STATISTICAL ANALYSIS OF EEG AROUSALS IN SLEEP APNEA SYNDROME

Vinayak Swarnkar and Udantha R. Abeyratne
School of Information Technology and Electrical Engineering
The University of Queensland, Brisbane, Qld 4072, Australia
Tel: +61-7-3346-9063, Fax: +61-7-3365-4999
E-mail: udantha@itee.uq.edu.au.

ABSTRACT
In this paper, we test the novel hypothesis that the electroencephalogram arousals (EEGA) are associated with functional asymmetries of the left and right hemispheres of the brain, as evident through Inter-Hemispheric Asynchrony (IHA) of surface EEG, using statistical analysis. We measured EEG data (using electrodes A1/C2 and A2/C3 of the International 10/20 System) from 22 patients. Spectral correlation coefficients (R) were computed between EEG data from the two hemispheres for each frequency band of interest. Results indicated that IHA varies with two types of sleep, NREM and REM. It tends to intensify with the occurrence of EEGA. Statistical analysis of the results shows high significance difference between the means of the spectral correlation coefficient for normal sleep and sleep affected by arousal events for both type of sleep, with \( P < 0.001 \). A negative relationship \( (r=-0.75) \) was established between the mean spectral correlation coefficient for beta band during NREM sleep and arousal index (AI). These results provide a basis for novel insights into the functional asymmetries of brain regions associated with EEG arousals during sleep apnoea.

KEY WORDS
Electroencephalogram, electroencephalogram arousals, inter-hemispheric asynchrony.

1. Introduction

Sleep disordered breathing (SDB) is the most common sleep disorder in the general population. It often remains undetected due to the complexity/cost of the diagnosis processes and the poor public awareness of the disease [1]. It is associated with increased risk of serious medical and psychiatric problems as well as impaired cognitive functions, accident at work and social adjustment.

The most important among these disorders is Sleep Apnoea. There are three main types of apnea: (i) obstructive apnea (OSA), which is due to a full or partial (structural) obstruction in the upper airways during sleep, (ii) central apnea (CSA) due to functional problems with the breathing muscles/processes, and (iii) mixed apneas, where components of both OSA and CSA are present in a patient. OSA is the predominant type of sleep apnea, and forms the focus of this paper. The severity of sleep apnea is measured by the index AHI, which represents the number of OSA events per sleep-hour, evaluated over the total overnight sleep time of the patient.

Episodes of OSA, by definition, interfere with breathing and thus lower the Oxygen saturation levels in blood (hypoxemia). This in turn causes elevated Carbon dioxide saturation levels (hypercapnia) in the blood. In the Severe cases of OSA the sleep is affected by thousands of short and long duration events of hypoxemia. Effects of these, on the brain remains largely unexplored. With immediate response to hypoxemia decrease in EEG potential and inhibition of spontaneous activity has been noticed [2]. Apart from effect of hypoxemia in OSA, the obstructions in the upper airways lead to increased respiratory effort by the patients. It is believed that all these factors are responsible for the phenomenon “EEG-arousals (EEGA)” associated with OSA.

In sleep medicine, the term EEGA carries a more general meaning than 'waking up'. The EEGA is formally defined as described in Appendix 5.1 based on objective measurements such as the EEG and EMG. The EEGA is a frequently occurring, poorly understood, complicated phenomenon which is critically important in studying the mysteries of sleep. It is transient in nature and generally do not result in natural awakening. It is widely recognized that the arousals play a significant role in determining the pathophysiology of sleep disorders. According to the criteria developed by the American Sleep Disorders Association (ASDA), arousals are a marker of sleep disruptions and as such should be treated as detrimental. The consequences of reoccurring EEGA are that the sleep apnoea patients experience fragmented sleep leading to such complications as daytime sleepiness, morning headaches, memory difficulties and lethargy [3, 4].

The phenomenon of OSA and associated hypoxemia and EEGA event, notwithstanding its scientific and clinical value, remains poorly understood. The characteristics, origins and effects of arousals are currently under active investigations by sleep clinicians and basic researchers alike.
In the past, researchers have developed various hypotheses and experimental methods to investigate the changes in EEG during OSA related hypoxemia and EEGA [2, 3, 5, 6]. Power spectrum analysis of EEG [5] has revealed that EEGA are associated with fluctuation in cortical activity and changes in EEG power in the δ-band of frequencies (0.5–4Hz) [5]. These studies, however, did not consider the issue of hemispheric asymmetry. Existing studies on the EEG frequency and cerebral metabolism, [7] has shown that cortical blood flow is coupled to the level of synaptic activity of the cortical neurons and affects the EEG, in the absence of cerebral anoxia. It has also been shown that the arousal EEG response is accompanied by an increase of the cortical blood flow [7]. All these findings form a sound base to investigate the interhemispheric neuronal asynchrony (IHA) in the OSA patients.

