Inter-Hemispheric Asynchrony of the Brain during Apnea Related EEG Arousals

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Abstract — Sleep in apnea patients is fragmented with frequent EEG arousals (EEGA) as determined via changes in the sleep-electroencephalogram. The EEGA is a poorly understood, complicated phenomenon which is critically important in studying the mysteries of sleep. In this paper, we present the novel hypothesis that the EEG arousals are associated with functional asymmetries of the left and right hemispheres of the brain, as manifested through Inter-Hemispheric Asynchrony (IHA) of surface EEG. We measured EEG data (using electrodes A1/C2 and A2/C3 of the International 10/20 System) from 3 patients undergoing routine Polysomnography (PSG) testing at the hospital. Spectral correlation coefficients (R) were computed between EEG data from the two hemispheres for each frequency band of interest. Our results indicated that the EEGA in sleep apnea are associated with IHA. In Rapid Eye Movement (REM) stages of sleep, R=0, leading to the conclusion that the two hemispheres were almost uncorrelated. In non-REM sleep (NREM), a significant reduction of R below the baseline was observed, but the level of reduction was smaller than that for REM. These results may provide a basis for novel insights into the functional asymmetries of brain regions associated with EEG arousals during sleep apnea.

I. INTRODUCTION

Sleep apnoea is one of the most common sleep disorders in the world. It often remains undetected due to the complexity/cost of the diagnosis processes and the poor public awareness of the disease [17].

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 OSA, the obstructions in the upper airways lead to increased respiratory effort by the patients. It is believed that 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 A2 based on objective measurements such as the EEG and EMG. The EEGA is a transient phenomenon 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 apnea patients experience fragmented sleep leading to such complications as daytime sleepiness, morning headaches, memory difficulties and lethargy [11].

The phenomenon of EEGA, 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 EEGA [6, 11, 15]. Spectral analysis of the EEG [6] has revealed that EEGA are associated with changes in EEG power in the δ-band (δ-waves) of frequencies (0.5-4Hz) [6, 8]. These studies, however, did not consider the hemispheric differences of EEGA as manifested in surface EEG.

The issue of the asymmetry of the brain during normal sleep has been investigated by groups of researchers [12],[1],[2]. The EEG spectral power was found to undergo interhemispheric shift at the state transitions between NREM and REM sleep in certain frequency bands [1]. 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 [2]. None of these studies, however, considered the significance of EEG 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 present the novel hypothesis that the EEG-arousals are associated with functional asymmetries of the left and right hemispheres of the brain during OSA, as manifested through Inter-Hemispheric Asynchrony (IHA) of surface EEG. Existing studies on the EEG frequency, cerebral oxygen uptake and blood [14] 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 [16]. All these findings form a sound base to investigate the interhemispheric neuronal asynchrony (IHA) in the OSA patients.

In Section II, we will describe the standard clinical data acquisition process and the method we used to estimate the spectral correlation coefficient $R$ from EEG data. Our results are presented and discussed in Section III, and conclusions are drawn in Section III.

II. METHODOLOGY

A. Clinical data Acquisition

The clinical data acquisition environment for this work is the Sleep Diagnostic Laboratory of The Prince Alexandra Hospital, Australia (the largest such laboratory in the state of Queensland). Patients suspected of suffering from OSA are referred to the hospital for a routine overnight diagnostic test known as the Polysomnography test (PSG).

In a typical PSG test, signals/parameters such as ECG, EEG, EMG, EOG, nasal/oral airflow, respiratory effort, body positions, body movements and the blood oxygen saturation are carefully monitored (see Fig.1). Altogether, a PSG test involves over 15 channels of measurements requiring physical contact with the patient. The AH1 index, or a more general version of it known as the respiratory disturbance index (RDI, see Appendix A.4), is then calculated to determine the severity of the disorder.

