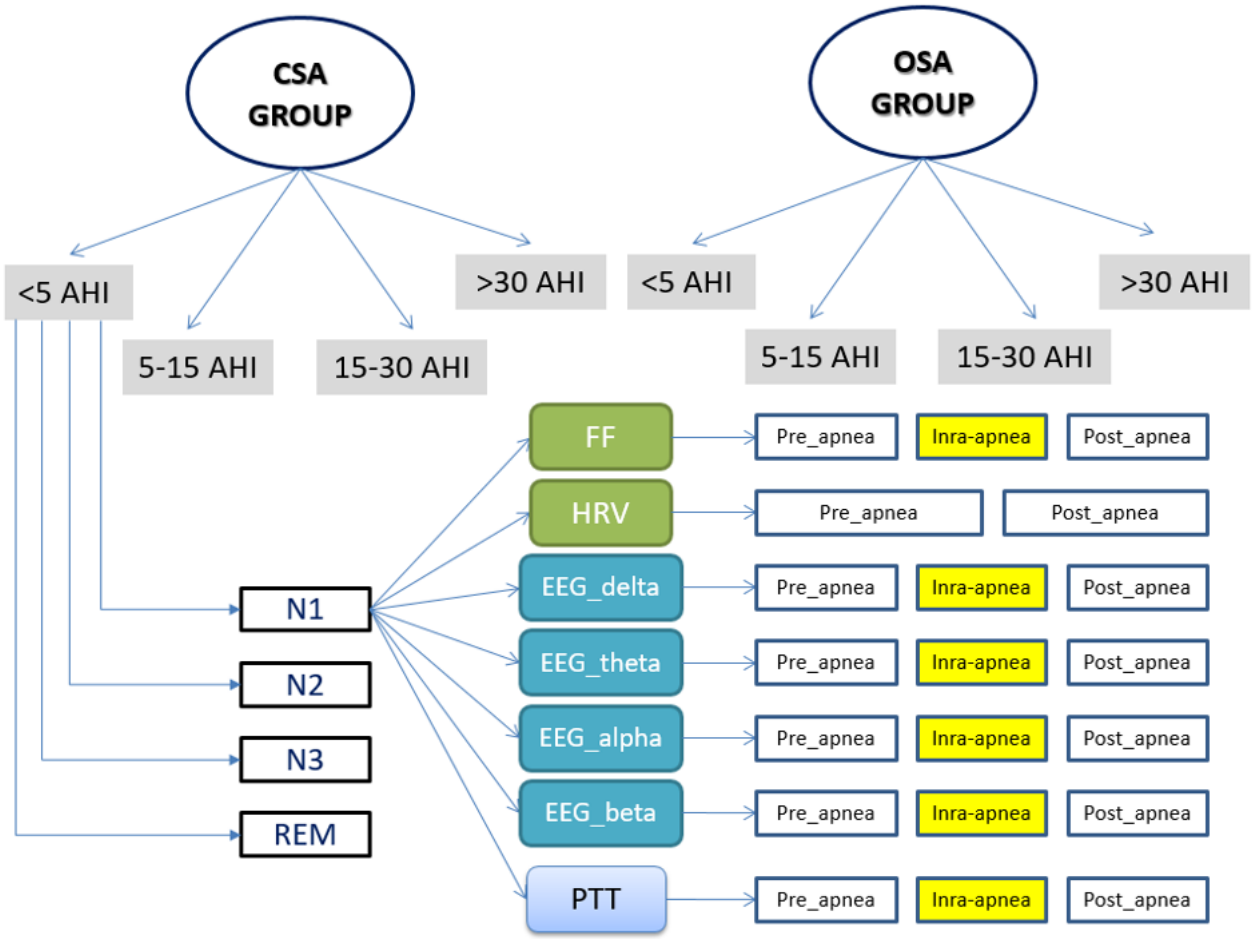

Figure 4

Data classification