The issue of the asymmetry of the brain during normal sleep has been investigated by groups of researchers [8, 9, 10, 11]. The EEG spectral power was found to undergo interhemispheric shift at the state transitions between NREM and REM sleep in certain frequency bands [10]. The REM sleep stages were associated with decreased correlation coefficients between right and left hemispheres EEG, leading to the hypothesis that dreams (which happen during REM) are mediated by the right hemisphere [11]. These studies, however, didn’t consider the significance of EEGA on the hemispheric correlations, or how the correlations behaved in the disease of OSA. These issues form the main focus of our work. In this paper, we test the novel hypothesis that the EEG-arousals are associated with functional asymmetries of the left and right hemispheres of the brain in OSA patients, as manifested through Inter-Hemispheric Asynchrony (IHA) of surface EEG.

In Section 2, we will describe the standard clinical data acquisition process and the method we used to estimate the spectral correlation coefficient R from EEG data. Statistical analysis of the results are presented and discussed in Section 3, and conclusions are drawn in Section 4.

2. Method

2.1 Clinical Data Acquisition

We collected our clinical data from the Sleep Diagnostic Laboratory of The Prince Alexandra Hospital, Australia [12]. Patients suspected of suffering from OSA are referred to the hospital for a routine overnight diagnostic test known as the Polysomnography test (PSG).

2.1.1 Polysomnography: In a typical PSG test, signals/parameters such as ECG, EEG, EMG, EOG,
2.2.1 Correlation Coefficient Computation: The method we used to calculate spectral correlation coefficient between EEG data recorded from the left and right hemisphere of the brain is described in Steps (S1)-(S5). The correlation coefficients were computed between C4-A1 and C3-A2 recordings.

(S1) Let the digitized EEG data ‘X’ recorded from hemisphere ‘i’ of the brain during PSG test be \( X_i \), where \( i = L \) and \( i = R \) respectively symbolize the left and right hemispheres of the brain. Segment \( X_i \) into \( M \) blocks of size \( L \) with the segment overlap given by \( L_o \). Let the symbol \( X_i(n) \) represent the \( n^{th} \) segment of \( X_i \).

(S2) Filter \( X_i(n) \) through 10\(^{th}\) order digital Butterworth filter with lower cut-off frequency \( f_l = 0.5 \) Hz and higher cut-off frequency \( f_h = 25 \) Hz and estimate the Fourier Transform \( X''(n) \). Obtain the amplitude spectrum defined by \( Y(n) = |X''(n)| \).

(S3) Differentiate \( Y_i(n) \) into frequency bands, Delta (\( \delta \), 0.5-4Hz), Theta (\( \theta \), 4.1-8Hz), Alpha (\( \alpha \), 8.1-12Hz), Beta (\( \beta \), 12.1-25Hz). Let the resulting spectral magnitudes be denoted by \( Y_{\delta L}(n) \) and \( Y_{\theta L}(n) \), where ‘L’ and ‘R’ signifies the left and right hemispheres respectively. The subscript \( j \) represents different EEG waves, i.e., \( j \) can assume one of \( \delta, \theta, \alpha \) and \( \beta \).

(S4) Using (1) calculate the spectral correlation coefficient for all EEG bands \( j = \{\delta, \theta, \alpha \) and \( \beta \} \) over all the \( M \) segments subjected to the following conditions: (i) \( R_{\delta}(n) \) from sleep epochs (30s blocks) clinically labeled as NREM-epochs and which are not affected by arousal episodes are averaged to form \( R_{\delta NRS} \); (ii) NREM-epochs which are affected by arousals lead to \( R_{\delta NRA} \). From REM sleep-epochs we estimate \( R_{\delta RS} \) and \( R_{\delta RA} \) using similar considerations.

(S5) Calculate the mean and the standard deviation of spectral correlation coefficient over all NREM epochs to obtain \( R_{\delta NREM} \), similarly, calculate \( R_{\delta REM} \) based on all epochs labeled REM.

\[
R_j(n) = \frac{\sum(Y_j(n) - \bar{Y}_j)(Y_{\delta}(n) - \bar{Y}_{\delta})}{\sqrt{\sum(Y_j(n) - \bar{Y}_j)^2} \sqrt{\sum(Y_{\delta}(n) - \bar{Y}_{\delta})^2}}
\]  

(1)

2.2.2 Statistical analysis: The statistical analysis of results was carried out by doing independent one tailed student t-test analyses. It is a technique for testing hypothesis on the basis of the difference between means of two samples from different populations. The analysis was carried out in two steps

- To test null hypothesis that mean spectral correlation for NREM sleep is greater than that for REM sleep, for delta, alpha and beta and inverse is true for theta frequency bands of EEG.
- Secondly we tested the hypothesis that IHA fluctuates with EEGA for which we considered the null hypothesis that mean spectral correlation coefficient for sleep epochs which are not affected by EEGA is greater than those epochs which are affected by EEGA.