As a part of the analysis, PSG data is manually scored by a sleep technician according to the standard Rechtschaffen and Kales (R&K) criteria [9] to determine the sleep stages and REM/NREM status of sleep. In the standard clinical scoring process, PSG data are conceptually segmented into data blocks called ‘epochs’, which are 30 seconds long. These epochs are then considered as fundamental data lengths for the purpose of sleep staging. Each epoch will get a label stating the sleep stage it belongs to.

Routine PSG data were measured using clinical PSG equipment (Siesta, Compumedics®, Sydney, Australia). Patient preparation, placement of electrodes and instrumental set up was done by expert sleep technician.

PSG data were accompanied by an edited annotation file with an event-by-event description of Apnoeas.

EEG data were recorded from the cortical regions of both hemispheres using electrode position, C4, C3, A2, A1, based on the standard international 10-20 system of electrode placement.

B. Correlation coefficient computation

The method we used is described in Steps (S1)-(S7).
(S1) Let the digitized EEG data 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. Let the total length of X_i be L_i Samples.

(S2) 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. Note that these segments are independent of the conceptual segmentation ('epochs') used in sleep staging of EEG data as described in Section II-A.

(S3) Pass X_i(n) through a 10th order digital Butterworth filter with lower cut-off frequency f_L=0.5Hz and higher cut-off frequency f_H=25 Hz (see Fig.2) to obtain the filtered segment X_i'(n). The filtering will remove the low frequency artifacts such as movement and blinking artifacts found in EEG. It also deals effectively with high frequency artifacts such as muscle noise and power line interference at 50Hz.

(S4) Estimate the Fourier Transform X''_i(n) of the segment X_i'(n) and obtain the amplitude spectrum defined by Y_i(n) = |X''_i(n)|. Differentiate Y_i(n) into frequency bands, Delta (δ, 0.5-4Hz), Theta (θ, 4.1-8Hz), Alpha (α, 8.1-12Hz), Beta (β, 12.1-25Hz). Let the resulting spectral magnitudes be denoted by Y_δ(n) and Y_θ(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 δ, θ, α and β.

(S5) Use (1) to compute the Spectral Correlation coefficient R_j(n) exhaustively for all EEG bands j=[δ, θ, α, and β] and segments n=1,2,…., M.

(S6) Calculate the Mean (and the standard deviation) spectral correlation coefficient for all EEG bands j=[δ, θ, α, and β] over all the M segments subjected to the following conditions: (i) R_j(n) from sleep epochs (30 blocks) clinically labeled as NREM-epochs and which are not affected by arousal episodes are averaged to form (R_δ NREM); (ii) NREM-epochs which are affected by arousals lead to (R_β REM). From REM sleep-epochs we estimate (R_β REM) and (R_α REM) using similar considerations.

(S7) Calculate the mean and the standard deviation of spectral correlation coefficient over all NREM episodes to obtain R_δ NREM; similarly, calculate R_β REM based on all episodes labeled REM.

\[ R_j(n) = \frac{\sum [Y_j(n) - \bar{Y}_j] \cdot [Y_j(n) - \bar{Y}_j]}{\sqrt{\sum [Y_j(n) - \bar{Y}_j]^2 \cdot \sum [Y_j(n) - \bar{Y}_j]^2]} \] (1)

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

III. RESULTS AND DISCUSSION

A. Variation in R_j(n) with REM/NREM/Wake sleep stages.

Initially, we are interested in exploring, at a macro-level, how the IHA varies varying sleep stages, i.e. NREM/REM/WAKE. Following steps (S1)-(S5) we estimated R_j(n) choosing L_o=50s, L_e=60s and L_s=M samples. Fig. 3(a)-(d) respectively show R_δ(n), R_θ(n), R_α(n) and R_β(n), for segments n=1,2,….,M. According to Fig.3, while gross variations can be seen for all EEG bands, they are pronounced and much more consistent in the δ and β bands.