One tailed Pearson’s correlation analysis evaluated the relationship between the mean spectral correlation coefficient and the arousal index for NREM and REM both type of sleep across the patients. Pearson’s correlation was also calculated between RDI and AI to find out the relationship between apnoea events and associated EEGA.

In Section 3 we present our results of the data analyzed using algorithm described in the section 2.

3. Results and discussion

3.1 IHA and REM/NREM/Wake sleep stages

To explore the variation in IHA at a macro-level, how the IHA varies varying sleep stages, i.e. NREM/REM/WAKE following steps (S1)-(S5) we estimated \( R(n) \) choosing \( L_e = 50s \), \( L = 60s \) and \( L_e = M \) samples. Figure 2(a)-(d) respectively show \( R_{\delta}(n) \), \( R_{\theta}(n) \), \( R_{\alpha}(n) \) and \( R_{\beta}(n) \), for segments \( n = 1, 2, \ldots, M \). According to Figure 2, while gross variations can be seen for all EEG bands, they are pronounced and much more consistent in the \( \delta \) and \( \beta \) bands. These gross variations in the spectral correlation coefficient with the REM/NREM/Wake sleep categories is also seen as reported in the work of [15]. Figure 3 shows the mean spectral correlation coefficients for NREM and REM epochs, calculated at Step (S5) outlined in Section 2.2.1 for all the 22 patients studied. Significant
changes in the spectral correlation can be seen between NREM and REM sleep stage. Quite interestingly, in the $\delta$ and $\beta$ bands, the left/right correlation is larger for NREM than for REM whereas in $\theta$ and $\alpha$ bands the opposite seems to be true in which 17 and 14 patients respectively showed increase in the mean spectral correlation coefficient from NREM to REM stage.

These gross variations in the correlations require closer study at a micro-level, especially in the context of OSA-related EEGA. In Section 3.2, we present the results of our work in that direction.

3.2 IHA variation with EEGA

To investigate the variation of the IHA with the occurrences of EEGA in OSA, we centered our attention on all non-awake epochs of data. In Figure 2(f) and Figure 2(g) we respectively show EEGA events and apnea events as determined through the routine PSG testing. According to Figure 2(f) and Figure 2(g), there is a strong relationship between apnea and EEGA events, with Pearson’s correlation coefficient $r=0.86$. However, this has to be interpreted taking in to account that not all the apnoea events are associated with EEG arousals as well as the complications of marking of both kinds of events and the human error.

Figure 4 summarizes the comparison of mean spectral correlation coefficient calculated in section 2.2.1 for all the 22 patients for delta, theta and beta band activity. It is quite clear from the graphs in Figure 4 that mean spectral correlation coefficient assumes low value during the sleep affected by EEGA, irrespective of type of sleep, indicating the induced IHA, in all the patients.

3.3 Statistical Analysis of IHA

The t-test analysis of the mean spectral correlation coefficient of the samples from the NREM and REM sleep showed significant difference between the means. Table 1 shows the statistical results for one patient with AI=20.3 and RDI=18.3. Out of 22 patients studied 19, 13, 18 patients reached the statistical significance in difference between the mean for NREM and REM sleep, with $\bar{R}_{NREM} > \bar{R}_{REM}$, respectively for delta, alpha and beta frequency band, with $P<0.05$. In theta frequency band where results in section 3.1 indicated $\bar{R}_{NREM} < \bar{R}_{REM}$, 16 patients achieved the statistical significance value with $P<0.05$. Pearson’s correlation analysis revealed significance inverse relationship between the

<table>
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<tr>
<th>Frequency Bands</th>
<th>t-stat value</th>
<th>P</th>
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<tbody>
<tr>
<td>$\delta$</td>
<td>1.98</td>
<td>0.05$&gt;$P$&gt;$0.025</td>
</tr>
<tr>
<td>$\theta$</td>
<td>1.86</td>
<td>0.05$&gt;$P$&gt;$0.025</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>2.34</td>
<td>0.025$&gt;$P$&gt;$0.010</td>
</tr>
<tr>
<td>$\beta$</td>
<td>2.78</td>
<td>P$&gt;$0.005</td>
</tr>
</tbody>
</table>
mean beta spectral correlation coefficient for NREM epochs and AI, r= -0.75. This signifies that with the increase in AI in the NREM sleep the IHA increases in the beta frequency band of EEG. No such kind of relationship was established between the mean spectral correlation coefficient and AI for other frequency bands.

The most consistent and significant changes across all 22 patients was the decrease in beta mean spectral correlation coefficient from normal sleep epochs to sleep epochs affected by arousals, in either form of sleep NREM/REM. For this all the 22 patients achieved the statistical significance value for NREM state and 16 patients in REM sleep, with P<0.05. Table 2 shows the statistical analysis result for the one patient. For the other band frequencies, the number of patients achieved t-test significance, in NREM state Figures are 14 – delta, 19 – theta, 13 – alpha and for REM state 8 – alpha, 14 – theta and 13 – alpha.

Table 1, Table 2, Figure 3 and Figure 4 lead to the following observations:

- EEGA events are associated with a decrease of the inter-hemispheric synchronization activities of the brain, as indicated by a lowering of correlation coefficients in both REM and NREM stages of sleep. (ie. IHA is increased with EEGA irrespective of sleep stage). The increase in IHA occurs in all the frequency band.

- IHA is significantly increased in EEGA events during REM sleep; this is true for all frequency bands, being more dominant in β frequency band.

- IHA assumes its largest value during EEGA affected REM sleep; the only exception to this observation is some of the wake states of sleep where correlation goes minimum.

- A inverse relationship exists between the arousal index (AI) and induced IHA in beta band frequency during NREM sleep.

These results indicate that the macro-analysis of sleep

<table>
<thead>
<tr>
<th>Frequency Band</th>
<th>t-stat value</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Statistical result for NRS/NRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>δ</td>
<td>2.10</td>
<td></td>
</tr>
<tr>
<td>θ</td>
<td>1.99</td>
<td>0.05&gt;P&gt;0.025</td>
</tr>
<tr>
<td>α</td>
<td>2.44</td>
<td>0.025&gt;P&gt;0.010</td>
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<tr>
<td>β</td>
<td>7.59</td>
<td>P&lt;0.005</td>
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<tr>
<td>Statistical result for RS/RA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>δ</td>
<td>1.15</td>
<td>0.1&gt;P&gt;0.05</td>
</tr>
<tr>
<td>θ</td>
<td>2.26</td>
<td>0.025&gt;P&gt;0.010</td>
</tr>
<tr>
<td>α</td>
<td>3.24</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>β</td>
<td>2.53</td>
<td>0.010&gt;P&gt;0.005</td>
</tr>
</tbody>
</table>

Figure 4 NRS/NRA and RS/RA comparison plot for different band activity, delta, theta and beta for 22 patients studied. X-axis represents number of patients, and Y-axis represents mean correlation coefficient multiplied with multiplication factor of 10 and error bar represents standard deviation multiplied with multiplication factor of 1. Different multiplication factor are used to improve visual clarity of illustration.
without considering the effects of EEGA is insufficient to understand how the brain behaves during episodes of OSA. Detailed micro-analysis of the states of NREM and REM sleep showed local variations of IHA during OSA episodes. Increase in IHA during the REM sleep in comparison to that of NREM may correspond to hemispheric dominance of dreaming. Several previous studies have concluded that right hemisphere of the brain mediates dreaming [8]. The strong asymmetry during the EEG-arousal episodes in the REM sleep is a significant finding.

4. Conclusion

In the present study we analyzed inter-hemispheric asynchrony related to EEGA in the 22 sleep apnoea patients. The EEG asymmetry was determined via the Spectral Correlation coefficient of data, which computed the correlation between EEG measured from the two hemispheres of the brain. Results showed that IHA intensify with the occurrence of EEGA. Statistical analysis of the results showed the significant difference between the mean spectral correlation coefficient, for different stages of sleep. This unequivocally indicates that EEG-arousals (EEGA) should be considered as another dimension in sleep analysis in OSA, alongside with the concepts of REM/NREM and Wake states.

Appendix

5.1 Definitions of EEG Arousals [5]
EEG Arousal is defined as abrupt shift in EEG frequency, which may include theta, alpha activity and/or frequencies greater than 16Hz (but not sleep spindles) subjected to the following scoring rules:
The subject must be asleep for a minimum period of 10s before declaring an Arousal event,
EEG frequency shift must be sustained for a 3s duration or more and,
EEG arousal from REM sleep requires presence of simultaneous increase in the submental EMG amplitude.

5.2 Definition of the Arousal Index (AI)
The average number of EEG-arousal events per hour of sleep, computed over the total sleep period, is termed as arousal index.

5.3 Respiratory Disturbance Index (RDI)
The average number of respiratory disturbance events (Obstructive, Central and Mixed Apnea event) per hour of sleep, as computed over the total sleep period is defined as the Respiratory Disturbance Index (RDI).

Acknowledgement

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