![M](image)

![M](image)

![M](image)

![M](image)

![M](image)

![M](image)

Fig. 2. a) Butterworth Filter magnitude response, plotted against the log scale, F_L=0.5Hz is the lower cut off frequency, and F_H=25 is the higher cut off frequency. b) Frequency response of raw EEG data X_i(n) corrupted with 50Hz electrical interference and high frequency noise. c) Frequency spectrum of filtered EEG data X_i'(n) showing the effect of band pass filter removing 50Hz electrical interference and other higher frequencies.

![M](image)

![M](image)

![M](image)

![M](image)

![M](image)

Fig. 3. Patient (1) with AI = 20.3 and RDI = 18.3. a) Delta b) Theta c) Alpha d) Beta, correlation coefficient during the NREM and REM sleep e) Sleep stages, line at 1 indicates NREM sleep and positive line at 6 indicates REM sleep.
Furthermore, a gross variation in the spectral correlation coefficient with the REM/NREM/Wake sleep categories is also seen as reported in the work of [4].

Table I shows the correlation coefficients calculated at Step (S7) outlined in Section II B. Significant changes in the spectral correlation can be seen between NREM and REM sleep. Quite interestingly, in the δ and β bands, the left/right correlation is larger for NREM than for REM, whereas in θ and α bands the opposite seems to be true.

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

B. The variation of spectral correlations with EEGA and sleep staging

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 Fig. 4, we show EEG data at each frequency band after removing segments classified as 'wake' epochs in Fig. 4. In Fig. 4(f) and Fig. 4(g) we respectively show EEGA events and apnea events as determined through the routine PSG testing.

According to Fig.4(f) and Fig.4(g), there is a strong relationship between apnea and EEGA events; however, there is no 1-to-1 correspondence between identified apnea and marked EEGA events. This has to be interpreted taking the accuracy of the EEGA and apnea marking processes into account. In both cases, the criteria for determining an event are not well suited for objective analysis, and manual classifications have to be used, often resorting to visualization techniques.

In Table II, we illustrate the mean spectral correlation coefficients computed at step (S5) of Section II B. Table II and Fig. 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)

- IHA is significantly increased in EEGA events during REM sleep; this is true for all frequency bands, δ, θ, α and β. The correlation coefficient becomes almost zero, indicating that the left and right hemispheric activities of the brain are almost uncorrelated.

- IHA assumes its largest value during Wake states; the only exception to this observation is EEGA events in REM sleep.

These results indicate that the macro-analysis of sleep 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 episodes OSA.

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 [12,13].

The strong asymmetry during the EEG-arousal episodes in the REM sleep is a significant finding. However, at this time we are unable offer an unequivocal explanation as to why asymmetry develops in the brain during EEGA related to OSA. We are currently investigating the reasons for this phenomenon.

### TABLE I
**DIFFERENCE IN CORRELATION COEFFICIENTS FOR NREM AND REM SLEEP. QUANTITIES WITHIN PARATHESIS ARE STANDARD DEVIATIONS**

<table>
<thead>
<tr>
<th></th>
<th>( R_{NREM} )</th>
<th>( R_{REM} )</th>
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<tr>
<td>Patient 1: RDI=18.3 AI=20.3</td>
<td>( \delta )</td>
<td>0.65 (0.10)</td>
</tr>
<tr>
<td></td>
<td>( \theta )</td>
<td>0.28 (0.09)</td>
</tr>
<tr>
<td></td>
<td>( \alpha )</td>
<td>0.27 (0.12)</td>
</tr>
<tr>
<td></td>
<td>( \beta )</td>
<td>0.55 (0.07)</td>
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<td>Patient 2: RDI=0.6 AI=9.7</td>
<td>( \delta )</td>
<td>0.45 (0.14)</td>
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<tr>
<td></td>
<td>( \theta )</td>
<td>0.25 (0.09)</td>
</tr>
<tr>
<td></td>
<td>( \alpha )</td>
<td>0.23 (0.12)</td>
</tr>
<tr>
<td></td>
<td>( \beta )</td>
<td>0.57 (0.14)</td>
</tr>
<tr>
<td>Patient 3: RDI=8.5 AI=14.6</td>
<td>( \delta )</td>
<td>0.50 (0.13)</td>
</tr>
<tr>
<td></td>
<td>( \theta )</td>
<td>0.27 (0.09)</td>
</tr>
<tr>
<td></td>
<td>( \alpha )</td>
<td>0.25 (0.22)</td>
</tr>
<tr>
<td></td>
<td>( \beta )</td>
<td>0.60 (0.12)</td>
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### IV. CONCLUSION

We investigated the inter-hemispheric asymmetry of the brain during EEG-arousals associated with Obstructive Sleep Apnea syndrome. We analyzed EEG-data from three patients referred to a Sleep Diagnostic laboratory for routine polysomnography. 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. Our results unequivocally indicate 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. The affect of this fourth dimension EEGA seems more pronounced during the REM episodes, which gives rise to almost total asymmetry between the two hemispheres of brain.

### TABLE II
**CORRELATION COEFFICIENTS FOR NREM-EPOCHS WITHOUT AROUSAL (\( R_{NRA} \)), NREM-EPOCHS AFFECTED BY AROUSALS (\( R_{NRA} \)), REM WITHOUT AROUSAL (\( R_{REM} \)) AND REM AFFECTED BY AROUSALS (\( R_{REM} \)). QUANTITIES WITHIN PARATHESIS ARE STANDARD DEVIATIONS**

<table>
<thead>
<tr>
<th></th>
<th>( \delta )</th>
<th>( \theta )</th>
<th>( \alpha )</th>
<th>( \beta )</th>
</tr>
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<tbody>
<tr>
<td>Patient 1: RDI=18.3 AI=20.3</td>
<td>( R_{NRA} )</td>
<td>0.60 (0.17)</td>
<td>0.21 (0.11)</td>
<td>0.23 (0.12)</td>
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<td>( R_{NRS} )</td>
<td>0.67 (0.11)</td>
<td>0.29 (0.10)</td>
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<td>( R_{RA} )</td>
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<td>0.07 (0.07)</td>
<td>0.03 (0.09)</td>
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<td>( R_{RS} )</td>
<td>0.56 (0.10)</td>
<td>0.44 (0.10)</td>
<td>0.34 (0.12)</td>
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<tr>
<td>Patient 2: RDI=0.6 AI=9.7</td>
<td>( R_{NRA} )</td>
<td>0.41 (0.16)</td>
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<td>0.24 (0.13)</td>
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<tr>
<td>Patient 3: RDI=8.5 AI=14.6</td>
<td>( R_{NRA} )</td>
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<td>( R_{NRS} )</td>
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<td>0.36 (0.22)</td>
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<tr>
<td></td>
<td>( R_{RS} )</td>
<td>0.47 (0.11)</td>
<td>0.31 (0.09)</td>
<td>0.40 (0.15)</td>
</tr>
</tbody>
</table>
APPENDIX

A.1 Sleep Staging in PSG testing [9]
There are two major categories of sleep known as REM (Rapid Eye Movement) and non-REM (NREM). NREM is further divided into four different stages of sleep, Stage-1 to Stage-4. Stage-1 sleep is a transitional stage between wakefulness and sleep with slowing of EEG and occurrence of 3-7Hz frequency, called Theta EEG activity. Stage-2 continues to be consist of Theta EEG frequency but is marked by the appearance of EEG sleep bundles (12-14Hz activity lasting up to 2s) and the K-complex[14]. Stage-3 & Stage-4 are collectively referred to as deep sleep or slow wave sleep (SWS) where low-frequency (0.5-2Hz), high amplitude EEG δ-wave activities can be seen.

REM sleep is characterized by bursts of rapid eye movements, detected by EOG and chin EMG signals. The former is used to detect the presence of eye movements and the latter can detect muscle twitches.

A.2 Definitions of EEG Arousals [15]
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 sub mental EMG amplitude.

A.3 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.

A.4) 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).

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